CLINICAL AND EXPERIMENTAL STUDIES OF NUTRITIONAL DEFICIENCY AND NUTRITIONAL THERAPY IN CROHN'S DISEASE

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1989

SYNOPSIS

This thesis examines aspects of malnutrition in Crohn's disease (CD) and evaluates nutritional therapy in Crohn's disease and in animal experiments. Chapters 1 and 2 are the introduction and methods. Section 1 (Chaps 3-7) examines the prevalence of malnutrition and depletion of various nutrients in 65 CD patients followed by investigation of the clinical significance of some of the abnormalities found. Of 65 patients only 52% were of normal weight and 29% were severely underweight. In 15 laboratory measurements, abnormalities (mostly reduced blood levels) included albumin(40%), calcium (35%), transferrin(34%), haemoglobin(32%), alkaline phosphatase(30%), zinc(27%), vitamin A(23%), vitamin E(23%) and magnesium(11%). Abnormalities were commonest in patients with extensive bowel involvement (average 4.3) and those severely underweight (< 80% of ideal weight) were more likely to be protein depleted and to have low levels of calcium and vitamin A. Eleven (17%) had 6 or more abnormalites. Most were underweight with active disease. 15 out of 17 in-patients were found to have magnesium (Mg) depletion, in three all with serum Mg levels < 0.60 mmol/l, symptoms (tetany) occurred. Requirements for long-term oral therapy were 30 to 60 mmol Mg a day. Osteomalacia (OM) was investigated with bone biopsies in 24 patients. The six (25%) with OM weighed less and had more active disease than those without OM but in only 2 had more than 200 cm of small bowel been resected. All with OM had steatorrhoea. Alkaline phosphatase readily detected severe OM. In milder cases, when alk phos may be normal, the use of a radiolabelled diphosphonate and serial measurements of Vitamin D levels in blood are suggested as screening tests. Vitamin A deficency is investigated in 52 of the patients. Plasma retinol levels (low in 21%) were very low (< 1.0 µmol/l) in 5. They weighed less than 80% of ideal, were protein depleted and 3 of 4 had steatorrhoea. 3 of the 5 (the only ones with retinol <0.8 µmol/l) had impaired dark adaptation (DA) and two complained of night blindness. Correction of protein depletion and vitamin A supplements relieved the symptoms and DA improved. Plasma retinol is useful as a screening test. The significance of abnormal

vitamin E levels was examined in 25 patients by searching for evidence of red cell membrane instability. While *in vitro* instability (haemolysis during incubation with hydrogen peroxide) was present in 19 (76%), there was no *in vivo* haemolysis and no adverse effects of vitamin E were detected.

Section 2 (Chaps 8,9) reports the author's experience over 5 years of artificial feeding with enteral (tube-fed) nutrition (EN) and intravenous nutrition (IVN) in 19 CD patients fed in total for approximately 3 patient-years. The feeding was short term (mean 5 weeks) but several patients had more than one period. Success of the therapy was judged by the outcome of predetermined primary aims: the treatment of weight loss together with one or more complications of CD. Short term EN largely failed with no overall improvement in weight and only 4 of 16 complication episodes successfully treated: diarrhoea(1), abdominal pain(2) and in maintenance treatment of intestinal failure at home(1). Amongst the failures were 6 fistulae treated for a total of 36 weeks and severe diarrhoea in 3 out of 4. IVN was successful in improving weight (mean 1.6Kg/week) and protein depletion and was successful in 19 out of 35 complication episodes notably in the intermittent treatment of intestinal failure. It was also helpful in relieving intestinal obstruction and allowed one pregnancy to proceed to term. Based on biochemical monitoring during IVN, recommendations for provision of Mg (10mmol or more a day) and zinc (100-200μmol/day) are made.

Section 3 (Chap 10) is a controlled experiment in intact rats to investigate the comparative efficacy 2 defined formula (DFD) and 3 polymeric (PD) enteral diets given isocalorically in terms of growth, nitrogen (N) balance and faecal residue. No differences in growth (weight gain) or N balance emerged although Vivonex resulted in less N accretion as judged by whole body N measurement than Flexical or Clinifeed. N excretion was highest in the feeds with high N content. Faecal residue was less with the two DFDs (Vivonex and Vivonex HN) than with the PD, Flexical, Clinifeed and Ensure.

Section 4 (Chaps 11,12) is discussion and an overview of the results followed by a short summary.

DEDICATION

The work of this thesis is dedicated to three of the patients whose lives were altered in different ways by nutritional therapy. They must remain anonymous but are described fully in the thesis.

Patient number 62 who died as a result of malnutrition and the complications of intravenous feeding.

Patient 53 in whom nutritional therapy during pregnancy allowed a new life to begin.

Patient 50 whose quality of life was undoubtedly improved by innovations in nutritional therapy. While I was still working in Glasgow, and after he had been started on a home enteral feeding regimen, he wrote an autobiography describing his personal reactions to illness and his own philosophy of coping.

> "The problems are extreme diarrhoea, incontinence, pain, malabsorption of protein and depression. The worst of them all can be the depressions because when you are in one you are very low in spirit and inclined to give up hope. So never give up hope even if you experience great pain and have to spend very long periods in hospital, there is always a light at the end of the tunnel. Perhaps it is very dim but it is always there and you only have to look, look, look and keep on looking until eventually you find it".

His last sentence seems to embody the spirit of enquiry which I hope has been the guiding principle behind this work and also hope that the reader will feel that a little light has been shed on the problems and therapy of this dreadful disease.

ACKNOWLEDGMENTS

My greatest debt of gratitude is to Dr Robin Russell who was the guiding force behind all this work and in whose Gastroenterology Unit in Glasgow Royal Infirmary I worked from May 1978 until December 1983. Other colleagues on the Unit whose help and collaboration are gratefully acknowledged are Dr Peter Mills, a second mentor and constructive critic, Dr Roger Morgan, fellow registrar, Dr Mike Hall, Dr John Mackenzie and the Unit's biochemist Dr Lesley Nelson who was especially helpful in assisting with the animal experiment reported in Chapter 10.

Much of the work had a strong biochemical bias and I am especially indebted to Dr Alan Shenkin, Dr Gordon Fell, Dr Alan McLelland and Dr Mattie Lough from the Department of Biochemistry at Glasgow Royal Infirmary, all of whom took a keen interest in our patients with nutritional difficulties and coordinated the close monitoring of their progress on nutritional therapy. They collaborated in the various studies reported in this thesis.

Although I have typed most of this thesis myself I am grateful for secreterial assistance from Gail Hume, Diane Halliley and Ann Butler in the typing of previous papers. A word of thanks also to Mr Alan Sugar whose skills as an entrpreneur, provided me with a word processor (Amstrad PCW 8512) at a sensible price.

The work was done between 1978 and 1983 and the delay in presenting the thesis is attributed to the acquisition of a new career, a wife and two sons all in a short period of time. Especial thanks to my wife Jill for putting up with neglect over the last six months, for editorial assistance and for helping me to shed several pages of unnecessary words.

LIST OF RELATED PUBLICATIONS

While much of the work has been previously published, chapters 1, 2, 3, 5, 8 and the discussion (chapter 11) are new. The remaining chapters have been extensively revised to convey the cohesion to the clinical work which was intended when the series of studies was planned for this thesis.

The data presented in Chapters 4 to 10 have been presented at scientific meetings and for the most part published in abstract form or as full papers. These are listed in chronological order and reprints or photocopies are bound in as the 'end-pages'

1. Main ANH, Morgan RJ, Hall MJ et al (1980)
   Home enteral tube feeding with a liquid diet in the long term management of chronic inflammatory bowel disease and intestinal failure.
   Scott Med J 25:312-314

2. Main ANH, Morgan RJ, Russell RI et al (1981)
   Magnesium deficiency in chronic inflammatory bowel disease and requirements during intravenous nutrition
   J Parent Ent Nutr 5: 15 - 19

3. Main ANH, Shenkin A, Black WP et al (1981)
   Intravenous nutrition to sustain pregnancy in patient with Crohn's disease
   Br Med J 283:1221-1222

4. Main ANH, Morgan RJ, Hall MJ et al (1981) (abstract)
   A clinical evaluation of intravenous nutrition (IVN) in inflammatory bowel disease (11 thesis patients and 1 with ulcerative colitis)
   Scott Med J 26:89

5. Main ANH, Hall MJ, Fell GS et al (1982)
   Clinical experience of zinc supplementation during intravenous nutrition in Crohn's disease: the value of serum and urine measurements
   Gut 1982; 23:984-991

6. Main ANH, Mills PR, Russell RI et al (1983)
   Vitamin A deficiency in Crohn's disease
   Gut 24: 1169-1175
   (also presented to the Medical Research Society-abstract in Clinical Science 1982; 63: 7P)

7. Lough M, Main A, Russell RI et al (1984) (abstract)
Vitamin E and selenium status in Crohn's disease
Proc Nutr Soc 43:125A

8. Main ANH, Nelson LM, East W et al (1984) (abstract)
Comparative effects of enteral liquid diets on growth, nitrogen (N) balance, whole body N, N wastage and faecal residue in rats
Gut 25 A1158

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CHAPTER 1

INTRODUCTION JUSTIFICATION AND AIMS

1.1 INTRODUCTION. Historical profile and definition of Crohn's disease; aetiology; clinical features; drug and surgical treatment

1.2 JUSTIFICATION

Section 1 - Nutritional depletion and its clinical significance.
Chapters 3 - 9

Section 2 - Nutritional therapy.
Chapters 8 and 9.

Section 3 - Comparative effects of enteral diets in rats.
Chapter 10

1.3 AIMS

1.1 INTRODUCTION

Historical Profile and definition

Crohn's disease has been aptly described as the most malignant of non-malignant diseases, malignant because of its tendency to recur after surgical resection of the bowel, but non-malignant because it seldom kills, despite the long-term misery it may cause some of its sufferers. It is to those severe sufferers, relatively few in number, but who require much medical and hospital treatment, that this thesis is dedicated.

In 1913, T.K, Dalziel, a Glasgow surgeon, described in nine patients on whom he had operated, a non-tuberculous inflammatory disease which affected the jejunum, ileum or colon and in which two fatal cases extensive small and large bowel involement was demonstrated.

Moschowitz, ten years later (1923) gave a similar description but it is to the well publicised paper of Burrill B. Crohn that most people turn for his description of 14 cases of "Terminal Ileitis", a non-tuberculous granulomatous disease which was confined in his cases to the terminal ileum. It is of interest that he changed the title of the paper to "Regional Ileitis" before publication (Crohn 1932), perhaps in recognition of earlier reports. Further descriptions (Harris 1933; Colp 1934) confirmed Dalziel's early assertion that the bowel could be widely involved, but it was not until much later that disease confined to the colon was properly recognised (Lockhart-Mummery 1960). Indeed, any part of the bowel can be involved and although the small and large bowel (including the anus) are the usual sites, the mouth (Issa 1971), oesophagus (Gelfand 1968) and stomach (Johnson 1966) can occasionally be affected. Perhaps the disease should have been named after Dalziel but Crohn's name has stuck and it is this eponym which I will use in this thesis.

A working definition is helpful and Kirsner's (1976) is adequate:

> *A transmural inflammation involving all coats of the diseased segment, commonly attacking the small bowel and/or colon but in rare instances involving any part of the alimentary tube.*

To this definition must be added the less common extraintestinal manifestations which will be briefly described later.

Aetiology

The search for the cause of Crohn's disease has been wide ranging and the main areas of research will be mentioned. There appear to be five main aspects: Epidemiology: The incidence and prevalence of the disease vary enormously throughout the world, being highest in Northern Europe and North America and relatively rare in developing countries (Mayberry 1984). There has been an apparent rise in incidence. for example a 26 fold rise in incidence in Cardiff (0.18 cases in 1934 to 4.8 cases per 100,000 population in 1977) (Mayberry 1979a). Such changes may help the search for a cause for Crohn's disease and have prompted investigations of dietary factors which will be described later.

Genetic factors: there is undoubtedly an increased prevalence of Crohn's disease amongst relatives of index cases, being 30 times more common in siblings and 13 times more common in all first degree relatives (Mayberry 1980). The association with ankylosing spondylitis (McBride 1963) suggests a genetic predisposition but no specific genetic marker has yet been identified. A genetic predisposition operating with other factors seems likely. Altered Immunity: The investigation of immunity in the pathogenesis as well as aetiology of Crohn's disease followed naturally from the histological appearance of the diseased bowel and its close similarity to sarcoidosis and other chronic Inflammatory conditions. The widespread manifestations which sometimes occur also suggest a systemic immune response. These immunological factors recently reviewed by Rhodes (1981) will not be described here. The central question remains: are the observed patholo gical lesions responsible for the disease or a response (perhaps normal) to an external antigen such as an infectious agent or a component of the diet? Infectious Agents: Crohn's disease had its origins in the earliest years of the 20th century when tuberculosis of the bowel was fairly common. Both Dalziel (1913) and Crohn (1932) took great care to exclude tuberculosis as a cause of the lesions they found in the bowel. Attempts to demonstrate a transmissable agent which causes Crohn's disease have failed (Cave 1976, Thayer 1979). There is no evidence of geographic clustering of cases (Miller 1975) or that medical

personnel in frequent contact with Crohn's disease sufferers have a higher prevalence of the disease than the general population (Goodman 1979). Evidence for bacteria or viruses as the cause of Crohn's disease is similarly lacking (Standford 1980; Parent 1978; Swarbrick 1979; Thayer 1969; Phillpotts 1980; Wharwell 1977). Diet: That a dietary antigen might provoke a granulomatous response has attracted much research. A possible association between milk exclusion and remission of Crohn's disease (Warthin 1969) was not, unfortunately, confirmed. Cornflakes were eaten more by Crohn's patients than controls in a study by James (1977), but this was not confirmed in later studies from other centres (Rawcliffe 1978; Archer 1978; Mayberry 1978). Numerous reports of excess sugar intake in patients with Crohn's disease reviewed by Mayberry and Rhodes (1984) highlight the unreliability of assesing pre-morbid food intake but there is a suggestion by Heaton (1979) that excluding refined carbohydrates may be beneficial in Crohn's disease. Dietary fibre consumption and its possible relationship with Crohn's disease has produced such conflicting results that an aetiological link seems unlikely (Kasper 1979; Mayberry 1981; Thornton 1979).

Although the exact aetiology of Crohn's disease remains obscure it seems likely that there is an external antigen or antigens producing an abnormal immune response, principally in the gut in a genetically predisposed individual. This notion is the basis for treating Crohn's disease with diets which exclude dietary antigens such as the elemental or defined formula diets or with intravenous nutrition coupled with exclusion of oral food for which the term 'bowel rest' has been adopted. This form of treatment will be explored in Section 2 of this thesis.

Clinical Features

Typically, a man or woman presents in early to mid-life (20 to 40) with diarrhoea sometimes accompanied by fresh rectal bleeding or by the passage of mucus or pus. Abdominal pain usually of a colicky and intermittent nature is often present. Recent or gradual weight loss may be evident. Occasionally the Crohn's patient presents to the surgeon with a complication of the disease such as intestinal

obstruction, an enterocutaneous fistula or anal disease. The main clinical features from three large series of over 1400 patients are presented in table 1.1. The commonest pattern is small and large bowel involvement. Characteristically spontaneous exacerbations and remissions occur. Active disease is suggested by frequent liquid stools, abdominal pain, general malaise, extraintestinal manifestions, fistulae, the requirement of anti-diarrhoeal drugs, the presence of an abdominal mass, anaemia and weight loss, all of which were used to derive the Crohn's Disease Activity Index (CDAI) in an attempt to assess the clinical efficacy of various drug regimes (Best 1976). I will use a simplified CDAI which correlates well with Best's index (Harvey 1980). This is reproduced in table 1.2A.

Diagnosis of Crohn's disease is suggested by the clinical features described above and visual appearances at surgery or endoscopically but is based more firmly on characteristic radiological, histological and laboratory findings which will not be reviewed in detail. The criteria for diagnosis used in this thesis are summarised in Table 1.2 B.

Death as a result of Crohn's disease or its complications is relatively rare. Mortality rate is about twice the expected figure for the general population (Mayberry 1980). Bowel cancer of which Crohn's sufferers have an increased risk (Weedon 1973) does not seem to contribute greatly to the mortality rate (Prior 1981). Morbidity (ill-health) is in contrast common and the CDAI is probably the best indicator we have, containing as it does, subjective factors including "well-being". In the national co-operative Crohn's disease study (NCCDS) in the USA, untreated patients with active disease (CDAI > 150) comprised about 60% of the total group. The prevalence of active disease in my patients is considered further in Chapter 3.

Treatment

There is no cure for Crohn's disease and treatment is aimed at alleviating symptoms or dealing with complications. The frustration of physicians and surgeons (and no doubt the sufferers) in the failure to find a consistently successful therapy is well expressed by a Leader writer in the Lancet (Leader 1983):

TABLE 1.1

CLINICAL FEATURES OF CROHN'S DISEASE

	Mekhjian 1979 n = 569	Farmer 1975 n = 615	Truelove 1976 n = 221	
Mean age at presentation (years)	31.5	32	n/s*	
Sex distribution: male	52	54	46	
female	48	46	54	
MAJOR SYMPTOMS				
a) Diarrhoea	92	virtually all patients	n/s	
b) Abdominal pain	95	61	38	
c) Lower GI bleeding	41	26	n/s	
d) Weight loss	85	n/s	n/s	
MAJOR COMPLICATIONS				
a) Intestinal obstruction or acute abdomen	n/s	32	22	
b) Anorectal fissures or fistulae	36	19	10	
c) Abscess/fistula (abdominal)	21	22	35	
EXTRAINTESTINAL MANIFESTATIONS including arthritis, spondylitis, skin, eye and liver disease	32	35	8	
BOWEL INVOLVEMENT				Average
Small bowel only	31	29	30	30
Large bowel only	11	30	26	22
Small and large bowel	58	41	44	48

Notes:
* n/s = not stated
Percentages quoted unless otherwise stated
Total number of patients: 1405

TABLE 1.2

A. SIMPLIFIED CROHN'S DISEASE ACTIVITY INDEX (Harvey 1980)

a) General well-being (0-4)
0 = very well. 1 = slightly below par.) previous
2 = poor. 3 = very poor. 4 = terrible) day

b) Abdominal pain (0-3)
0 = none. 1 = mild. 2 = moderate.) previous
3 = severe) day

c) Number of liquid stools per day

d) Abdominal mass (0-3)
0 = none. 1 = dubious 2 = definite
3 = definite and tender

e) Complications Score: 1 each
Arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma, anal fissure, new fistula, abscess.

B. CRITERIA FOR DIAGNOSIS OF CROHN'S DISEASE

Small intestinal disease (Winship 1979)

a) Chronic inflammatory disease of the small intestine with either typical radiological appearances or histological confirmation on surgical full thickness biopsy.
b) Typical visual appearance of small bowel at surgery confirmed by presence of non-caseating granuloma in mesenteric lymph node.

Colonic disease (adapted from Lennard-Jones 1976)

Either Typical granulomata and one of the following
Or No granulomata (but possibly other suggestive histological features) and 3 of the following:

1) Skip lesions (radiologically, operatively or endoscopically)
2) Deep fissuring (radiologically or on operative specimen)
3) Enterocutaneous fistula
4) Severe anal disease
5) Ileal disease extending more than 18 inches in association with colonic disease.

"There are enthusiasts and nihilists in both medical and surgical camps and publications abound to support almost any viewpoint"

The disappointing results of various studies of therapy are in part due to the formidable difficulties of conducting controlled trials in Crohn's disease.

Why should this be?

1. The unpredictable natural course of the disease characterised by spontaneous exacerbations and remissions, makes assessment of therapy hard and necessitates the inclusion of large numbers of patients over long periods of time.
2. Placebo controlled studies which are double blind are hard to achieve and may be considered unethical.
3. Stratification of patients is desirable at entry with respect for example to extent of disease, prior surgical or drug treatment to provide comparable treatment and placebo groups

For these reasons, multicentre trials were undertaken to assess promising drug treatments. The effect of treatment in these studies was based on the Activity Index of Best (1976). The results of these and other controlled studies are summarised in Table 1.3. Large groups of patients were necessary to demonstrate significant benefit and there is little guidance for the clinician as to the choice of patient most likely to respond. Anti-diarrhoeal drugs such as loperamide and codeine phosphate may be useful and cholestyramine may be helpful in patients with bile-acid induced diarrhoea.

Surgical resection of diseased bowel does not effect a cure. There is recurrence or relapse of disease requiring further surgery at the rate of 5-15% of patients per year (De Dombal 1971; Greenstein 1975; Lee 1980). Nevertheless, most patients will have at least one operation (Cooke 1980) and many of the indications for surgery are beyond debate: bowel perforation, acute intestinal obstruction, toxic megacolon, severe haemorrhage and abscess. The controversy surrounds the less acute complications such as failure of medical therapy to relieve symptoms, growth retardation, recurrent sub-acute obstruction, poor quality of life, chronic protein loss and fistulae, all of which have been suggested as indications for operation (Kyle 1982). Of interest is a form of surgical 'bowel rest' in which

TABLE 1.3

DRUG TREATMENT OF CROHN'S DISEASE
CONTROLLED STUDIES

1. ACTIVE DISEASE (All Sites)		REFERENCES
a) prednisolone (0.25 - 0.75mg/kg)	better than placebo	1
b) azathiaprine (2-3mg/kg)	ineffective	1,2,3.
c) metronidazole	effective early (< 2months)	4
d) sulphasalazine	better than placebo (except ileal disease - see below)	1,5
2. ACTIVE DISEASE (By Site)		
Ileal disease		
sulphasalazine	no better than placebo	1,6,13
metronidazole	ineffective	4
prednisolone	better than placebo	1
Ileo-colonic disease		
sulphasalazine	better than placebo	1,5
prednisolone	better than placebo	1,13
Colonic disease		
sulphasalazine	better than placebo	1,5
prednisolone	no better than placebo (small numbers)	1
sulphasalazine + prednisolone	better than placebo	13
3. AFTER RESECTION/INACTIVE DISEASE/MAINTENANCE TREATMENT (All Sites)		
sulphasalazine	no reduction in relapse rate after surgery	1,7,8,9
prednisolone (7.5-15mg/d)	no benefit	1,7,10
azathiaprine (2mg/kg)	effective in maintaining remission	11,12

REFERENCES

1. Summers (1979)
2. Rhodes (1971)
3. Klein (1974)
4. Ursing (1982)
5. Anthonisen (1974)
6. Bergman (1976)
7. Multicentre trial (1977)
8. Wenckert (1978)
9. Smith RC (1978)
10. Willoughby (1971)
11. Rosenberg (1975)
12. O'Donaghue (1978)
13. Malchow (1984)

surgical bypass of a diseased segement may result in an improvement of symptoms for a time (McILrath 1971). Nevertheless most surgeons now adopt a conservative approach. There have been promising results of medical management of recurrent small bowel obstruction (Yaffe 1983). Stricturoplasty, resection of small segments of diseased bowel and short segment bypass are promising forms of conservative surgery for multiple strictures especially when previous surgery makes bowel conservation important (Lee 1982; Hawker 1983). While some patients remain well and only one in four require a second operation within ten years of their first ileal resection (Kyle 1982), a few become the victims of multiple operations and eventually are left with insufficient bowel to maintain a normal nutritional state. This is the condition of short bowel syndrome or intestinal failure in which poor absorption and excess losses result in chronic malnutrition and in which artificial feeding may have a place. This condition is one of the circumstances in which nutritional therapy will be evaluated in this thesis.

1.2 JUSTIFICATION

SECTION 1. NUTRITIONAL DEPLETION AND ITS CLINICAL RELEVANCE IN CROHN'S DISEASE Chapters 3 - 7

Causes of malnutrition in Crohn's disease

1. Low dietary Intake
   a) symptoms such as vomiting, abdominal pain and distension (obstruction) or diarrhoea precipitated by eating
   b) poor appetite due to general malaise
2. Impaired Absorption of Nutrients
   Diseased bowel, previous resections, bacterial overgrowth (blind loops) or fistulae (food bypasses functioning bowel).
3. Exudation From Diseased Bowel
   Losses from ulcerated and inflamed bowel (blood and protein in exudate and desquamated cells). Fluid, electrolyte and other losses.

Dietary intake is often impaired in acutely ill patients but their

recall of premorbid food intake is often unreliable. Furthermore a means of assessing the intake of many of the nutrients examined in Section 1 was not available. Dietary intake therefore has not been systematically examined. Impaired absorption as a mechanism of nutritional depletion will be examined in relation to the individual nutrients investigated.

Consequences of nutritional depletion in Crohn's disease

The importance of nutritional depletion in the general clinical picture in Crohn's disease is recognised in the make-up of the Crohn's Disease Activity Index (Best 1976) in which weight loss is taken as a major factor in active disease. What then are the clinical consequences of impaired bowel function? There is evidence that depletion of certain nutrients has specific effects in bowel disease. The most familiar are iron, folic acid and vitamin B_{12} depletion which cause anaemia. Folic acid and zinc depletion can result in depressed cell-mediated immunity (Golden 1978; Gross 1975) and might result in increased susceptibility to infections. Protein-energy malnutrition (PEM) can result from gut disease including Crohn's disease. It is manifest in its most severe form as body weight loss perhaps >20% of standard (for age and sex) and may be associated with oedema, weakness, apathy and immobility (Davidson et al 1979). Some new clinical consequences will be reported in this thesis.

Quantifying nutritional depletion

Some studies which show evidence of impaired nutrient absorption and attempts to quantify various nutritional abnormalities in Crohn's disease are summarised in Table 1.4. Investigators have searched for what Beeken (1975) described as "remediable defects". The studies in the first section of this thesis are confined to quantifying some of the nutritional 'defects' of Crohn's disease and make an attempt to place them in their clinical context including an examination of the mechanisms by which they occurred. Some attempt will also be made to determine how 'remediable' they were by assessing therapy.

TABLE 1.4

NUTRITIONAL DEPLETION IN CROHN'S DISEASE

A. EVIDENCE FOR MALABSORPTION IN CROHN'S DISEASE.	REFERENCES
Vitamin B_{12} malabsorption	1-4
Bile salt malabsorption	5,6
Fat malabsorption	3-7
B. NUTRITIONAL DEPLETION IN CROHN'S DISEASE	
Weight loss	8,14,15,16
Anaemia	22,23,24
Iron depletion	1,8
Folate/B_{12} depletion	1,8-10
Impaired immune function	11
Electrolyte depletion (K^+, Na^+, Ca^{++}, Mg^{++})	1,8,18,25
Hypoproteinaemia/excess protein loss	1,4,8,12,20,21,26
Vitamin deficiency	17,18,19

REFERENCES

1. Booth (1964)
2. Hertzberg (1969)
3. Smith AN (1972)
4. Gerson (1973)
5. Meihoff (1968)
6. Hardison (1967)
7. Dotevall (1968)
8. Beeken (1975)
9. Hoffbrand (1968)
10. Schofield (1965)
11. Harries (1984)
12. Steinfeld (1960)
13. Mekhjian (1979)
14. Harries (1983)
15. Lanfranchi (1984)
16. Dyer (1973)
17. Harries (1983)
18. Krawitt (1976)
19. Driscoll (1977)
20. Beeken (1972)
21. Cobb TC (1969)
22. Van Patter (1954)
23. Krause (1971)
24. Dyer (1972)
25. Lehr (1982)
26. Jeejeebhoy (1981)

Chapter 3 reports a broad survey of body weight and various nutrients in 65 patients with Crohn's disease to determine the prevalence of depletion, usually in blood levels in an unselected group of patients with Crohn's disease at their first point of contact with the author. Abnormalities are related to the site of disease, extent of body weight loss and activity of Crohn's disease. Some of the abnormalities found were further investigated to assess their clinical significance in the studies reported in Chapters 4 to 7.

Justification for Chapter 4

Magnesium (Mg) is an essential mineral, the fourth most plentiful cation in the body, with many biological functions, (Wacker 1968) and especially as a cofactor in enzyme reactions involving adenosine triphosphate (ATP). The clinical importance of Mg deficiency relates not only to skeletal muscle function but also to heart muscle function. (Iseri 1975). A tendancy to digitalis toxicity may exist in patients rendered Mg deficient by long-term diuretic therapy (Lim 1972). Low Mg content of soft water has been suggested as a possible explanation for increased mortality following myocardial infarction (Chipperfield 1973). Mg is present in most foodstuffs (McCance 1960) and Mg depletion due to poor dietary intake alone is therefore unusual. In normal adults, about one-third of ingested Mg is absorbed almost entirely from the small bowel but the proportion of dietary Mg absorbed may vary according to the dietary Mg content (Graham 1960) and dietary factors such as phytate content may inhibit Mg absorption (Davies 1979). Less may be absorbed in malabsorption states or after extensive bowel resection. Booth and his colleagues noted subnormal serum Mg levels in 15/42 patients with various types of small bowel malabsorption (Booth 1963) and hypomagnesaemia was noted by Beeken in 9/63 patients with Crohn's disease (Beeken 1975). In Chapter 3, a prevalence of hypomagnesaemia of 11% is reported. Several patients had very low levels and symptoms (tetany) also occurred. To examine these findings further and specifically to assess the clinical relevance of Mg depletion and its treatment in Crohn's disease the study reported in Chapter 4 was done.

Justification for Chapter 5

In Chapter 3, abnormalities of total serum calcium were the second commonest single abnormality (35%). Abnormal total alkaline phosphatase was also common and like calcium not associated with any disease pattern. Studies of osteomalacia in Crohn's disease have been confined to patients with small bowel resections, (Compston 1978; Driscoll 1982), and it would seem justified in the light of my findings to extend investigation to include all degrees of severity and extent of disease so that the clinical context in which osteomalacia is likely to occur is characterised and an early diagnosis made. To achieve this aim bone biopsies were taken from patients with varying extent and severity of disease and the histological findings were related to clinical and biochemical measurements. It has been suggested that osteomalacia can be diagnosed in every case only by means of bone histology (Compston 1978) and that mild cases are often associated with normal clinical and biochemical features. Bone biopsy while relatively easy to perform, cannot be regarded as a non-invasive or screening test. Our second aim therefore has been to attempt using non-invasive methods of investigation to identify Crohn's patients in whom treatment for presumed osteomalacia would be justified without the need for bone biopsy.

Justification for Chapter 6

Among various reports of vitamin A deficiency in gastrointestinal and liver diseases, (Russell RM 1973 and 1978; Vahlquist 1978; Carney 1980), few patients with Crohn's disease have been studied. Yet protein depletion and fat malabsorption to which Crohn's patients are prone may result in Vitamin A deficiency. In Chapter 3, I found that 23% of my patients had depletion of plasma retinol (Vitamin A). Shortly after that survey was done, two patients with extensive small bowel disease complained of night blindness and were found to have a severe defect of dark adaptation, one of the clinical manifestations of severe Vitamin A deficiency. These findings prompted a more detailed clinical and biochemical evaluation of 52 of these patients and a close investigation of in-patients who were found to be Vitamin

A depleted to determine the clinical consequences of Vitamin A depletion and to measure the effects of therapy in selected patients.

Justification for Chapter 7

Like Vitamins A and D, Vitamin E (tocopherol) is a fat-soluble vitamin whose main function appears to be in stabilising cellular and sub-cellular membranes including that of the red blood cell (RBC) against various stresses imposed on them including those of oxidation. The causes of Vitamin E deficiency include any cause of severe maldigestion or malabsorption of fat, as well as abnormalities of lipoprotein metabolism. Most reports have been in children with congenital abnormalities such as cystic fibrosis, coeliac disease, severe liver disease and biliary atresia. In its severest form it occurs in the rare condition of abetaliproteinaemia in which the consequences of severe Vitamin E deficiency have been most vividly described: severe and relentless spinocerebellar degeneration (Müller 1983). In adults any adverse clinical effect of Vitamin E deficiency is often difficult to detect. Severe neurological disease is extremely rare and the the subject of occasional case reports including one in a patient who developed severe spinocerebellar degeneration more than 30 years after a gastrectomy associated with subsequent blind loop syndrome (Brin 1985). Abnormalities of red cell function are associated with reduced plasma levels of Vitamin E. Examples include reduced red-cell survival improved slightly by administration of Vitamin E, (Leonard 1971), and increased in vitro haemolysis of red cells in the presence of hydrogen peroxide (often used as indirect evidence of Vitamin E deficiency). However there has been no evidence of significant in vivo haemolysis. Thus in the study reported in Chapter 7, I have confined investigations to the search for evidence of haematological abnormalities. Reports of Vitamin E deficiency in adults with bowel disease have been infrequent and in all cases consisted of subjects with a number of different diseases. These are described in the discussion (Chapter 11). Yet the high prevalence (23%) of Vitamin E depletion in the general survey (Chapter 3) and severe fat malabsorption in some patients with Crohn's disease gives ample justification for a search

for the clinical relevance of abnormalities of Vitamin E metabolism. The study reported in Chapter 7 is the first study of the haematological consequences of Vitamin E depletion in Crohn's disease. The overall aim was to determine whether there was any justification in providing Vitamin E supplements for patients with Crohn's disease who had abnormalities of Vitamin E metabolism and steatorrhoea.

SECTION 2. NUTRITIONAL THERAPY IN CROHN'S DISEASE Chapters 8,9

Justification for Chapter 8

It seems rational to consider providing nutritional therapy for three reasons:

1. because of the deleterious effects of nutritional depletion to consider providing extra food to correct the depletion and reverse weight loss.
2. the possible beneficial effect of excluding dietary antigens such as food proteins which may have a role in the aetiology or in producing symptoms (Rhodes 1986; Mayberry 1979b).
3. For the provision of what Rosenberg called 'bowel rest' by excluding food by mouth and thus:
   "minimizing trauma and irritation of inflamed denuded bowel and diverting the function of the damaged mucosa from a digestive and absorptive one to a healing and regenerative process." (Rosenberg 1979). Intravenous nutrition can be combined with total 'bowel rest', while the low residue composition of enteral feeds provides a partial 'bowel rest'. Rosenberg's enthusiasm however is not shared by all and controlled studies in Crohn's disease (Lochs 1983; McIntyre 1986) and in ulcerative colitis (Dickinson 1980; McIntyre 1986) have shown no advantage in depriving patients of oral food during intravenous nutrition.

Nutritional therapy is a form of feeding which is artificial. The two forms of nutritional therapy to be considered in this thesis are Enteral Nutrition (EN) and Intravenous Nutrition (IVN)- also known as Parenteral Nutrition. It is artificial both in its composition and the means by which it is delivered to the patient. Nevertheless it offers a number of attractive possibilities to aid the Crohn's

disease sufferer (Table 1.5). The literature cited will be subjected to critical analysis and the merits of EN and IVN in Crohn's disease will be discussed in the Chapter 11. For reasons described in Chapter 11 my approach to a detailed study of nutritional therapy in Crohn's disease is an uncontrolled audit of the outcome of pre-determined clinical aims concentrating on the main complications being treated. This approach is aimed to help the practicing clinician faced with a sick underweight patient suffering from an exacerbation and complications of the disease and in whom other treatment options may have failed.

Justification for Chapter 9

The utilisation of high energy phosphate groups is crucial during protein synthesis. The essential role of magnesium (Mg) in the functioning of Adenosine Triphosphate (ATP) described earlier emphasises the importance of Mg during periods of anabolism expected with IVN. Mg depletion is common in severe Crohn's disease as I will demonstrate (Chapter 4), and might be exacerbated during successful IVN when there is an increased requirement for Mg in the metabolism of high energy phosphates involved in protein synthesis. However recommendations for intravenous provision of Mg during IVN have varied considerably from 2 up to 21 mmol/day. (Dudrick 1969; Gruppo 1970; Dudrick 1971; Meng 1971; Jeejeebhoy 1976; Driscoll 1978). By examining serum and urine Mg measurements throughout IVN in our Crohn's patients and relating them to the amount of intravenous Mg given, I have been able to offer recommendations for Mg provision during IVN in Crohn's disease.

Zinc (Zn) is an essential element in man and is required for the function of over 70 metallo-enzymes (Riordan 1976). Clinical manifestations of Zn deficiency include acrodermatitis, hair loss, hypogonadism, growth retardation, delayed wound healing, and impaired immune competence (Ecker 1978; Halstead 1972; Wacker 1976; Golden 1978). Zn deficiency has been described in Crohn's disease (Solomons 1977; McClain 1980a), the causes including low intake, poor absorption (Sturniolo 1980) and excess faecal losses (Wolman 1979).

TABLE 1.5

NUTRITIONAL THERAPY IN CROHN'S DISEASE
SUGGESTED INDICATIONS

INDICATIONS FOR NUTRITIONAL THERAPY	ENTERAL NUTRITION	INTRAVENOUS NUTRITION
Failure of Medical Management		15
Restoration of body weight	1,4,7,25	13-15
Growth Retardation	2	12,13
Complications:		
diarrhoea	-	15,18
perianal disease	3,8	-
intestinal obstruction	1,3	15,19
short bowel syndrome	1,	17,19,21-24
fistulae	1,4,10	13,16,18,19,21
cholerrheic diarrhoea	5	-
Reduce: disease activity	2,4,10,25	13,14,18
protein loss	6,9	-
Before or After Surgery	1,4,7	15,19
'Bowel Rest'	11	14,15,18,20

REFERENCES

1. Voitk (1973)
2. Ó'Moráin (1979)
3. Russell (1979)
4. Rocchio (1974)
5. Nelson (1977)
6. Logan (1981)
7. Goode (1976)
8. Calam (1980)
9. Axelsson (1977a)
10. Axelsson (1977b)
11. Rosenberg (1979)
12. Layden (1976)
13. Strobel (1970)
14. Lochs (1983)
15. Reilly (1976)
16. Meng (1971)
17. Jeejeebhoy (1983)
18. Greenberg (1976)
19. Eisenberg (1974)
20. Dickinson (1980)
21. Rault (1977)
22. Ladefoged (1978)
23. Broviac (1974)
24. Jeejeebhoy (1976)
25. Ó'Moráin (1984)

IVN can be complicated by the development of Zn deficiency (McClain 1980b; Arawaka 1976; Solomons 1976; Greene 1975). Patients with extensive Crohn's disease may need IVN and may become Zn deficient when they become anabolic. (McClain 1980; Kay 1976). Zn is thus an important component of the intravenous diet but daily requirements are not certain, as they will vary according to losses principally in faeces and urine, and also in fistula fluid, wound exudates, shed skin and hair.

Determination of Zn in serum and urine is readily available as part of the biochemical monitoring of patients receiving IVN. As we have used a wide range of intravenous Zn supplements in our patients, we have sought to relate the results of such Zn measurements to the quantity of Zn given, to clinical progress, and nutritional indices. Serum and urine Zn values are considered in relation to serum protein changes, body weight, skinfold thickness and muscle circumference, and nitrogen balance.

SECTION 3 COMPARATIVE EFFECTS OF ENTERAL DIETS IN INTACT RATS.

Justification for Chapter 10

The formulation of the earlier defined formula diets (DFD) or elemental diets such as Vivonex (Eaton Laboratories) was designed to present the bowel with a complete repertoire of foods in their simplest forms in order that digestive requirements would be minimised and that absorption would be readily achieved in the upper small bowel. Fibre content was negligible and these diets seemed ideal for use in patients with Crohn's disease in the circumstances indicated in Table 1.5. They are however, unpalatable, expensive and may cause diarrhoea. The need to assess other liquid diets in alimentary failure has been recognised (Woolfson 1976). These polymeric diets (PD) differ from DFDs in being cheaper and more palatable mainly due to the use of whole or hydrolysed natural protein instead of peptides or aminoacids as the nitrogen source. They also differ in other respects as will be discussed in Chapter 10. Two qualities of these diets are of special interest in relation to their use in Crohn's disease:

1. Nutritional efficiency

Experiments in animals and humans have shown that whole protein or protein hydrolysates are as good or better than the equivalent aminoacid mixtures in achieving nitrogen retention (Anderson 1969; Rose 1954; Metta 1960; Watts 1964). Isocaloric feeding of rats over a two week period demonstrated greater weight gain with the whole protein liquid diet 'Ensure' than with the DFDs 'Vivonex' or 'Flexical' (Young 1980). The DFD Vivonex HN for example caused much greater nitrogen wastage than a similar solid protein food in a carefully controlled balance study (Smith JL 1982). The ratio of energy to nitrogen provision in the feed may also affect nitrogen retention (Anderson 1969).

2. Faecal residue

DFDs reduce faecal weight (Winitz 1970; Bounous 1974) and stool frequency (Bounous 1974) in humans but more information is required about the relative merits of the commercially available whole protein hydrolysed protein liquid diets and the older extensively studied DFDs. Two properties of these diets might be examined in relation to their use in Crohn's disease: the efficiency of their absorption and effects on growth and the relative effects on faecal residue. The aim of controlled feeding experiments in intact rats was therefore to compare five commercially available enteral feeds with respect to nutritional efficiency and faecal residue. It was hoped to indicate which commercial liquid feeds, efficiently utilised and with low faecal residue in the intact animal, might be useful in under-nourished patients with impaired bowel function in whom efficient nitrogen utilisation and low faecal residue were considered desirable.

1.3 AIMS

The unifying theme of this thesis is nutrition in Crohn's disease: to what extent depletion of some nutrients contributes to morbidity and whether attempting to correct nutritional depletion is helpful.

Section 1. Nutritional depletion and its clinical significance

The general aim of this section was to investigate the prevalence of

nutritional depletion in a group of 65 patients with Crohn's disease. For this purpose a number of clinical, haematological and biochemical measurements were made to discover whether depletion is related to simple clinical features such as site, duration and activity of disease so that future patients at risk of depletion might easily be identified. In the general survey reported in Chapter 3, no attempt has been made to assess the clinical significance of abnormalities found. The remaining studies (Chapters 4-7) search for new information about the clinical significance of some commonly found 'depletions', those of magnesium, Vitamin D and calcium, Vitamin A, and Vitamin E. Detailed investigations were performed on selected patients.

Section 2. *Nutritional therapy in Crohn's disease*

For reasons mentioned earlier, controlled experiments of nutritional therapy in Crohn's disease were not done. Instead I have subjected the patients chosen for nutritional therapy to a stringent clinical audit in which the clinical aims of nutritional therapy were defined before starting treatment and their success or failure assessed after treatment. I hoped to provide a clearer understanding of the clinical indications for nutritional therapy, the relative merits of enteral and intravenous nutrition and to determine the longer term benefits, if any, of nutritional therapy in Crohn's disease. Doubts about the appropriate provision of magnesium and zinc during intravenous nutrition in Crohn's disease prompted a biochemical study to determine safe levels of provision of these essential nutrients.

Section 3. Comparative effects of enteral diets in rats

The aim was to indicate in preliminary animal experiments which commercial liquid feeds, efficiently utilised and with low faecal residue in the intact animal, are most likely to be useful in under-nourished patients with complications of Crohn's disease.

Section 4 *Discussion and Summary*

The results of each chapter are discussed followed by an assessment

of the contribution which this thesis makes to the understanding of nutrition in Crohn's disease. Lastly there is a brief summary.

CHAPTER 2

METHODS

2.1 PATIENTS STUDIED

2.2 CLINICAL MEASUREMENTS

2.3 LABORATORY MEASUREMENTS

2.4 SPECIAL TECHNIQUES

2.5 REFERENCE RANGES AND CONTROL GROUPS

2.6 STATISTICAL METHODS

This chapter describes the methods used in the various clinical studies. The methods selected for each chapter are then briefly listed within the chapter. For the animal experiments, it seemed more coherent to describe the detailed methods within the chapter 10).

2.1 PATIENTS STUDIED

The clinical studies in this thesis (chapters 3-9) were carried out on 65 patients with Crohn's disease. The diagnosis was made using the criteria outlined in Chapter 1 and detailed below .

Patients excluded

90 patients were considered for inclusion in the studies. Of these 90, 65 were selected. Reasons for exclusion were: inadequate information about extent of disease or previous bowel resections (15), clinical or histological doubt about diagnosis (usually in patients with large bowel disease in which ulcerative colitis was an alternative diagnosis) (8), or unwillingness to take part in the studies (2).

How the diagnosis was made

In 36 patients (55%) the diagnosis was based upon the visual and histological appearances of bowel resected at laparotomy. In a further 14 (22%), with disease confined to the distal ileum or proximal colon, diagnosis was based solely on radiological appearances on large or small bowel barium enema examinations. In the remaining 15 (23%), diagnosis was based upon appearances at colonoscopy or sigmoidoscopy and on histological studies of biopsy specimens.

Sites of disease

Patients were categorised according to the site of disease in a manner used in large previous epidemiological and therapeutic studies in Crohn's disease (Truelove 1976; Mekhjian 1979; Fielding 1972; Blichfeldt 1978)

No patients with disease of the stomach, oesophagus or mouth were included. Previous bowel resections in which there was histological

evidence of Crohn's disease were taken as evidence of disease at the site resected.

For descriptive purposes in some of the studies patients were also described by the extent of small bowel involvement (or resections):

TI - Disease or resections confined to the distal 60 cm of terminal ileum

W - more widespread small bowel involvement

These divisions and their definitions were as follows:

1. SMALL BOWEL (SB) (including Caecum)
   a) Site of disease confined to the distal 60cm of ileum (SB-TI)
   b) More widespread disease; site of disease or resections included small bowel more proximal than the distal 60cm of ileum (SB-W)
2. LARGE BOWEL (LB)
3. SMALL AND LARGE BOWEL (SB+LB)
   a) Small bowel component confined to distal 60cm of ileum. (SB-TI+LB)
   b) Widespread disease: site of disease included small bowel more proximal than distal 60cm of ileum. (SB-W+LB)

Clinical details of the 65 included patients

Details of site, sex, age, duration of disease and the number of patients with previous surgical operations are summarised in Table 2.1 from individual patient details in Appendix 2.1. Table 2.1 also shows the age distribution of patients confirming the conventional notion that it is a disease most prevalent in younger adults (about half in their 20s or 30s), and predominantly in females.

How typical is this series of patients?

The relationship between the distribution of patients in my series and in the 3 large series shown in Table 1.1 is illustrated in Figure 2.1 which shows that my series contained a slight excess of patients with SB disease and with LB disease. All 65 patients took part in the general survey (Chapter 3). The selection of patients for more detailed studies (Chapters 4-9) is set out in Table 2.1 from

TABLE 2.1

CLINICAL DETAILS OF 65 PATIENTS STUDIED IN CHAPTERS 3 TO 9

SITE OF DISEASE	NUMBER (%)	SEX Male	Female	AGE(yrs) Mean (range)	DURATION OF SYMPTOMS(yrs) Mean(range)	RESECTIONS No(%) of patients
Small Bowel	24 (37)	4	20	38 (16-64)	7.2 (0.5-22)	16 (67)
Large bowel	17 (26)	6	11	43 (20-76)	4.5 (0.25-18)	5 (29)
Small and large bowel	24 (37)	10	14	38 (16-73)	9.3 (2-27)	15 (63)
TOTAL	65	20	45	39 (16-76)	7.3 (0.25-27)	36 (55)

Male/female ratio: 1 to 2.25

AGE DISTRIBUTION (Years) - (at start of study)

	≤ 20	21 - 30	31 - 40	41 - 50	51 - 60	61 - 70	> 70
Number	6	18	15	9	6	6	4
Percent	9	28	23	14	9	9	6

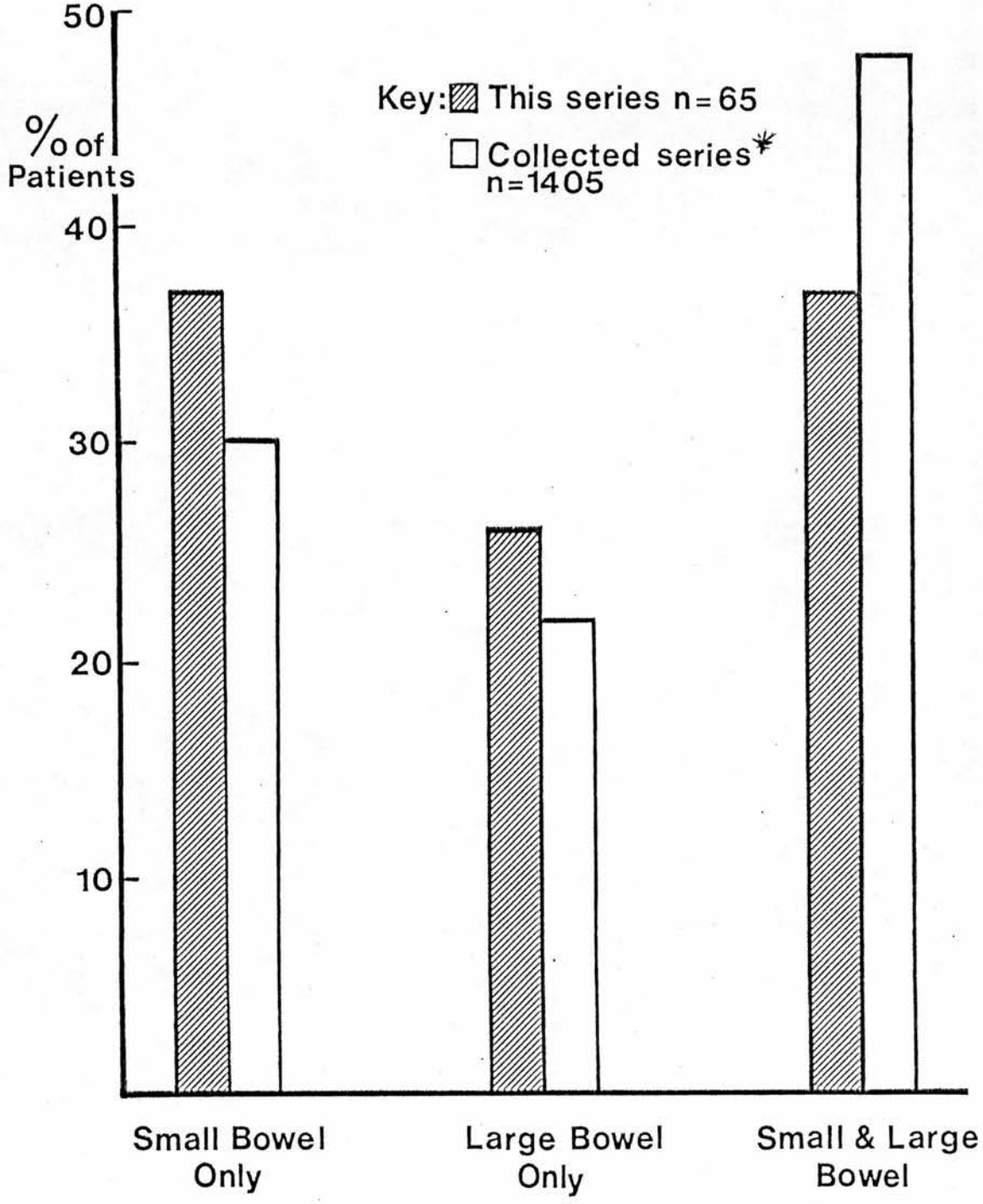
SELECTION FOR CLINICAL STUDIES BY SITE OF DISEASE

CHAPTER ---	3 Survey No	(%)	4 Mg No	(%)	5 OM No	(%)	6 Vit A No	(%)	7 Vit E No	(%)	8 EN/IVN No	(%)	9 Mg+Zn No	(%)
Total	65		17		24		52		25		19		10(IVN)	
SB	24	(37)	3	(18)	9	(38)	20	(38)	9	(36)	3	(16)	1	(10)
LB	17	(26)	2	(12)	4	(17)	12	(23)	3	(12)	6	(32)	1	(10)
SB+LB	24	(37)	12	(71)	11	(46)	20	(38)	13	(52)	10	(53)	8	(80)
SB*	25	(38)	13	(76)	14	(58)	21	(40)	16	(64)	11	(58)	8	(80)

* = widespread small bowel involvement - see text

FIGURE 2.1

SITES OF DISEASE
THIS SERIES COMPARED WITH THE COLLECTED LITERATURE



* Based on data in Table 1.1

This series of 65 patients had fewer patients with both small and large bowel disease

individual details in Appendix 2.2. These studies tended to select in-patients with widespread SB disease with or without LB disease except in Chapter 6 (study of vitamin A) which was more typical of the whole series.

2.2 CLINICAL MEASUREMENTS

Anthropometric measurements

Three measurements thought to provide an overall indication of nutritional state (Shenkin 1978) were made. Body weight measured in kilograms was expressed as a percentage of ideal body weight based on height and calculated from standerised tables (Jeliffe 1966). Triceps skinfold thickness (SFT) which gives an estimate of fat stores (Blackburn 1977) was measured using a Harpenden fat caliper half way between the olecranon and the acromial process of the left arm. At the same point, the midarm circumference (MAC) was measured and from these two measurements the mid-arm muscle circumference (MAMC) was calculated from the formula MAC- (TSF x 0.314) = MAMC, giving an estimate of lean body mass (Blackburn 1977). Results were expressed as a percentage of standard for sex and height (Jeliffe 1966). SFT was measured in mm and MAMC was in cm, expressed as a percentage of the mean standard based upon a large population (Jeliffe 1966)

Crohn's Disease Activity Index

A simple index was used (Harvey 1980). Disease activity is based upon a simple questionnaire assessing the patient's clinical state over the previous 24 hours The details are in Table 1.2.

2.3 LABORATORY MEASUREMENTS

Blood samples

In-patients were fasted but outpatients were not. Blood was placed in glass or plastic tubes free of trace metal contamination, for estimates on serum and with added heparin for plasma estimations, citrate for plasma glucose and potassium EDTA for full blood count.

Analyses

1. Haemoglobin (Hb) concentration and full blood counts including percentage of reticulocytes from a Coulter counter and blood films were examined by a haematologist.
2. Measurements on serum of sodium (Na), potassium (K), urea, creatinine, albumin (alb), calcium (Ca) (adjusted for albumin - Payne 1973) and phosphate (phos) provided on a Technicon Sequential Multiple Analyser Computer Mark 2 (S.M.A.C. 2). Alkaline phosphotase (EC 3.1.3.1.- ALk Phos) (Anon 1970) and gamma glutamyl transpeptidase (γGT) (Szasz 1974) were measured colorimetrically. Plasma glucose was measured using a Yellow Springs Glucose analyser.
3. Vitamin D metabolites: plasma 25 hydroxycholecalciferol (25-OH D_3) by a modification of the method of Preece (1974); plasma 1,25 dihydroxycholecalciferol (1,25 OH D_3) by the method of Caldas (1978) using a binding protein from Vitamin D deficient chickens (Lawson 1974). Parathyroid hormone concentration (PTH) in plasma by a double antibody radioimmunoassay employing highly purifed bovine PTH as standard (MRC 76/568) and a guinea-pig anti-bovine PTH which recognises both ends of the PTH molecule (Burroughs Wellcome AS 211/32).
4. Serum magnesium (Mg) and zinc (Zn) by flame atomic absorption spectrometry (Peaston 1973)
5. The following additional serum proteins were measured: transferrin (TF) by automated immunoprecipitation (Technicon); retinol-binding protein (RBP) and prealbumin (PA) by a radial immunodiffusion technique using a commercial kit (LC-Partigen, Behring company, W. Germany) based on the method of Mancini (1965).
6. Vitamins. Plasma retinol (vitamin A) and Vitamin E were assayed by fluorimetry based on the method of Kahan (1966) with modifications by Thompson (1973).
7. Erythrocyte glutathione peroxidase activity (GSH-Px) in red cell haemolysates adjusted to approximately 10g/l Hb, using a coupled enzyme assay with t-butylhydroperoxide as substrate (Beutler E 1977). GSH-Px activity in plasma was also measured. Selenium in plasma was estimated by direct electrochemical atomic absorption

spectrophotometry (Saeed K 1979).

8. Haptoglobin concentration was measured after immunoprecipitation by a specific antibody. Light scattered by the complexes thus produced were measured in a fluoronephelometer (Technicon Autoanalyser 2 Specific Protein Analyser) (Ritchie 1973).
9. In vitro stability of red blood cells to oxidative stress was measured using hydrogen peroxide (H_2O_2) by comparing the optical density at 540 nanomoles (nm) of a 100% haemolysate of the sample with the H_2O_2 treated sample.

Urine Samples

Urine was collected in stainless steel urinals and transferred to clean plastic bottles, free of trace metal contamination. Care was taken to avoid faecal contamination of urine, but occasional samples were discarded. 24 hour urine collections were made on 2 consecutive days. The urine volume was measured and aliquots taken from each day's sample. The measurements listed below were made and the average of two measurements was recorded: Na, K, Ca, phos and creatinine were measured using standard laboratory techniques. Mg and Zn measurements are described above. Total nitrogen (N) was measured by a microkjeldahl technique. The method was based upon the digestion of organic nitrogen by sulphuric acid to ammonium, convers ion of ammonium to ammonia by the Kjeldahl reaction and measurement of the ammonia thus produced colorometrically by the Berthelot reaction (Fleck 1965; Munro 1969).

Faecal sampling

Three to five day collections of faeces were submitted for measurement of daily faecal fat excretion (Van de Kamer 1949) and for the measurement of triglyceride absorption by means of a dual-isotope fat absorption technique developed in our laboratory in which an absorbable triglyceride labelled with ^{14}C (glycerol trioleate) is ingested along with a non-absorbable ether labelled with ^{3}H, (glycerol triether). The ratio of ^{3}H to ^{14}C radioactivity in the stool gives a measure of the triglyceride absorbed (normal >96%) and the technique has the advantage of not requiring complete faecal

collections (Nelson 1980). In occasional patients total faecal N was also measured as in urine.

2.4 SPECIAL TECHNIQUES

1. Bone biopsy and diagnosis of osteomalacia (Chapter 5)

Full thickness transiliac bone biopsies were obtained under local anaesthetic using a bone biopsy needle with an internal diameter of 8mm and were fixed in neutral phosphate buffered formalin. The specimens were dehydrated in graded alcohols and embedded in methylmethacrylate. 10μm serial sections were cut from each biopsy specimen on a Jung K sledge microtome. Four representative sections from each specimen were stained (1% aqueous toluidine-blue) for quantitative histology, and the following variables were measured by point-counting and line intersect measurement with a Zeiss 2 eyepiece graticule in order to establish the diagnosis of osteomalacia: total osteoid surface (Whyte 1982), maximum number of birefringent lamellae of osteoid (Wood 1968) visualised under polarised light, and the extent of calcification fronts along osteoid seams (Rasmussen 1974). Calcification rate was measured using fluorescent microscopy following double tetracycline labelling by oral administration of 2 separate pulses of demethylchlortetracycline before biopsy. Criteria for diagnosis of osteomalacia (Boyce 1982) are two or three of the following histomorphometric measurements:

1. total osteoid surface greater than 25 %.
2. maximum number of lamellae greater than 4.
3. calcification fronts less than 60 % of the surface.

2. Bone Turnover

24 hour whole-body retention of a diphosphonate (hydroxy-ethylidene diphosphonate labelled with radioactive technetium (Tc-99^{m}HEDP) is increased in several metabolic bone disorders including osteomalacia (Fogelman 1978) and is believed to be an index of bone turnover rate. Tc-99^{m} is a short half-life isotope and the total dose of radioactivity administered was 50 micro Curies. 24 hour whole body retention of Tc-99^{m} HEDP, expressed as a percentage of the injected

activity was measured using a standard shadow shield whole-body monitor (Warner 1966). A normal 24 hour retention of less than 25% was previously established.

3. Dark Adaptation Testing

Dark adaptation testing was performed using a Tubinger Perimeter adapted for dark adaptation testing (Oculus Optikgeräte, Wetzlar, West Germany). After bleaching retinal visual pigment by exposing the retina to white light of luminous intensity 3000 apostilbs (approximately 9500 candelas/m^2 for 15 minutes, a small area 12-14° on the nasal side of the left eye was the focus of light of increasing intensity until the light was first perceived (the visual threshold). This was retested every 2 minutes until no improvement could be achieved, usually after 20-30 minutes. This final visual threshold is generally accepted as a sensitive indicator of Vitamin A dependent regeneration of visual pigment.

4. Intravenous Nutrition

Techniques:

In all patients intravenous nutrition (IVN) was administered by means of a silicone cannula (Centrasil: Travenol laboratories or Nutricath S: Vygon) inserted by percutaneous puncture at the junction between the subclavian and internal jugular veins. Using X-ray control the distal tip of the catheter was placed in the superior vena cava. The procedure was performed using aseptic techniques. The proximal end of the cannula was secured by silk stiches just beyond the skin puncture site. Intravenous nutrients were delivered to the cannula by means of a double-limbed giving set (Baxter Code no. FK C0180 Travenol Laboratories Ltd). In earlier patients, the nutrients were delivered by gravity feed with roller-clamps to control the rate. The nutrients were contained in 500ml bottles or bags which required to be changed 8 hourly. In later patients, some of the nutrients (aminoacids, glucose, electrolytes and water-soluble vitamins) were premixed in a three litre bag in the hospital pharmacy. In addition, flow-control pumps were introduced (IVAC 530 IVAC-UK Ltd). These innovations made nursing care simpler and comparison of complications before and after

introduction of the new techniques form part of the study (Chapter 8). The skin puncture site was dressed with sterile gauze and changed by an experienced nurse using aseptic technique every second day, when a bacteriological swab was taken from the skin puncture site.

IVN regimens:

The nutrients consisted of aminoacid solutions containing approximately 9, 14, and 17g of nitrogen (Synthamin 9, 14, 17- Travenol Laboratories), with added electrolytes, hypertonic glucose 10-50% providing 400-2000 kcal/l (1.7-8.4 MJ/l), and fat emulsion (Intralipid 10 or 20% Kabi-Vitrum) providing additional energy 550-1000kcal/500mls (2.3 or 4.2MJ/500mls). To these basic solutions one vial each of a trace metal supplement (Addamel - Kabi Vitrum) water soluble vitamins (Solivito - KabiVitrum) and fat-soluble vitamins (Vitlipid - KabiVitrum) were added (Appendix 2.3). Individual patients' requirements varied, the aim being to give sufficient nitrogen (aminoacid solution) to maintain positive nitrogen balance as judged from 24 hour urinary nitrogen excretion (measured twice weekly throughout IVN) and an additional arbitrary faecal allowance of 2g/day. In most patients 9-17g of nitrogen were supplied. Energy was provided from glucose and fat emulsion to maintain a kilocalorie to nitrogen ratio between 150 and 250 to 1. Individual patients' IVN regimens are contained in Chapter 8.

5. Enteral Nutrition

Technique:

Provision of liquid enteral diets was by means of pump delivery from a 1.5 litre reservoir bag (Viomedex Ltd), connected by a giving set to a fine-bore nasogastric feeding tube. The tube was usually a 125cm paediatric feeding tube (Code No 393.06 - Vygon U.K.) for short term feeding (< 3 weeks). For longer term feeding a polyurethane tube was preferred (Dobbhoff Enteric Feeding Tube - Viomedex Ltd). The feeding tube was passed via the nose into the stomach. The position in the stomach was confirmed by X-ray, aspiration of acid and by injecting air while auscultating over the epigastrium before feeding was commenced. To prevent the tube becoming obstructed by viscous

solutions it was flushed with water twice daily. Feeding was provided throughout the 24 hours. To prevent diarrhoea and vomiting sometimes associated with rapid introduction of feeds, the volume was gradually increased from 600 or 1200ml/day to a maximum of 3000ml/day over a period of 4-5 days. As with IVN, the aim was to maintain the patient in positive nitrogen balance.

EN regimens:

The individual regimens are in Chapter 8. Five commercially obtained enteral diets were used: one elemental or defined formula diet (DFD) (Vivonex), three polymeric diets (PD) (Triosorbon MCT, Ensure and Isocal- the last for long-term home enteral feeding in one patient). These four were chosen as 'complete' nutrition containing in a very low residue formulation all the basic ingredients of a complete diet. The fifth product, Caloreen was for provision of additional energy as carbohydrate. The composition of the diets is shown in Appendix 2.4

6. Monitoring of Nutritional Support

On specially designed proformata (Appendix 2.5), data were recorded before (Baseline) and during IVN and EN. From these data, day to day requiremants of nutrients and fluids were calculated and complications (eg pyrexia) detected early. When pyrexia occurred during IVN a "drawback" sample of blood from the intravenous line was obtained for bacteriological culture as well as a sample from the skin puncture site. The results of these investigations are in Chapter 8.

2.5 REFERENCE RANGES AND CONTROL GROUPS

Reference (normal) ranges for the haematological and biochemical measurements and the means by which these ranges were obtained are shown in Table 2.2. Special control groups for direct comparisons in individual studies are described in the relevant chapters.

It was necessary for some of the special biochemical measurements to obtain concurrent control groups. My colleague, Dr Peter Mills and I obtained samples from 100 fasted patients (50 men and 50 women) about

TABLE 2.2

REFERENCE RANGES AND THEIR SOURCES

BLOOD	UNITS		LOW	HIGH	SOURCE
RBC					
Haemoglobin (Hb)	g/dl	M -	13	18	Lab. ref. range
		F -	11.5	16.5	
Reticulocytes (retics)	%		--	< 6	Lab. ref. range
Serum/plasma					
Sodium (Na)	mmol/l		135	144	Lab. ref. range
Potassium (K)	mmol/l		3.4	4.9	Lab. ref. range
Urea (U)	mmol/l		2.5	7.0	Lab. ref. range
Albumin (Alb)	g/l		35	49	Lab. ref. range
Transferrin (TF)	g/l		2.0	4.0	100 Ortho pats.
Prealbumin (PA)	mg/l	M -	215	400	50 Ortho pats.
		F -	165	365	50 Ortho pats.
Retinol binding protein (RBP)	mg/l	M -	32	91	50 Ortho pats.
	mg/l	F -	28	76	50 Ortho pats.
Calcium (Ca)	mmol/l		2.20	2.60	Lab. ref. range
Alkaline phosphatase (Alk phos)	I.U./l		80	280	Lab. ref. range
gamma glutamyl transpeptidase (γGT)	U/l		--	< 36	Lab. ref. range
25 hydroxyvitamin D (25(OH)D)	nmol/l		> 16	--	25 Lab. staff
1,25 (OH)D	pmol/l		detect.	100	Lab. staff
Parathyroid Hormone (PTH)	ng/l		--	< 600	Lab. ref. range
Magnesium (Mg)	mmol/l		0.7	0.95	30 Ortho pats.
Zinc (Zn)	μmol/l		10.0	17.5	36 Ortho pats.
Retinol (Vit A)	μmol/l		1:2	2.9	100 Ortho pats.
Tocopherol (Vit E)	μmol/l		12	39	100 Ortho pats.
RBC Glutathione peroxidase (GSH-Px)	U/g Hb		13	25	Lab. staff
Selenium	μmol/l		0.6	1.8	Lab. staff
Haptoglobin	mg/l		> 0.2	--	Lab. ref. range
H_2O_2 stability	percent		--	< 20	Lab. staff
URINE					
Mg	mmol/day		> 2	--	20 lab. staff
Zn	μmol/day		4.6	10.6	25 lab. staff
Nitrogen (N)	g/day		--	< 2	Lab staff
FAECES					
Fat	mmol/day		--	< 21	Lab. ref. range
Fat absorption	percent		> 96	--	Nelson (1980)
Nitrogen (N)	g/day		--	< 2	Lab. ref. range

Abbreviations:
g/dl=grams per decilitre. m=milli-. μ=micro-. n=nano-. p=pico-. I.U.=International Units. Detect = detectable. Ortho = Orthopaedic pats. = patients

to undergo elective orthopaedic operations. We excluded any patients with infection, rheumatoid arthritis and any other systemic illness. When the values were very similar in the two sexes, the ranges based on 95% confidence limits were merged (eg Vitamin A and E) but when they were significantly different as with prealbumin and retinol binding protein separate reference ranges for men and women were used.

2.6 STATISTICAL METHODS

The following statistical methods were used:

1. Mann-Whitney test*
2. Wilcoxon's Rank Sum Test Wilcoxon F Biometrus Bulletin 1945;1:80
   Wilcoxon's Signed Rank Test - as above.
3. Student's t test Student Biometrica 1908;6:1
4. Chi-squared test*
5. Fisher's Exact Probability Test*
6. Linear Regression Analysis*
7. Calculation of the 'z' statistic**

* Swinson TDV (1981)

** Personal Communication. Dr Morven Leece, Statistician, Research Laboratory, British Museum, London

CHAPTER 3

A SURVEY OF CLINICAL AND LABORATORY ABNORMALITIES

3.1 AIMS

3.2 PATIENT SELECTION

3.3 METHODS

3.4 RESULTS

3.5 SUMMARY

3.1 AIMS

1. To determine the prevalence of individual abnormalities in laboratory tests and to discover the most fruitful path for further investigations into their clinical significance (Chapters 4 - 7).
2. To determine whether a knowledge of the site of disease, its clinical activity and the simplest indicator of nutritional state, body weight, would allow some prediction of the likelihood of discovering an abnormality in the blood (usually a depletion in the serum or plasma level).
3. To examine the clinical features of patients with multiple abnormalities.

3.2 PATIENT SELECTION

Patients were investigated at their first point of contact with the author, either as in-patients or out-patients, to glean point-prevalence information representative of a hospital gastroenterology practice. Thus it was <u>not</u> an examination of untreated patients and some were receiving treatment for previously detected abnormalities, anaemia in almost all cases. There were slightly fewer patients with involvement of both small and large bowel compared with the combined series quoted in Fig 2.1. 24 patients had small bowel disease only (SB), 17 had large bowel disease only (LB) and 24 had small and large bowel disease (SB+LB)

3.3 METHODS

Clinical and laboratory data

The following were measured:

Body Weight (% Ideal Weight for Height and Sex); Simplified Crohn's disease Activity Index (CDAI - see Table 1.2-A); fifteen blood levels: haemoglobin (Hb), mean cell volume (MCV), sodium (Na), potassium (K), urea, total calcium (Ca), magnesium (Mg), zinc (Zn), albumin (Alb), transferrin (TF), prealbumin (PA), retinol-binding protein (RBP), alkaline phosphatase (Alk phos), retinol (vit A) and tocopherol (vit E). Some analyses were not available on earlier patients which accounts for the lower number of recordings for

example of prealbumin and retinol-binding protein. Routine electrolytes were sometimes omitted on outpatients.

Data analysis

I have looked for differences in the numerical grouped data and compared the prevalence of abnormal results among the patients split up in three different ways:

1. Patients with disease of small bowel, versus large bowel and those with both small and large bowel
2. Patients well nourished (weight ≥ 90% of ideal weight) versus two degrees of malnourishment: moderate (weight 80 - 89% of ideal) and severe (weight < 80% of ideal).
3. Patients with inactive Crohn's disease (CDAI < 5) versus those with active disease (CDAI ≥ 5)

Statistical methods

Comparisons between grouped numerical data were made using a Student t test for normally distributed data and a Wilcoxon sum of ranks test for non-parametric data. Differences in prevalence of abnormalities were examined with a chi-squared test. Abnormalities were defined as being values outside the reference ranges described in Chapter 2. The significance of low values (high in the case of alkaline phosphatase) compared with the reference ranges which represented 95% confidence limits (2½% at top and bottom) was tested with single sided test of the 'z' statistic using the formula:

$$z = \frac{|p - \hat{p}|}{\sqrt{p(1-p)/n}}$$

where p = reference group proportion: in this case 0.025 (2½%)

$\hat{p}$ = Crohn's group proportion: 0.10 (10% was the lowest prevalence)

n = No of Crohn's subjects (see Table 3.1)

3.4 RESULTS

Clinical details

Body weight was recorded for 63 patients. 32 (52%) were of normal weight (≥ 90% of ideal); 13 (21%) were moderately underweight (80-89% of ideal) and 18 (29%) were severely underweight (< 80% of ideal). Active disease (CDAI ≥ 5) was present in 38 of 62 (61%)

Laboratory data

The main findings for the whole group of 65 patients are presented in Table 3.1. The commonest abnormalities were in Alb (40%), TF(34%), Hb (32%) and total Ca (35%), but other abnormalities were common being >10% in all cases. Using 10% as the lowest prevalence in any measurement, the 'z' statistic was

$$z = \frac{|0.025 - 0.10|}{\sqrt{(0.025 \times 0.975)/65}} = 3.75.$$

This was highly significant ($p < 0.01$) so that all abnormalities were significant and this was also true when n was < 65 as in a number of the tests performed (Table 3.1).

Anaemia

While 20 patients had low Hb concentrations, severe anaemia, as judged by a Hb <10 g/l, was present in 13. Of these, seven had evidence of iron deficiency (3 despite treatment with iron). Only one of these had overt blood loss, from active rectal disease. One patient had a severe macrocytic anaemia which responded to oral folic acid. The remaining five had a normocytic anaemia. Four of the patients were taking sulphasalazine which may cause a haemolytic anaemia, but there was no evidence of haemolysis. A number of patients with normal Hb concentrations were already taking iron or folic acid supplements. Anaemia in Crohn's disease is not further investigated.

TABLE 3.1

LABORATORY MEASUREMENTS ON 65 PATIENTS

LAB MEASUREMENT	NO OF TESTS	ABNORMALITIES Number (%)	Mean Value	Stand. Dev.	NUMERICAL DATA Units	Reference Range
					Blood/RBC	
Haemoglobin	63	20 (32)	12.2	2.4	g/l	M - 13-18 F - 11.5-16.5
Mean Cell Volume	56	8 (14)[1]	87.4	9.5	fl	76-96
					Plasma/serum	
Sodium	53	6 (11)	137	3.2	mmol/l	135-144
Potassium	53	8 (15)[2]	4.1	0.7	mmol/l	3.4-4.9
Urea	53	14 (26)[3]	4.6	3.2	mmol/l	2.5-7.0
Total Calcium	65	23 (35)	2.16	0.28	mmol/l	2.2-2.6
Magnesium	63	7 (11)	0.76	0.11	mmol/l	0.7-0.95
Zinc	45	12 (27)	12.0	4.1	µmol/l	10.0-17.5
Albumin	65	26 (40)	35.2	7.7	g/l	35-49
Transferrin	58	20 (34)[4]	2.5	0.9	g/l	2.0-4.0
Prealbumin	37	7 (19)	248	89	mg/l	M - 215-400 F - 165-365
Retinol-Binding Prot.	37	6 (16)	42.2	13.4	mg/l	M - 32-91 F - 28-76
Alkaline Phosphatase	63	19 (30)[5]	323	309	Units/l	80-280
Retinol	62	14 (23)	1.58	0.72	µmol/l	1.2-2.9
Vitamin E	60	14 (23)	19.4	10.6	µmol/l	12-39

Unless otherwise stated, all abnormal values were numerically lower than the limits of the reference range

Key: 1 = MCV: 2 elevated; 4 low
2 = 2 se K levels elevated; 6 were low
3 = 5 blood urea levels elevated; 9 low
4 = 1 se TF elevated; 19 low
5 = In all cases Alk Phos elevated

Abnormalities of routine eletrolytes

These were uncommon and minor. Hyponatraemia was severe (serum Na < 130 mmol/l) in only one patient (No 52) who had severe diarrhoea due to active colonic disease described in Chapter 8. All the remaining 5 had diarrhoea when the measurement was made. Hypokalaemia in six patients was severe (serum K <3.0 mmol/l) in two, both with diarrhoea. Hyperkalaemia in 2 cases was associated with vomiting and dehydration and readily corrected with intravenous fluid replacement. Minor elevation of plasma urea was again due to dehydration and readily corrected. Of some interest were the 6 patients with very low plasma urea (<2 mmol/l). All six were measured just before a period of nutritional therapy and may have been an indirect indicator of severe protein depletion

Calcium, magnesium and zinc

Prevalence of total plasma Ca depletion (35%) was second only to Alb depletion. More severe depletion (serum Ca < 2.00 mmol/l) occurred in only nine patients (14%). The dependence of Ca on Alb concentration in the plasma is examined further in Chapter 5. Plasma Mg depletion was less common (11%). However a few patients with severe depletion had symptoms (tetany), and further studies of Mg were performed (Chapters 4 and 9). Plasma Zn depletion (27% of 45 patients) is a complex issue and is investigated further in Chapter 9. Alk phos activity was commonly high (30%). Chapter 5 examines this in relation to calcium, Vitamin D and osteomalacia.

Protein depletion

Alb depletion, was present in 40% of the patients. Nine (14%) had mild depletion (30-34g/l), nine had moderate depletion (25-29 g/l) and in the remaining eight (12%), it was severe (< 25 g/l). TF was low (<2.0 g/l) in 20 (34%) and very low (<1.5 g/l) in 9 (16%). In 17 of the 26 patients with low plasma Alb (65%), plasma TF was also low. Twelve patients with Alb depletion received nutritional therapy (Chapter 8). Only 37 patients had measurements of PA and RBP performed. These fast turnover proteins are further examined in relation to vitamin A (Chapter 6)

Vitamins A and E

Nearly a quarter of the patients had low plasma levels of these fat-soluble vitamins. Further studies are described in Chapters 6 and 7.

The individual numerical and prevalence data in the three clinical groupings are in Appendix 3.1 to 3.3. Significant differences are presented here.

Differences according to site of disease (Appendix 3.1)

No differences were demonstrable in the grouped numerical data between the any 2-way combinations of SB(24), LB(17) and SB+LB(24). However with regard to prevalence, abnormalities of four blood constituents were found more commonly in SB+LB than SB. These were: Zn (38% v 8% - $p<0.05$); TF 52% v 9% - $p<0.05$); Alk phos (42% v 13% - $p<0.05$); Vitamin E (43% v 5% - $p<0.01$).

In addition magnesium depletion was commoner in SB+LB than LB: 25% v 0% - $p<0.05$).

Differences according to body weight (Appendix 3.2)

Differences in numerical data and prevalence were demonstrated only between those with normal weight (32) and those severely malnourished (18).

Numerical data: malnourished patients had lower levels of the following compared with those with normal weight. Mean concentrations are shown:

Alb (g/l): 30.4 v 38.7 ($t=4.4$; $p<0.001$)

TF (g/l): 1.96 v 3.03 ($t=4.7$; $p<0.001$)

Total Ca (mmol/l): 2.06 v 2.23; ($t=2.0$; $p<0.05$)

Vitamin A (µmol/l): 1.25 v 1.75; ($t=2.3$; $p<0.05$)

The most prevalent abnormalities in the severely malnourished group were Alb (78%), Ca (56%), Hb (53%), and TF (50%). However abnormalities were also common in the other weight groups as shown in Appendix 3.2 and the only differences reaching conventional levels of significance were between the severe group and those of normal weight: Albumin: 78% v 22%; ($p<0.001$) and TF: 52% v 19% ($p<0.05$)

Differences according to disease activity (Appendix 3.3)
The only difference between inactive and active disease was that a low serum Vit A was more common in active disease (36% v 9%; $p<0.05$).

Patients with multiple abnormalities
A better clinical perspective about the prevalence of abnormal laboratory measurements was obtained by counting the number of abnormalities in each patient. Table 3.2 gives the results. If none or a single abnormality are considered as 'normal', only 23 (35%) were normal. The 3 sites of disease were compared. It was not surprising that most abnormalities per patient (more than four) occurred in the patients with the most widespread disease.
Some clinical features of the eleven most severely depleted patients (more than five abnormalities) are shown in Table 3.2. Small and large bowel disease were present in most. Disease had been present for 10 years or more in six of the eleven and seven had undergone one or more bowel resections. All but one were underweight, seven severely malnourished (weight < 80% of ideal). Disease was active in eight. Nine of the eleven were investigated just before a period of nutritional therapy. Three of these were regarded as having intestinal failure (Patients 50, 51 and 62) as described in Chapter 8. Combinations of two clinical features were tested against the remainder and the only combination in which a significant difference was approached (but not reached) is illustrated in Fig 3.1. The median number of abnormalities (4) in the 12 patients severely underweight and with active disease was no greater than the rest (median 2).

3.5 SUMMARY

In a group of 65 patients with Crohn's disease only 32 (52%) were of normal body weight, while 18 (29%) were severely underweight (< 80% of ideal weight). Those with active disease accounted for 61%. Laboratory abnormalities varied between 11% (serum Na) and 40 % (serum Alb). Severe depletion however was less prevalent. In order of prevalence and using arbitrary numerical definitions of 'severe' depletion, anaemia was severe (Hb <10 g/l) in 21%, TF depletion

TABLE 3.2

PREVALENCE OF ABNORMAL LABORATORY MEASUREMENTS
PATIENTS WITH MULTIPLE ABNORMALITIES

Number of abnormalities per patient	Small bowel n=24 No of patients (% of total)	Large bowel n=17 No of patients (% of total)	Small & Large Bowel n=24 No of patients (% of total)
0 - 1	10 (42%)	7 (41%)	4 (17%)
2 - 3	7 (29%)	3 (18%)	6 (25%)
4 - 5	5 (21%)	6 (35%)	6 (25%)
>5	2 (8%)	1 (6%)	8 (33%)
Mean number of abnormalities per patient	2.2	2.6	4.3

PATIENTS WITH MORE THAN FIVE ABNORMALITIES

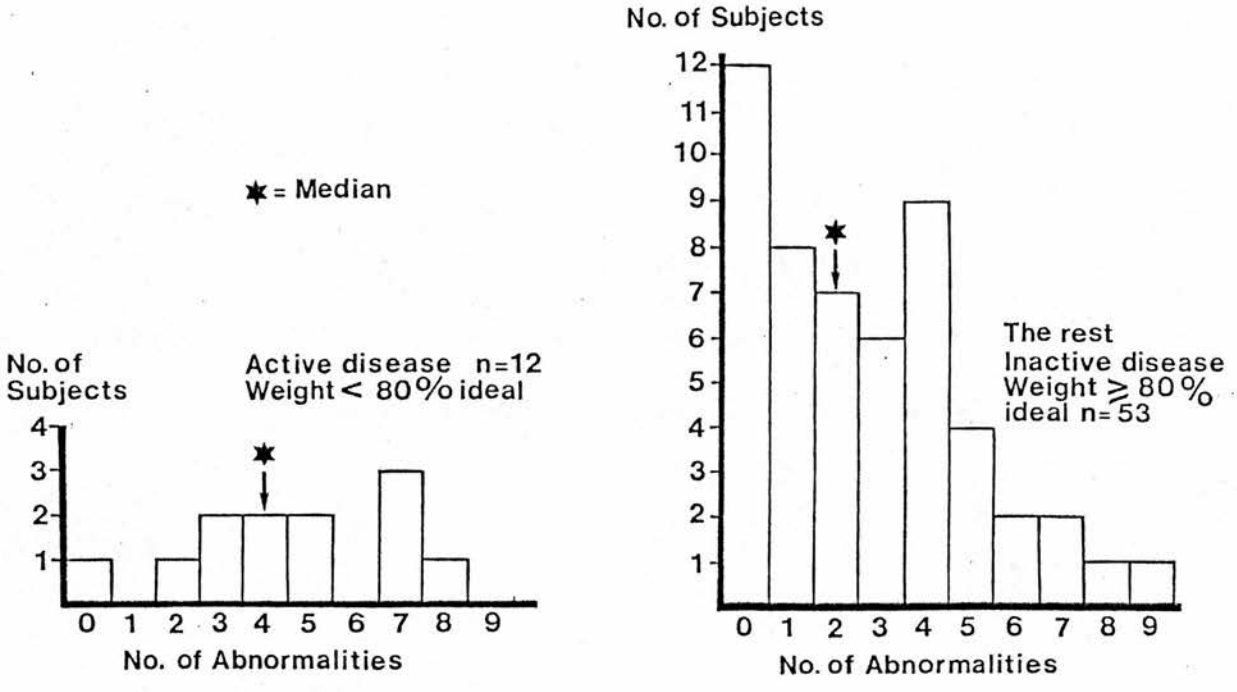
Number	Site	Duration (years)	Resections (number)	Weight (% Ideal)	CDAI	LABORATORY ABNORMALITIES
1*	SB	3	NONE	69	4	Hb, MCV(low), Na, urea, Zn, ALb, PA, RBP, Alk Phos,
20	SB	3/12	T,Il,	64	4	Hb, urea, Ca, Alb, TF, PA
27*	LB	10	NONE	70	11	Na, K, urea, Ca, Zn, Alb, TF
47*	SB+LB	7	R, Hemicol,	83	8	urea, Ca, Mg, Zn, Alb, TF, vitamin E
48*	SB+LB	14	All of colon	80	7	Ca, Mg, Zn, Alb, TF, Alk phos vitamin E
50*	SB+LB	14	R, Hemicolon ? internal fistula	78	14	urea, Ca, Mg, Alb, TF, Alk phos vitamin A, vitamin E
51*	SB+LB	10	> half of ileum	64	13	Hb, MCV(low), K, urea, Ca, Zn, Alb, TF
52*	SB+LB	10	NONE	63	6	Na, K, urea, Ca, Mg, Alb, TF
53*	SB+LB	2	T,Il, + most of colon	110 (pregnant)	7	Hb, K, urea, Zn, Alb, TF, vitamin A
58	SB+LB	8	3 small bowel resections	80	5	Hb, Ca, Mg, Zn, Alb, TF, Alk phos, vitamin A and E
62*	SB+LB	12	NONE	54	2	Hb, Ca, Zn, Alb, TF, PA, RBP, Alk phos, vitamin A and E

* Assessment done just before a period of nutritional support (See Chapter 8)

FIGURE 3.1

PREVALENCE OF ABNORMAL LABORATORY MEASUREMENTS

Active disease and severely underweight versus the rest



(<1.5 g/l) in 16%, Ca depletion (<2.00 mmol/l) in 14%, Alb depletion (<25 g/l) in 12%, severe Mg depletion (< 0.5 mmol/l) in 3%. Abnormalities were examined in relation to site of disease, body weight and disease activity. Depletion of Zn, TF, vit E and increased activity of alk phos were commoner in SB+LB disease than in SB disease. Those severely underweight (<80% ideal) were more likely to be protein depleted (Alb and TF) than those with normal weight. In addition to these two measurements, Ca and Vit A concentration were lower in the severely malnourished group. Apart from higher prevalence of Vit A depletion in patients with active disease, patients with active disease did not have more abnormalities than those with inactive disease. Patients with both small and large bowel disease had more abnormalities (average 4.3 each) than those with large bowel disease (2.6) and small bowel disease (2.2). Patients with more than five abnormalities were characterised as being underweight, having active disease usually of long duration and requiring nutritional therapy.

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 4

MAGNESIUM DEFICIENCY

4.1 AIMS

1. To assess magnesium (Mg) status in patients with severe Crohn's disease.
2. To determine long-term Mg requirements in Mg depleted patients after discharge from hospital.

4.2 PATIENT SELECTION

Seventeen of the 65 patients requiring admission to hospital were studied as shown in Table 4.1: 3 (18%) with small bowel disease, 2 (12%) with large bowel disease and the remaining 12 (71%) had both small and large bowel disease. Those with widespread small bowel involvement accounted for 13 (76%) of the sample. Therefore the study was of a more severely affected group than those in the general survey of whom only 38% had widespread disease of the small bowel. In addition all the patients were suffering from exacerbations or complications of Crohn's disease. Indeed many received nutritional therapy as described in Chapter 8. In Chapter 9 Mg requirements during intravenous nutrition were examined.

4.3 METHODS

Mg status in all patients was determined by measuring serum Mg and 24-hour urine Mg on patients and controls as described in Chapter 2. Biochemical Mg deficiency was defined as a serum Mg of <0.7 mmol/l and/or urine Mg <2mmol/24hour. A Mann-Whitney test was used to compare the Crohn's group with controls. Serial serum Mg measurements were performed on an outpatient basis 2-20 months after discharge from hospital in selected patients and were used to assess their requirements of oral Mg supplements.

4.4 RESULTS

Magnesium Status in Patients with Severe Crohn's Disease. (Table 4.2)

Using the criteria for Mg depletion described, only 2 patients had normal Mg status. Serum Mg concentration in the Crohn's group (median 0.73 mmol/l) was lower than in the controls ($p<0.01$). Symptoms likely to be due to Mg deficiency occurred in 2 patients and in a third (No 50) a man with multiple deficiencies his symptoms may in part have

TABLE 4.1

PATIENT DETAILS AND REASONS FOR ADMISSION TO HOSPITAL

No	Sex	Age	Extent of disease	Present problem
1	F	16	SB-TI	Anorexia, weight loss
19	F	23	SB-W	Rectovaginal fistula
20	F	25	SB-W	Acute intestinal obstruction
25	F	22	LB	Diarrhoea and urgency
27	F	60	LB	Weight loss, rectovaginal fistula
42	F	33	SB-TI+LB	Abdominal pain, anorexia, anaemia and secondary amenorrhoea
47	F	60	SB-W+LB	Weight loss; subacute intestinal obstruction
48	M	48	SB-W+LB	Weight loss; diarrhoea, hypoalbuminaemic oedema, muscle stiffness, paresthesiae
49	M	16	SB-W+LB	Steatorrhoea, vitamin deficiencies, delayed puberty
50	M	34	SB-W+LB	Enterocutaneous fistula, recurrent weight loss, chronic diarrhoea
51	F	19	SB-W+LB	Diarrhoea, weight loss, pubertal failure, severe anorectal disease
52	M	19	SB-W+LB	Severe diarrhoea, protein losing enteropathy
55	F	29	SB-W+LB	Problems with ileostomy
58	M	27	SB-W+LB	Right iliac fossa mass, weight loss
62	F	18	SB-W+LB	Pubertal failure, severe steatorrhoea, tetany
63	F	64	SB-W+LB	Ileocolonic fistula, severe diarrhoea
64	M	28	SB-W+LB	Weight loss, diarrhoea, abdominal pain

TABLE 4.2

MAGNESIUM STATUS IN 17 PATIENTS

	Normal Range	Crohn's (n=17) Median (range)	Controls (n=30) Median (range)
Serum Mg (mmol/l)	0.70-1.00	0.73 (0.38-0.89)	0.82 (0.68-1.00)
Urine Mg (mmol/day)	2.00-4.00*	0.85 (0.05-2.85)	- - -

	Number	%	Mg depleted
Low serum + low urine Mg	5	29	15 (88%)
Low serum + normal urine Mg	1	59	
Normal serum + low urine Mg	9		
Normal serum and urine Mg	2		

* urine Mg levels based on 24 hour samples from 20 laboratory staff.

been due to Mg deficiency:

Patient 48, a man with diffuse small bowel Crohn's disease, a very low serum Mg level was found (0.40 mmol/l). Skeletal pain and muscle cramps had been prominent symptoms. Extensive investigation of his calcium status including a bone biopsy revealed no evidence of calcium deficiency at this time although he later developed osteomalacia.

Patient 50, described in a number of chapters, had severe malnutrition and generalised weakness such that he was unable to stand unaided. On admission his serum Mg concentration was 0.38 mmol/l. He did not have tetany.

Patient 62, a young girl with growth failure associated with diffuse disease and severe steatorrhoea, had suffered several attacks of tetany corrected on occasions by calcium infusion and at other times with Mg infusion. Despite oral Mg supplementation she was still Mg deficient on admission with a serum Mg concentration of 0.59 mmol/l.

No other patient had a serum Mg concentration less than 0.61 mmol/l.

Outpatient Followup and Long-term Mg status

After treatment in hospital during which 10 of the patients received intravenous nutrition, serum Mg concentrations were checked regularly. Only the 3 patients described above required oral Mg therapy as indicated in Table 4.3. Patient 48 had intermittent trouble with bone pain and muscle cramps and subsequently developed histological osteomalacia as described in Chapter 5. Patient 50, who up till the time of this study had undergone three periods of IVN, had constant diarrhoea and steatorrhoea. He was subsequently maintained at home on a noctural enteral feeding regime containing Mg supplements as decribed in Chapter 8. Patient 62, who had suffered tetany before IVN, subsequently had tetany despite oral supplements, but after Mg intake was increased to 60 mmol/day she had no further symptoms.

TABLE 4.3

OUTPATIENT MAGNESIUM STATUS AND THERAPY

Patient	Admission**	Months after discharge	Serum Mg (mmol/l) (0.7-1.0)*	Oral Mg supplement (mmol/day)
48	1	1	0.42	Nil
		2½	0.52	20
		12	0.62	60
		20	0.78	60
50	1	2	0.58	Nil
		4	0.48	Nil
	2	2	0.54	Nil
	3	3	0.83	11-20
		10	0.70	25
62	1	2 weeks	0.96	30
		1½	0.38	30
		6½	0.57	60

* - Reference range
** - In all cases admission included a period of intravenous feeding See Chapter 8

4.5 SUMMARY

A biochemical and clinical investigation of Mg deficiency has been performed in 17 patients with predominantly extensive Crohn's disease. 15 out of 17 had biochemical evidence of Mg depletion with low serum concentrations (<0.7 mmol/l) and/or low urine output(<2 mmol/24 h). Three patients were symptomatic all with serum Mg concentrations less than 0.60 mmol/l while all the remaining patients without symptoms of Mg depletion had higher serum Mg concentrations. These three patients required a daily supplement of between 30 and 60 mmols of oral Mg after discharge from hospital.

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 5

DIAGNOSIS AND TREATMENT OF OSTEOMALACIA

5.1 AIMS

1. To relate the diagnosis of osteomalacia (OM) to clinical and biochemical measurements in Crohn's disease.
2. To attempt to identify patients with Crohn's disease in whom treatment would be justified for presumed OM without the need for bone biopsy.

5.2 PATIENT SELECTION

Of the 24 patients selected, 9 (38%) had small bowel disease, in 4 (17%) disease was confined to the large bowel and the remaining 11 (46%) had small and large bowel disease, proportions similar to the general survey. From a larger sample, patients were excluded for the following reasons: non-consent to Bone Biopsy (4), anticoagulant therapy (1), therapy within the previous year with drugs known to affect bone metabolism such as corticosteroids or cholestyramine (4). Two already taking calcium or Vitamin D supplements before a bone biopsy was done were also excluded

5.3 METHODS

Clinical details

In addition to the site of disease, the following information was recorded: body weight (% of ideal weight), Crohn's disease activity index(CDAI) as previously, duration of disease, and the extent, if any, of surgical resections. By direct questioning, the presence or absence of bone pain and other musculoskeletal symptoms were determined and patients were examined for signs of muscle weakness.

Experimental methods

The means of obtaining samples for bone biopsy, the method of histomorphometry, criteria for diagnosing osteomalacia, and the method of estimating bone turnover are described in Chapter 2.
The following blood measurements were made:

1. Vitamin D metabolites: plasma 25-hydroxy cholecalciferol (25(OH)D)
   plasma 1,25 dihydroxy cholecalciferol (1,25(OH)D)
2. Serum measurements of Calcium (Ca) adjusted to allow for the

influence of low levels of its main binding protein, albumin (Payne 1973), phosphate (phos), alkaline phosphatase (alk phos) and gamma glutamyl transpeptidase activity (γGT), serum magnesium (Mg), parathyroid hormone (PTH).

3. Faecal measurements: fat absorption and faecal fat excretion.

Statistical Methods

Wilcoxon's Sum of Ranks test was used for comparison of numerical values between groups. A Chi-squared test or Fisher's Exact Probability Test were used for comparison of incidences between groups

5.4 RESULTS

Bone Histology

Six patients (OM group) had osteomalacia . The remaining 18 did not have osteomalacia (non-OM group), despite minor abnormalities of individual histomorphometric measurements in 3 patients.

Clinical and Biochemical Results.

a)Characteristics of Whole Group

The 24 patients consisted of 9 men and 15 women of mean age 40 years (range 21-73). Body weight (mean 96 (56-149)% ideal) was low (<90%) in 9 patients. Active disease (CDAI >4) was present in 14 (58%) and musculoskeletal symptoms in 12 (50%). Duration of disease varied from 1-27 years (mean 9.1). 13 patients (54%) had undergone one or more resections of small bowel. In the Crohn's patients plasma 25 (OH)D levels (28.8±17) (mean ± SD) were similar to controls (29.7±13), only 4 patients having low levels (<16 nmol/l). All measurements were taken between November and January. However, of the 6 OM patients only 2 had pretreatment 25 (OH)D levels measured and these (both 4 nmol/L) were by far the lowest levels encountered in the study. 9 patients in whom plasma 1,25(OH)D was measured had normal levels (detectable - 100pmol/l).

b) Comparison between OM and non-OM patients

The results in Table 5.1 indicate that the only significant differences between the groups were lower body weight, higher disease activity and higher serum alk phos in the OM group. This last measurement distinguished best between the groups. Furthermore the OM patient with a normal alk phos was judged to have only mild OM and had mild non-specific symptoms. Although 5 of the six OM patients had muscle or bone pain, so did 7 of the non-OM patients. Similarly, while all of the OM patients had impaired fat absorption, so did 4 of the six non-OM patients who were investigated. Individual details of the OM patients before treatment was commenced are in Table 5.2.

Bone Turnover

Figure 5.1 illustrates the retention of radiolabelled diphosphonate in the OM and non-OM patients. Unfortunately access to the equipment was delayed in 3 of the 6 patients with OM until shortly after treatment for OM had begun (illustrated with open circles in Fig 5.1). Thus all six with OM (3 in the early phases of treatment) had evidence of raised bone turnover. The remaining 18 did not have OM, but 3 had elevated WBR of Tc99-m HEDP. In one, there was a slight increase in total osteoid surface but in the other 2 whose retentions were only slightly elevated (30% and 31%) histomorphometry was normal.

These results suggest that OM is most likely to occur in patients with impaired fat absorption who also have an elevated alk phos level of bony origin and increased bone turnover. OM seems unlikely or will be mild if alk phos and bone turnover are normal.

Effect of Therapy

Five of the 6 patients in whom osteomalacia was severe received oral therapy with calcium and 1-α hydroxy-vitamin D. Details and effects of therapy are shown in Table 5.3.

TABLE 5.1

CLINICAL AND BIOCHEMICAL RESULTS

Comparison between OM and non-OM patients

	OM (6) Median	(Range)	Non-OM (18) Median	(Range)	Difference
Body weight (% ideal)	87	(56-100)	97	(72-149)	$p < 0.05$
CDAI (Activity score)	7	(6-9)	3	(0-10)	$p < 0.05$
Duration of symptoms (years)	11		8.5		NONE
Bowel resections: none	1		10	)	
< 100cm	3		5	)	NONE
100-200cm	0		2	)	
> 200cm	2		1	)	
Musculoskeletal symptoms	5		7		NONE
Abnormal biochemistry					
Low adjusted calcium* (<2.20 mmol/l)	2/5		0/17		NONE
Low magnesium (<0.7 mmol/l)	1/4		0/18		NONE
Low phosphate (<0.7 mmol/l)	1/4		0/17		NONE
Elevated Alk phos (<280 IU/l)	5/6		1/18		$p < 0.01$
Elevated PTH (>600 ng/l)	2/4		1/18		NONE
Low 25)OH)D (<16 nmol/l)	2/4		1/17		NONE
Low fat absorption (<96%)	6/6		4/6		Insufficient

* see Payne (1973)

TABLE 5.2

DETAILS OF PATIENTS WITH OSTEOMALACIA

Patient No	Age/ Sex	Weight Kg	% ideal	Symptoms	Length of small bowel remaining	PTH ng/l	Serum conc, Ca*	Phos	Mg (all mmol/l)	TG, Abs, (%)	Faecal Fat Excretion (mmol/day)
47	60 F	55	100	Vague weakness Bone pain	All but 60 cm	690	2,11	0,90	n/a	15	204
48	50 M	39	87	Tender ribs Looser's zones	All small bowel Remaining	200	2,25	1,20	0,41	44	172
49	22 M	35	56	Waddling gait Proximal myop, Looser's zones	140 cm jejunum	n/a	n/a	n/a	n/a	35	114
50	36 M	62	88	Generalised bone pain and myopathy	All but 15cm term, ileum	n/a	2,13	n/a	0,74	70	160
51	22 F	34	67	Waddling gait Proximal myop, Pseudo-fracture of ulna	140 cm jejunum	760	2,29	0,65	0,86	82	49
59**	54 F	44	89	Vague weakness	All but 20cm of term, ileum	<105	2,40	0,95	0,70	37	105
					Normal Values	<600	2,20-2,60	0,7-1,4	0,7-1,2	>96 %	< 21

Notes:
For Alkaline phoshatase activity before treatment see Table 5.3
* see Payne (1973)
** patient with mild OM
n/a = not available
TG. Abs. = triglyceride absorption.

FIGURE 5.1

BONE TURNOVER IN 24 PATIENTS

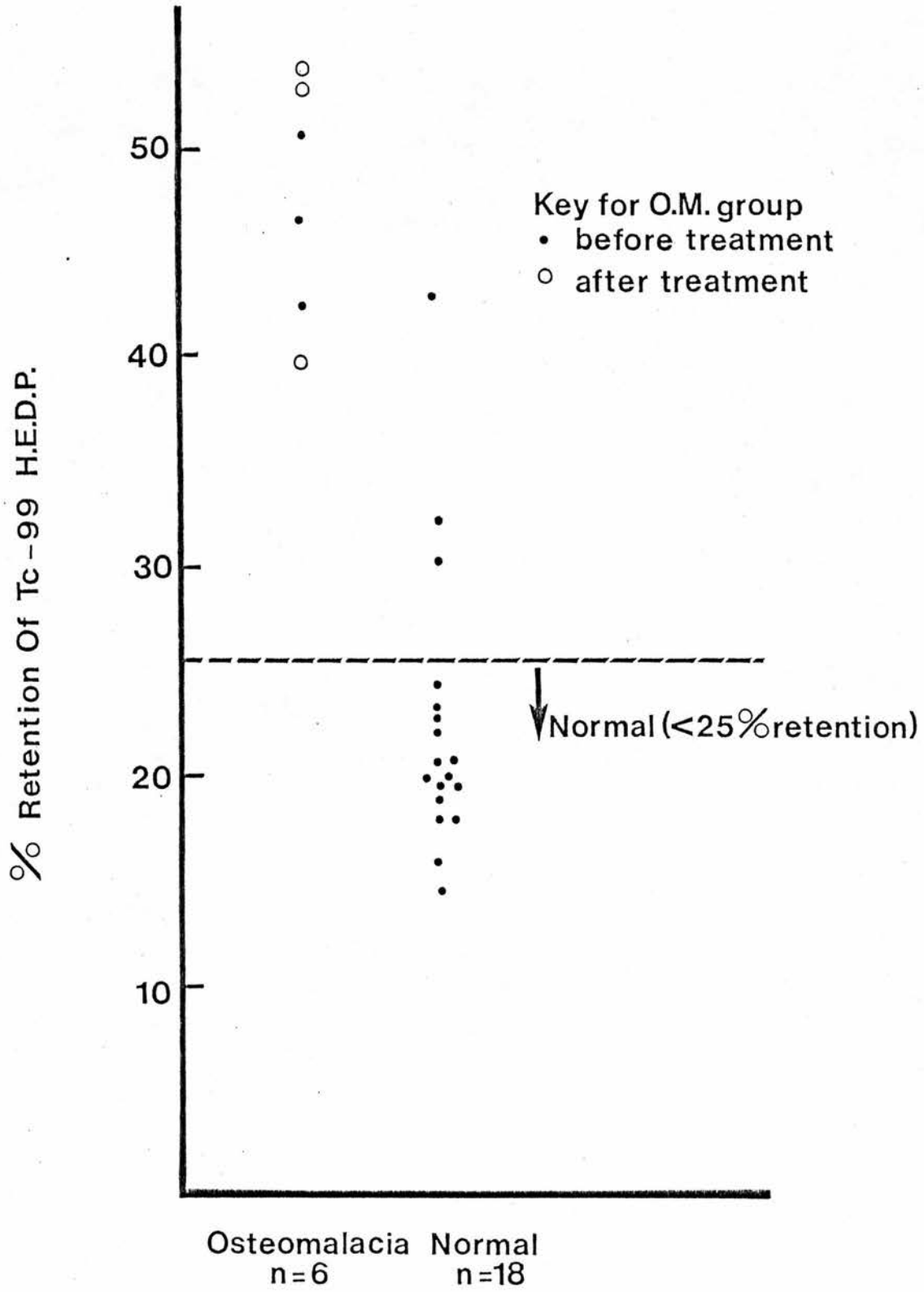


TABLE 5.3

EFFECTS OF ORAL THERAPY IN PATIENTS WITH OSTEOMALACIA
(compare with Table 5.2)

Patient No	Oral therapy	Duration of Therapy (months)	Alkaline phosphatase Before (I,U,/l)	After	Symptoms	Bone biopsy after Treatment	Comments
47	Calcium and 1-α (OH) D (1 µg/day)	12	742	506	Bone pain resolved after 2 months	Healed OM	--
48	Calcium, Mg,	22	481	171	Bone tenderness and x-rays resolved	Healed OM	Low se Mg despite treatment
49	Calcium and 1-α (OH) D (3 µg/day)	66	981	300	Waddling persisted for 14 months	Healing OM	--
50	Home Enteral Nutrition* Calcium, Mg, 1-α (OH) D- (2 µg/day)	17	1313	903	Bone pain and myopathy resolved after 2 months	Healed OM	
51	Calcium and 1-α (OH) D (5 µg/day)	14	1815	2900	Symptoms persist Fracture healed	Not done	Low serum phosphate
59	No therapy	--	245	--	Vague weakness	Not done	--

Normal - < 280 I,U,/l

* see Chapter 8 and Case Report (Main 1980)

5.5 SUMMARY

Bone biopsies were performed on 24 patients with varying severity of Crohn's disease and the histological findings related to clinical and biochemical features to define the clinical context in which OM is likely to occur, and to determine whether it is possible in future Crohn's patients to detect osteomalacia without the need for bone biopsy. 6 of the 24 had osteomalacia and were characteristically underweight (<90% ideal body weight), had active disease and steatorrhoea. 4 of the 6 had had less than 100 cm of small bowel resected and 1 had an intact small bowel. The diagnosis of severe osteomalacia was possible by finding an elevated serum alk phos in association with a normal γGT level. For the detection of mild OM associated with normal serum biochemistry the monitoring of Vitamin D status (plasma 25 hydroxyvitamin D) and whole-body retention of Tc-99m HEDP are suggested as screening tests. In the therapy of osteomalacia in Crohn's disease, phosphate and magnesium may be required in addition to calcium and Vitamin D. Parenteral therapy or the use of 1-α hydroxyvitamin D may occasionally be necessary.

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 6

VITAMIN A DEPLETION AND NIGHT BLINDNESS

6.1 AIMS

6.2 PATIENT SELECTION

6.3 METHODS

6.4 RESULTS

6.5 SUMMARY

6.1 AIMS

1. To examine Vitamin A and plasma protein status in a large subset (52 patients) of the original survey and to relate the findings to clinical features.
2. To examine in greater depth in-patients with Vitamin A depletion and to assess the effects of therapy on those with symptoms of Vitamin A deficiency (night blindness).

6.2 PATIENT SELECTION

Of the 52 selected, 31 were out-patients seen at routine review (group 1) and 21 were in-patients admitted with exacerbations or complications of the disease (group 2). Twenty (38%) had small bowel disease, 12 (23%) had large bowel disease and the remaining 20 (38%) had small and large bowel disease. They were therefore fairly representative of the whole group of 65. None were receiving Vitamin A supplements.

6.3 METHODS

Clinical data

Body weight (expressed as a percentage of ideal weight), extent of small bowel disease (by criteria described in Chapter 2) and previous surgical resections were recorded. Patients were examined for evidence of eye disease relating to Vitamin A deficiency (xerophthalmia) according to the WHO classification (Anon 1982).

Laboratory investigations

The following were measured by methods described in Chapter 2: Plasma protein concentrations: albumin (Alb), transferrin (TF), prealbumin (PA) and retinol-binding protein (RBP). Plasma vitamin A (retinol), serum zinc (Zn), fat absorption, daily faecal fat excretion. In selected patients dark adaptation testing was performed.

Statistical methods

The relationship between retinol concentration and the various plasma proteins was tested by linear regression analysis. Differences

between populations were judged using a Mann-Whitney test. In addition mean values and standard deviations are quoted.

6.4 RESULTS

The 52 patients consisted of 17 men and 35 women of mean age 30 years. Their mean (range) body weight was 90% (54-149%) ideal. Outpatients (group 1) tended to weigh more: 100% (80-149%) than inpatients (group 2):76% (54-103%). Twenty patients had extensive small bowel disease, 10 in each group. Results of the biochemical analyses are shown in Table 6.1. Plasma proteins, apart from RBP were lower in group 2 than in group 1. There was no association between plasma retinol levels and serum Alb or TF, but a significant correlation was shown between retinol and RBP (Fig. 6.1), between retinol and PA ($r=0.71$; $p<0.001$), and between RBP and PA ($r=0.81$; $p<0.001$).

Based on our normal range, 11 of the 52 patients (21%) had low plasma retinol levels. Five were in group 1 (Table 6.2) and these outpatients were not further studied. The remaining six patients with plasma retinol <1.2 µmol/l (<34 µg%) were inpatients. These and a further three patients with plasma retinol >1.2 but <1.4 µmol/l were selected for further studies. These nine were compared with the remaining 12 patients in group 2 (Table 6.3) which indicates that the patients with low plasma retinol levels were more likely to have widespread small bowel disease and had lower levels of TF, RBP and PA. The results of further studies on these nine 'high risk' patients are shown in Table 6.4. Five (nos 47, 48, 50, 51 and 62) had impaired fat absorption and a marked increase in faecal fat excretion. Three (nos 49, 50 and 62) had impaired dark adaptation testing as indicated by a raised final visual threshold (<43.4 neg $\log_{10}$ apostilbs) but only patients 50 and 62 complained of night blindness. None of the patients had conjunctival or retinal signs of xerophthalmia.

Patient 49 had only 140 cm of small bowel remaining after previous resections for obstructive Crohn's disease. After an exacerbation with severe diarrhoea and weight loss he had a plasma retinol concentration of only 0.2 µmol/l (5.7 µg%), associated with low RBP (24 mg/l) and low PA (95 mg/l). Despite abnormal dark

TABLE 6.1

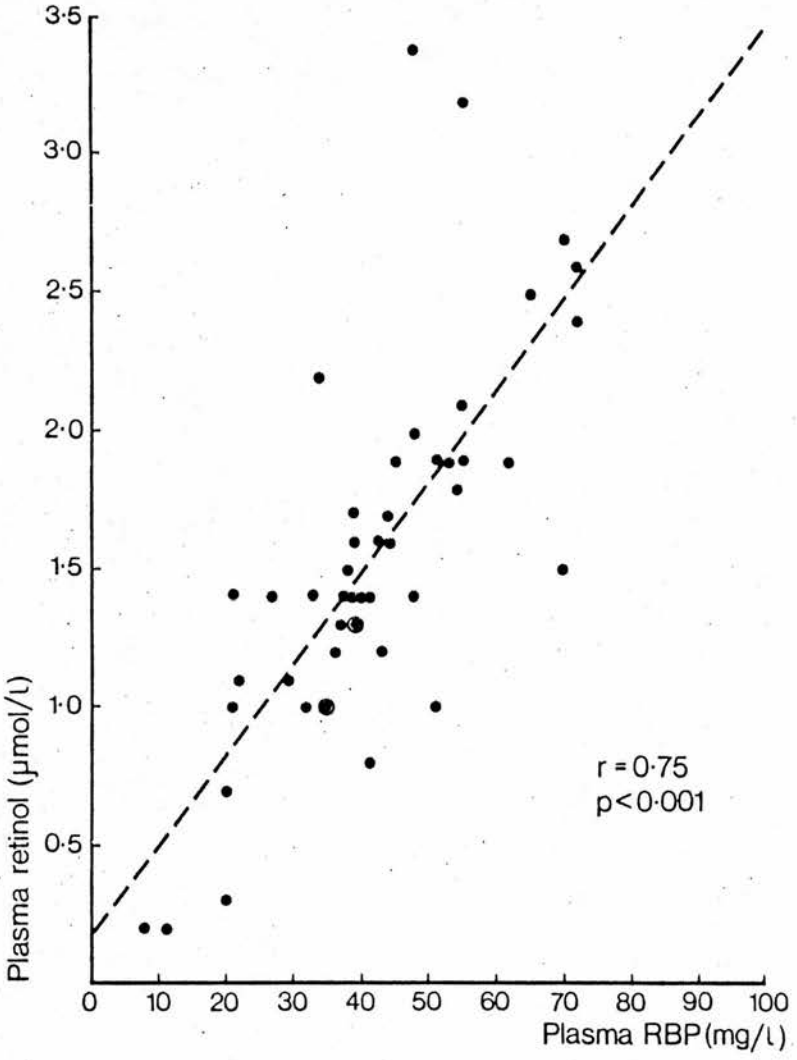
BIOCHEMICAL RESULTS IN OUTPATIENTS (GP 1) AND INPATIENTS (GP 2)

	Albumin (g/l)	Tranferrin (g/l)	Retinol binding protein (mg/l)	Prealbumin (mg/l)	Retinol µmol/l (µg%)
Normal ranges	35-50	2,0-4,0	M 32-91 F 28-76	M 215-400 F 165-365	1,2-2,9 (34-83)
All patients (52)	37,2±6,2*	2,8±0,8	42,0±15,1	235±+87	1,7±0,9 (48,6+25,7)
Group 1 (31)	39,8±4,4	3,2±0,6	44,6±12,3	270±77	1,8±1,0 (51,5+28,6)
Group 2 (21)	33,7±6,6	2,2±0,7	37,2±18,7	172±66	1,5±0,8 (42,9±22,9)
p value #	<0,01	<0,001	NS	<0,001	NS

*Mean + SD, # Comparisons between group 1 and group 2, NS = not significant,

FIGURE 6.1

CORRELATION BETWEEN PLASMA CONCENTRATIONS OF RETINOL AND RETINOL-BINDING PROTEIN



◉ *indicates two or more identical values*

TABLE 6.2

DETAILS OF OUTPATIENTS WITH LOW PLASMA RETINOL

Patient/ Sex	Age	Extent of small bowel disease	Weight (%ideal)	Retinol (μmol/l)	Ret.binding protein (mg/l)	Prealb (mg/l)
16 M	30	W	97	1.1	29	155
21 F	29	W	85	1.0	35	185
46 F	27	L	85	1.0	35	255
56 F	31	L	90	1.1	22	145
59 F	54	W	90	1.0	32	235
W = widespread L = localised.		Normal ranges		1.2-2.9 (34-83)	M 32-91 F 28-76	M 215-400 F 165-365

TABLE 6.3

COMPARISON BETWEEN HIGH AND LOW RISK PATIENT INPATIENTS (GROUP 2)

	Plasma retinol <1,4 µmol/l (9) (<40 µg%)		Plasma retinol >1,4 µmol/l(12) (>40 µg%)	
Presence of extensive disease	7 out of 9	p < 0,05	3 out of 12	
Mean body weight (% ideal)	71%	NS	82%	
Serum values (mean±SD)				Normal range
Albumin (g/l)	31,1±6,2	NS	34,3±7,7	35-51
Tranferrin (g/l)	1,7±0,8	p<0,05	2,4±0,7	2,0-4,0
Retinol binding protein (mg/l)	26,5±15,5	p<0,05	49,2±18,1	32-91
Prealbumin (mg/l)	135±66	p<0,05	213±49	215-400
Zinc (µmol/l(µg%))	9,0±1,5 (59±10)	NS	12,6±6,2 (82±40)	10,0-18,0 (65-117)

NS = not significant.

TABLE 6.4

FURTHER STUDIES OF INPATIENTS WITH PLASMA RETINOL <1.4 µmol/l

Patient/ Sex		Age	Extent of small bowel disease	Body wt (%ideal)	Final visual threshold (neg $\log_{10}$ apostilbs)	Plasma retinol (µmol/l) (µg%)	Serum zinc (µmol/l) (µg%)	TG Abs. (%)	Faecal Fat (mmol/day)
1	F	16	L	69	57	1,3(37,2)	10,0(65)	96	16
27	F	71	L	70	45	1,3(37,2)	8,5(55)	-	22
47	F	60	W	83	44	1,2(34,3)	7,2(47)	15	179
48	M	48	W	80	44	1,0(28,6)	11,0(72)	44	168
49	M	16	W	74	38	0,2(5,7)	10,5(68)	98	27
50	M	34	W	78	35	0,7(20,0)	12,5(81)	70	121
51	F	19	W	64	46	0,6(17,2)	6,5(42)	82	49
54	F	26	W	70	46	0,8(22,9)	10,0(65)	-	-
62	F	18	W	54	25	0,2(5,7)	4,5(29)	16	153
W = widespread L = localised				Normal ranges:	>43,4	1,2-2,9 (34-83)	10,0-18,0 (65-117)	>96%	<21

adaptation he complained of no visual impairment.

Patient 50 a man with diffuse small bowel disease and steatorrhoea, had required four periods of intravenous nutrition (IVN) before 1981 because of recurrent weight loss and hypoproteinaemia. During the seven months before he noticed night blindness there was a fall in serum Alb and TF and very low levels of retinol, RBP and PA were noted (Fig 6.2). Dark adaptation testing at that time was impaired (Fig 6.3 - upper curve). As shown in Fig 6.2 there was a rapid improvement in proteins and plasma retinol over a 14 day period on IVN including vitamin A supplements, concurrent with resolution of his visual symptoms and return of his dark adaptation testing to normal (Fig 6.3 - lower curve).

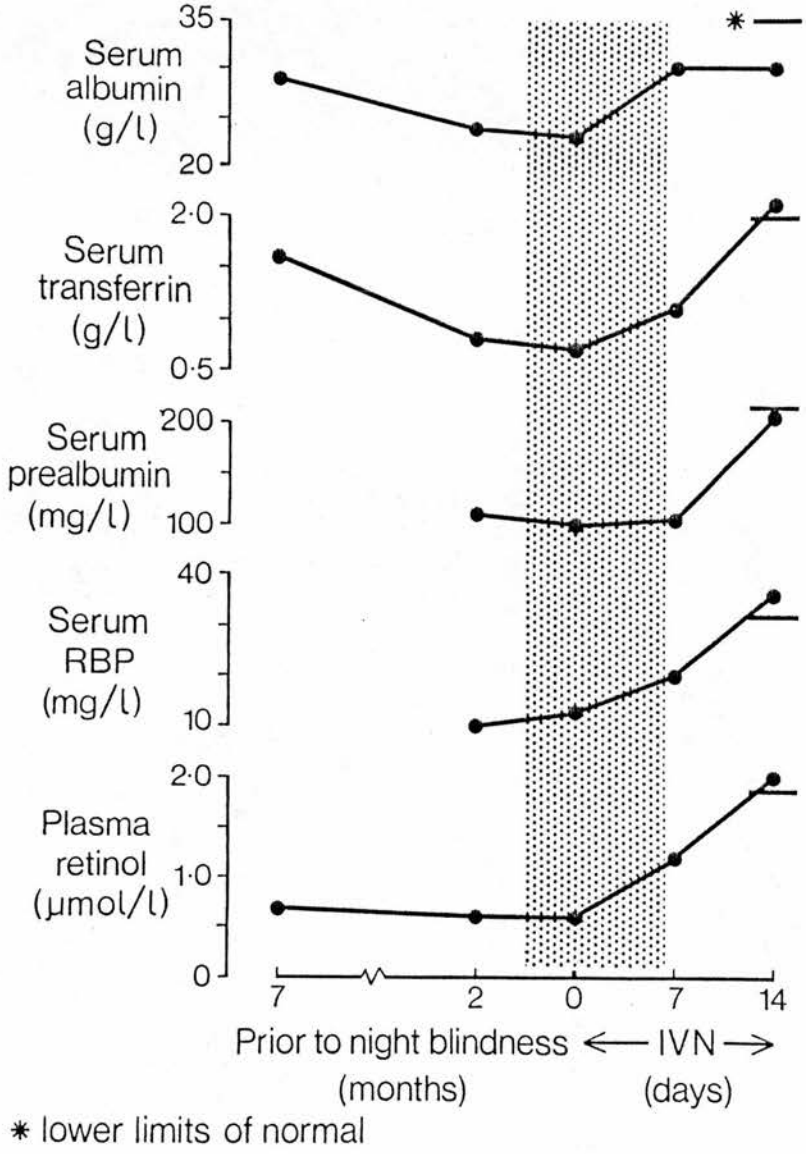
Patient 62 was a girl with chronic diarrhoea and steatorrhoea of 11 years duration. She complained of severe night blindness and dark adaptation (Fig 6.4-upper line) was grossly abnormal. Plasma retinol was very low (0.2 μmol/l) as were RBP (14 mg/l) and PA (115 mg/l). After oral vitamin A therapy (6000 IU/day) her symptoms rapidly improved with improvement of dark adaptation (Fig 6.4-lower line).

6.5 SUMMARY

Fifty two patients with Crohn's disease (31 outpatients and 21 inpatients) were investigated for evidence of vitamin A deficiency. As a group, the inpatients were more protein depleted than the outpatients, with respect to serum albumin ($p<0.01$), transferrin ($p<0.001$), and prealbumin ($p<0.001$) but retinol binding protein levels were not significantly lower. Eleven (21%) had low plasma retinol concentrations (<1.2 μmol/l (34.3 μg%)). Five of these were outpatients and plasma retinol was only slightly reduced (>1.0 μmol/l (28.6%)). All outpatients weighed 80% or more of ideal, and were considered at low risk of developing vitamin A deficiency. In contrast, of the six inpatients with low plasma retinol concentration, five had a level of <1.0 μmol/l (28.6 μg%) and weighed <80% ideal. Three of these had impaired dark adaptation and a plasma retinol concentration of <0.8 μmol/l (<22.9 μg%). It is suggested

FIGURE 6.2

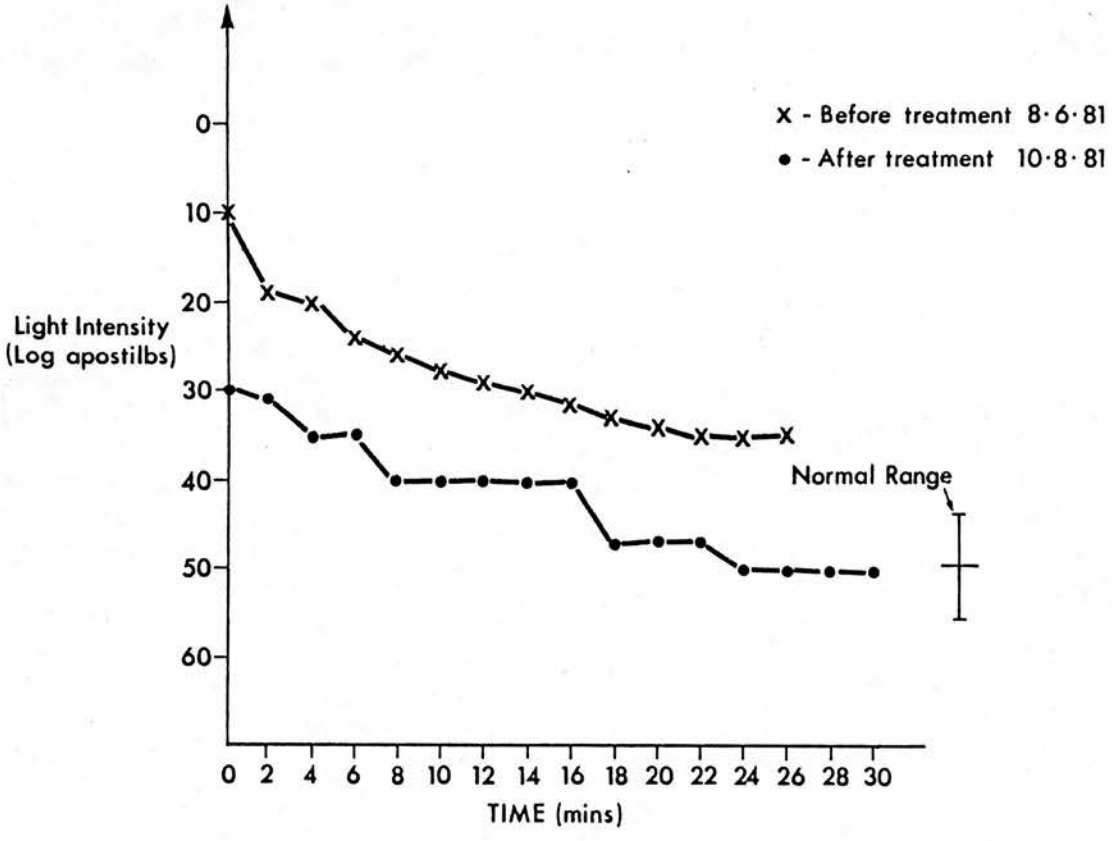
BIOCHEMICAL CHANGES BEFORE AND AFTER INTRAVENOUS NUTRITION INCLUDING VITAMIN A (2500 I.U. / DAY) IN PATIENT 50



The cross-hatched area indicates the time during which he complained of night blindness.

FIGURE 6.3

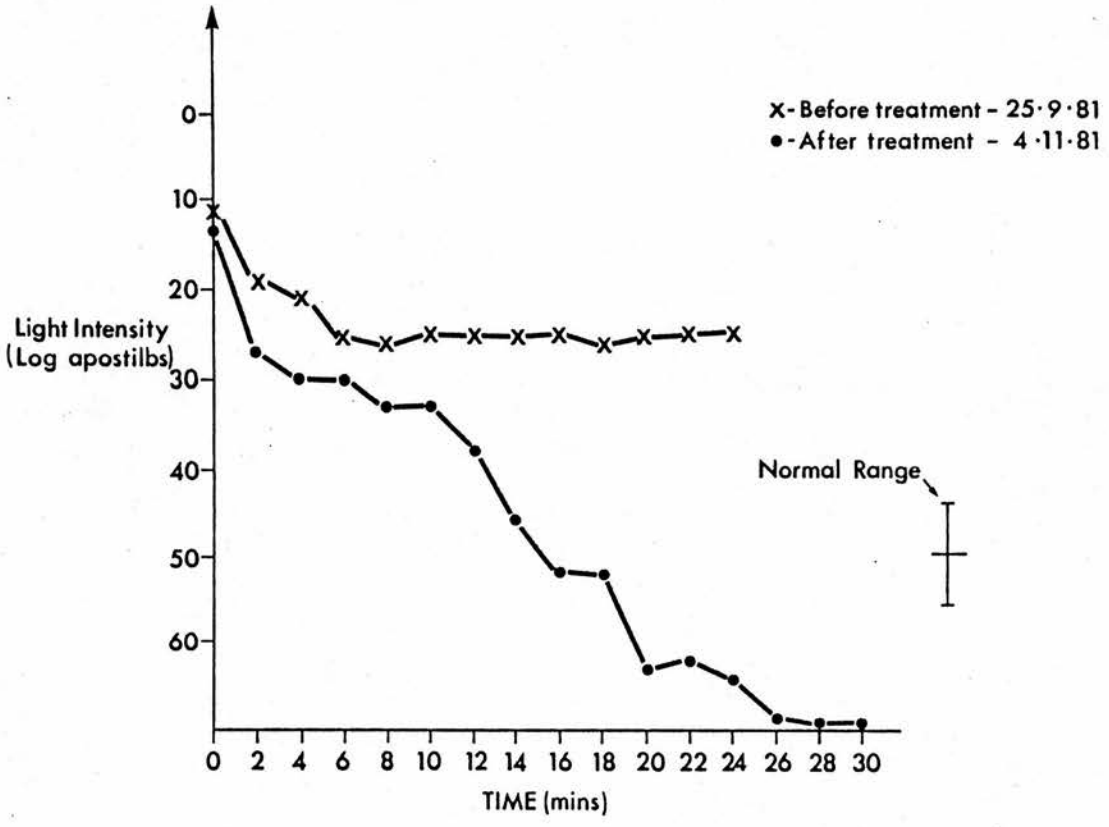
PATIENT 50 BEFORE AND AFTER TREATMENT



Dark adaptation testing before (upper curve) and after IVN followed by oral vitamin A therapy

FIGURE 6.4

PATIENT 62 BEFORE AND AFTER TREATMENT



Dark adaptation testing before (upper curve) and after oral vitamin A therapy

that patients with extensive small bowel Crohn's disease, who weigh <80% of ideal weight, merit measurement of plasma retinol concentration. Those with plasma retinol <0.8 µmol/l (<22.9 µg%) run a high risk of night blindness. Vitamin supplements should be given and protein depletion corrected.

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 7

VITAMIN E AND SELENIUM STATUS

7.1 AIMS

1. To measure Vitamin E and selenium status in severe Crohn's disease
2. To determine the clinical relevance of abnormalities in relation to red blood cell (RBC) stability and *in vivo* haemolysis.

7.2 PATIENT SELECTION

25 in-patients were selected: a higher proportion having small and large bowel disease (13 out of 25 : 52%) than in the general survey (37%). Furthermore the prevalence of widespread small bowel disease or resections as defined in Chapter 2 was higher (16 out of 25 : 64%) than in the whole group (38%).

7.3 METHODS

The following measurements were made as described in Chapter 2.

(i) Plasma concentrations of Vitamin E, selenium and haptoglobin

(ii) Red cell concentration of glutathione peroxidase (GSH-Px) and haemoglobin and plasma concentration GSH-Px.

(iii) Peripheral whole blood film microscopic examination to determine percentage of reticulocytes and to search for evidence of red-cell fragmentation.

(iv) 24 hour faecal fat excretion (16 patients) - mean daily excretion from a 3 day sample.

(v) Percentage haemolysis of a RBC sample incubated with hydrogen peroxide, (hydrogen peroxide stability).

(vi) Control groups are described in Chapter 2.

7.4 RESULTS

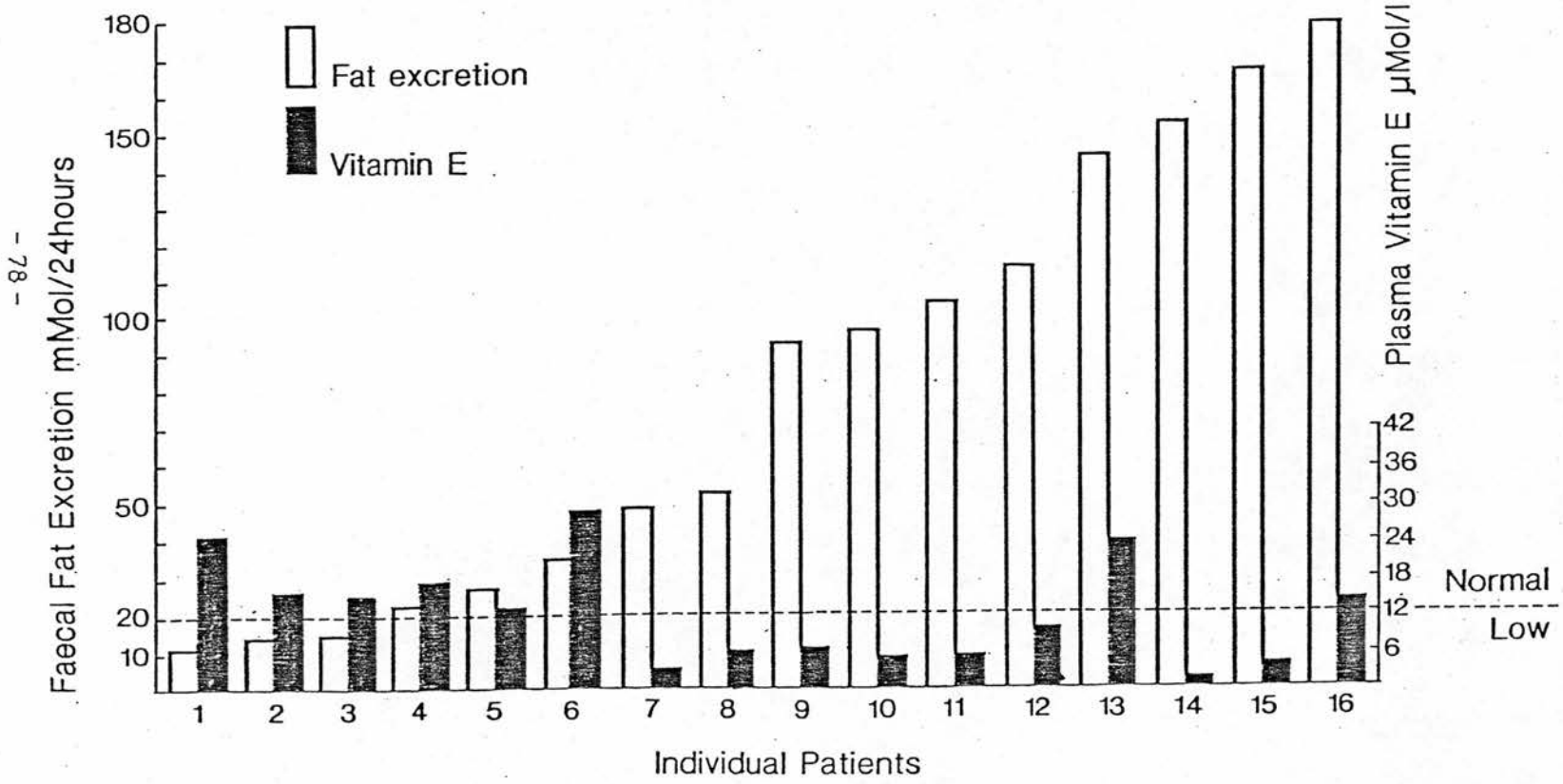
The results are presented in Table 7.1 , 7.2 and Figs. 7.1 and 7.2.

Vitamin E and Fat Excretion (Fig 7.1)

Twelve of the sixteen whose faecal fat excretion was measured had steatorrhoea (>21 mmol/l) and all but one of these had widespread small bowel disease or resections. As illustrated in Fig 7.1, all eight patients with low Vitamin E levels had steatorrhoea.

FIGURE 7.1

COMPARISON OF FAECAL FAT EXCRETION WITH PLASMA VITAMIN E



Vitamin E and hydrogen peroxide stability (Fig. 7.2)

Stability of RBCs to hydrogen peroxide in vitro was impaired in 19 of the 25 patients (>20%). A significant correlation was demonstrated between plasma Vitamin E levels and hydrogen peroxide stability (r=0.68). However the relationship was not close and although all patients with low plasma Vitamin E levels had RBCs with abnormal hydrogen peroxide stability, so did many others.

Selenium status and hydrogen peroxide stability(Table 7.1)

Only 3 patients had low selenium levels in plasma while 5 had low red cell GSH-Px concentrations. There was no correlation between selenium concentration or red cell GSH-Px activity and hydrogen peroxide stability.

Haematological status(Table 7.2)

All the 11 patients (44% of sample) who had either abnormal Vitamin E/selenium status or abnormal haematological investigations (blood count, film, reticulocyte or haptoglobin levels) are presented in Table 7.2. Although all 11 had abnormal <u>in vitro</u> hydrogen peroxide stability, there was no evidence of <u>in vivo</u> haemolysis since all patients had less than 6% reticulocytes. Of the 2 with low haptoglobin concentrations, one had entirely normal investigations apart from 47% in vitro RBC haemolysis. Minor evidence of RBC membrane instability (occasional RBC fragments seen on a random blood film) was present in 3 patients.

<u>Patient 22</u> had grossly abnormal hydrogen peroxide stability (83%), 5% reticulocytes (upper limit of normal) and marginally low Vitamin E concentration (11 µmol/l).

<u>Patient 26</u> had evidence of iron deficiency

<u>Patient 60</u> had only marginally low selenium levels.

7.5 SUMMARY

Twenty five patients with Crohn's disease were studied to determine the significance of abnormal Vitamin E and selenium status by examining <u>in vitro</u> stability of red-blood cells to oxidative stress with hydrogen peroxide and <u>in vivo</u> haemolysis, the concurrent

FIGURE 7.2

HYDROGEN PEROXIDE STABILITY

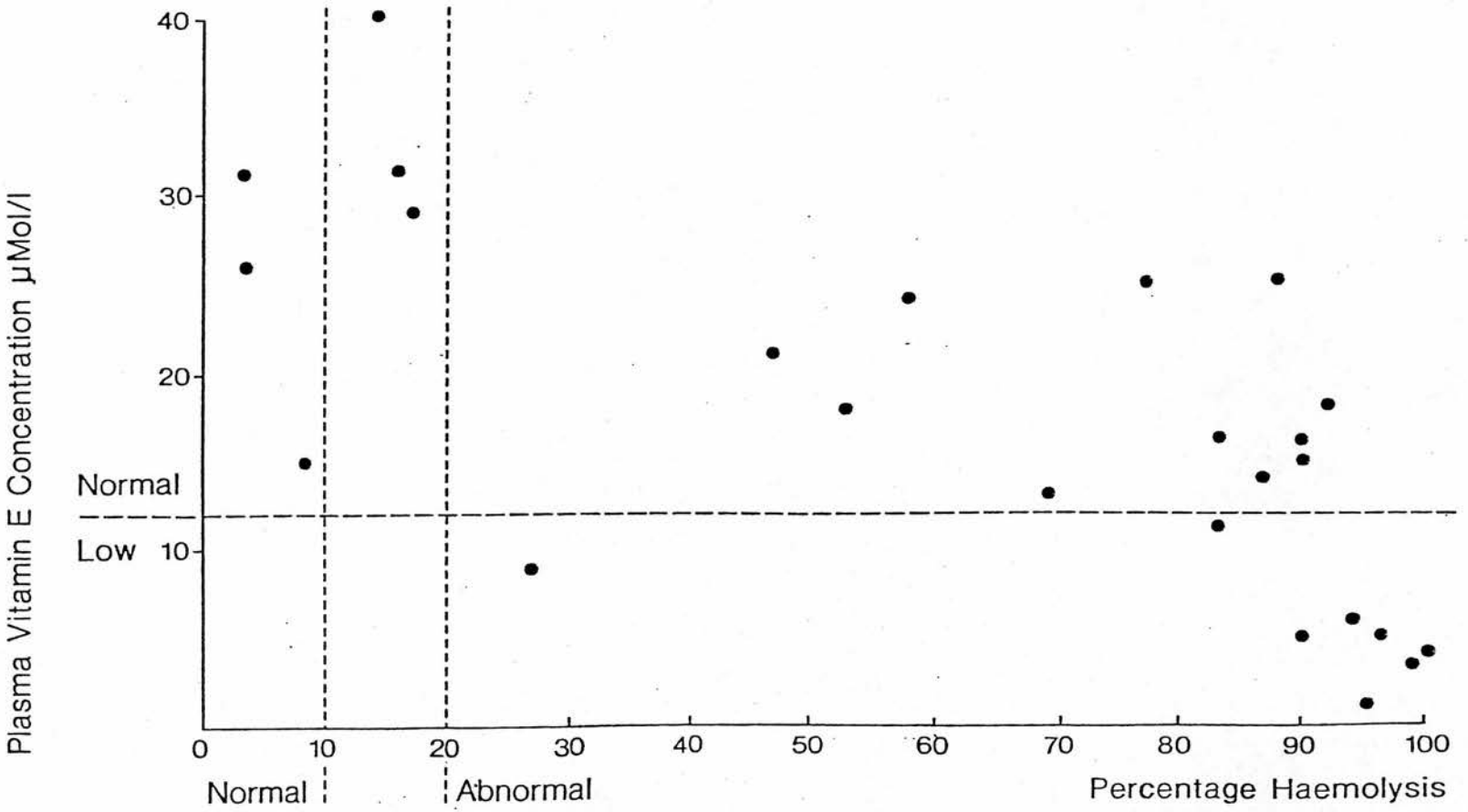


TABLE 7.1

VITAMIN E AND ASSOCIATED MEASUREMENTS

MEASUREMENT (UNITS)	No of Patients	MEAN±1 SD *MEDIAN(RANGE)	No (%) abnormal	Reference Range
Plasma Vitamin E (μmol/l)	25	* 16 (1-50)	8 (32)	12 - 39
Plasma selenium (μmol/l)	25	1.21 ± 0.46	3 (12)	0.6 - 1.8
Red cell GSH-Px (Units/g Hb)	25	17.6 ± 6.8	5 (20)	13 - 20
Faecal fat excretion (mmol/l)	16	(see Fig 7.1)	12 (81)	< 21
hydrogen peroxide stability (% of RBCs haemolysed)	25	* 83 (3 - 100)	19 (76)	< 20
Plasma haptoglobin (mg/l)	25	1.75 ± 0.97	2 (8)	>0.2

TABLE 7.2

PATIENTS WITH ABNORMALITIES OF VITAMIN E AND OTHER MEASUREMENTS

1. Low plasma Vitamin E and/or low plasma selenium concentration

Patient Number	M F	Hb 11,5-16,5 (g/dl)	MCV 76-96 (fl)	Vit E 12-39 (µmol/l)	Selenium 0,6-1,8 (µmol/l)	Faec. Fat <21 mmol/day)	Haptoglobin >0,2 (g/l)	Retics. <6 (%)	RBC Frag. <20 (%)	FILM AND COMMENTS
22	F	11,0	105	11	1,34	94	0,4	5	83	Normal apart from occ. RBC fragments
26	M	10,5	69	6	1,04	52	3,0	4	94	Iron deficiency + fragmented RBCs
48	M	13,4	85	4	1,19	168	2,7	2	100	Rouleaux. Otherwise normal
49*	M	15,5	97	9	1,11	114	2,4	2	27	Poikilocytosis
50*	M	13,0	94	5	0,11	98	1,2	2	96	Normal
51*	F	8,1	68	3	0,79	49	2,0	2	99	Severe Iron Deficiency
59	F	14,0	83	5	1,06	105	2,0	2	90	Normal
60	F	12,5	91	24	0,58	143	1,3	5	58	Some fragments Poikilocytosis
62*	F	10,2	137	1	0,40	153	<0,2	5	95	Macrocytosis Low Folate

2. Other patients who were anaemic

Patient Number	M F	Hb 11,5-16,5 (g/l)	MCV 76-96 (fl)	Vit E 12-39 (µmol/l)	Selenium 0,6-1,8 (µmol/l)	Faecal Fat <21 (mmol/day)	Haptoglobin >0,2 (g/l)	Retics. <6 (%)	RBC Frag. <20 (%)	FILM AND COMMENTS
3	F	8,9	73	25	1,37	-	2,2	1	88	Poikilocytosis Iron deficiency
21	F	6,3	71	13	1,01	28	1,7	3	69	Severe iron deficiency

Note:
* = also had low RBC GSH-Px concentration.
M = male. F = female. dl = decilitre. fl = femptolitre

measurement of haptoglobin concentration and reticulocyte count in the peripheral blood. Low plasma Vitamin E levels in the general survey, (Chapter 3) were common (23 % of 60 patients). In this subsequent study of 25 of these patients, plasma Vitamin E concentration (median (range)) was 16 μmol/l (1-50), with 8 patients (20%) having low values (<12μmol/l). Plasma selenium concentration (mean ± 1 sd) of 1.21 ± 0.46 μmol/l was low (<0.6μmol/l) in only 2 patients. Red cell GSH-Px concentration was 17.6 ± 6.8 Units/g Hb. with 5 low values (<13 Units/g Hb). In 16 of the 25 patients 24 hour faecal fat measurements were made. Twelve had steatorrhoea (24 hour faecal fat >21mmol), and all 8 with low plasma Vitamin E concentrations also had steatorrhoea. In vitro stability of RBCs to hydrogen peroxide was grossly impaired (median 83% haemolysed) and 19 patients (76%) had abnormally fragile red cells (>20% haemolysis). There was a correlation between plasma Vitamin E concentration and Hydrogen peroxide stability (r=0.68) and all patients with low plasma Vitamin E concentrations had abnormally fragile RBCs in vitro. However there was no evidence of significant in vivo haemolysis since no patient had an abnormal reticulocyte count (>5%) and only two had a low haptoglobin concentration. The study demonstrates a high prevalence of Vitamin E abnormalities in severe Crohn's disease but these abnormalities of static measurements and in vitro evidence of RBC membrane instability appear to have no clinical significance.

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 8

NUTRITIONAL THERAPY

8.1 AIM

8.2 PATIENT SELECTION

8.3 METHODS

8.4 RESULTS

8.5 COMPLICATIONS OF NUTRITIONAL THERAPY

8.6 SUMMARY

8.1 AIM

To audit Nutritional Therapy (NT) in Crohn's disease.

8.2 PATIENT SELECTION

Nineteen patients were selected for NT. Three had disease of the small bowel only, in six disease was confined to the large bowel and the majority (10 out of 19) had small and large bowel disease. Thus patients with extensive disease predominated (53%) compared with 37% in the general survey. 12 of the 19 had undergone previous abdominal surgery: two had no resection (one defunctioning colostomy) while the remaining 10 had all or part of the colon removed (4-colon only; 4-colon and terminal ileum; 2-colon and extensive small bowel resection).

8.3 METHODS

General indications for NT

In most cases simpler forms of supervised oral feeding with soft consistency or liquid diets had failed to reverse weight loss or improve symptoms and in many cases drug therapy had failed. The decision to give NT was on the basis of failure of other therapy in relation to specific pre-determined primary and secondary clinical aims (indications) listed below. In general, <u>both</u> primary aims had to be fulfilled before NT was considered. In several patients an attempt to avoid further surgery can be regarded as a further aim
Thus the success or failure of NT was judged by the outcome of these pre-determined primary aims described below

Which type of NT?

In most patients EN was considered as first choice. IVN was used in the following circumstances:

a)Patient refused or could not tolerate fine-bore nasogastric tube.
b)Severe or rapid nutritional decline.
c)Symptoms of nausea or vomiting.

d)Previous extensive small bowel resections likely to compromise absorption of the enteral diet.

e)poor tolerance or complications of EN

f)failure of EN to halt decline or improve symptoms

Thus in the comparison between IVN and EN it must be remembered that patients were not randomly allocated to IVN or EN.

Specific indications for NT

These are summarised in Table 8.1 and individually enumerated in Table 8.2.

The primary indications: a combination of weight loss and one or more complications of the disease. In all but 3 patients (4 NS periods) both of the primary indications were fulfilled. The 3 exceptions were:

Patient 1 to correct rapid weight loss in association with a secondary aim: severe protein depletion but without a primary aim.

Patient 25 (2 NT periods) for severe diarrhoea unresponsive to other therapies (normal weight).

Patient 26 to aid the healing of an enterocutaneous fistula (normal weight).

The remaining 16 patients received NT because of weight loss despite other therapy combined with one or more of the complications, generally characterised as being either severe symptoms unresponsive to other therapy or specific complications such as bowel obstruction or fistula (Table 8.2).

The secondary indications:

1. Correction of specific deficiencies.
2. To determine the effects of NT on disease activity.

Methods of providing NT

EN or IVN was administered as described in Chapter 2. The duration and type of NT for each patient is set out in Appendix 8.1 and the individual regimens and crude nitrogen balance results are in Appendix 8.2. Adjustments to the regimens were made to maintain positive nitrogen balance. Eleven patients had only one period of NT

TABLE 8.1

SUMMARY OF INDICATIONS FOR NUTRITIONAL THERAPY

M A I N I N D I C A T I O N S	E N (12) Number of periods	I V N (20) Number of periods
PRIMARY INDICATIONS		
1. REVERSE WEIGHT LOSS / INCREASE WEIGHT	10*	19*
2. TREATMENT OF COMPLICATIONS:		
Improve severe diarrhoea	4	4
Non-obstructive abdominal or rectal pain	1	6 (2 patients)
sub-acute bowel obstruction	3	4
Fistula or sinus in abdomen or perianal region	6	3
Intestinal failure	1 (at home)	12 (see text)
Miscellaneous:		
Promote linear growth/puberty	0	4
Treatment of 2^{ary} amenorrhoea	0	1
Sustaining pregnancy	1	1
SECONDARY INDICATIONS		
1. CORRECT SPECIFIC DEFICIENCIES:		
Protein Depletion		
* Albumin - mild - Pl. albumin 25-34 g/l	5	4
- severe- Pl. albumin <25 g/l	3	12
* Transferrin - Pl. transferrin <2 g/l	5	11
Other deficiencies		
Depletion of plasma magnesium (<0.7mmol/l)	0	7
Depletion of plasma zinc (<10.0 µmol/l)	0	6
Symptomatic calcium depletion (tetany)	0	3
Symptomatic vitamin A depletion (night blindness)	0	2
2. EFFECT ON DISEASE ACTIVITY**	A L L P A T I E N T S	

* 2 patients on EN and 1 on IVN were not underweight (see text)
** Patient No 1 had inactive disease by the simplified CDAI (CDAI=2)

TABLE 8.2

INDICATIONS FOR NUTRITIONAL THERAPY IN 19 PATIENTS

KEY o = Indication for E N
● = Indication for I V N

			COMPLICATIONS				DEFICIENCIES					
		INCREASE	IMPROVE	PAIN	S-A							Vit
No	Period	WEIGHT	DIARRHOEA	(abdo/rect)	OBST	FIST.	Alb	TF	Mg	Zn	Ca	A
1	1	●					●			●		
2	1	o				o						
19	1	o			o		o					
	2	●			●		●	●				
25	1		●									
	2			o								
26	1					o						
27	1	o				o	o	o				
28	1	o				o	o	o				
29	1	o				o	o					
30	1	o	o									
42	1	●		●			●			●		
47	1	●		●	●		●	●	●	●		
48	1	●	●				●		●	●	●	
	2	o	o		o		o	o				
49	1	●										
	2	●			●						●	
	3	●		●			●	●				
50	1	●				●	●	●	●			
	2	●				●	●	●	●	●		●
	3	●				●	●	●	●	●		
	[4]	Prolonged E N at home										
	5	●					●				●	
	6	●					●	●				●
51	1	●	●	●			●	●				
	2	●		●								
	3	●		●			●	●				
52	1	o	o					o	o			
	2	●	●					●	●	●		

(continued)

TABLE 8.2 (continued)

INDICATIONS FOR NUTRITIONAL THERAPY IN 19 PATIENTS

				COMPLICATIONS				DEFICIENCIES			
No	Period	INCREASE WEIGHT	IMPROVE DIARRHOEA	PAIN (abdo/rect)	S-A OBST	FIST.	Alb	TF	Mg	Zn	Ca
53	1	o (pregnant)			o		o	o			
	2	● (pregnant)			●		●	●			
54	1	o	o			o	o				
62	1	●					●		●		

(4 IVN; 7 EN), five had 2 periods, two had 3 periods and the remaining patient(No 50) in addition to 5 periods of IVN in hospital has been maintained for more than 3 years on EN at home. IVN was used for a total of 102 patient-weeks (average duration 5 weeks) while EN (excluding home EN in Patient 50) was used for 58 patient-weeks (average 5 weeks).

On special proformata, (Sheets 1-4: Appendix 2.4) all relevant clinical data were recorded to include pre-NT (baseline) information, and daily recordings to assess progress and especially to detect complications.

Various biochemical measurements were made as described in Chapter 2.

8.4 RESULTS

Short clinical biographies of all 19 patients who received NT are contained in Appendix 8.3. They include the indications, aims and results of NT in the context of other therapy.

PRIMARY INDICATIONS - WAS NUTRITIONAL THERAPY SUCCESSFUL?

1.WEIGHT AND ANTHROPOMETRY

Table 8.3 summarises the changes in weight and in triceps skinfold thickness (SFT) and mid-arm muscle circumference (MAMC) during nutritional therapy and summarises the overall energy intake and nitrogen balance results. Improvements in all anthropometric measurements occurred during IVN but not during EN and although mean starting values appeared higher in the EN group the differences did not reach conventional levels of statistical significance. Body weight increased in all patients receiving IVN the mean weekly increase being 1.6 Kg per week. However there were marked differences from 0.7 to 2.61 Kg per week. The overall weight change for the 20 periods of IVN is illustrated in Fig 8.1. Patients receiving EN had a lower weight gain (Mean 0.59 Kg per week). 4 patients lost weight during EN (Fig 8.1). 3 of these required subsequent IVN.

2.TREATMENT OF COMPLICATIONS

a)<u>Diarrhoea</u> (Table 8.4)

TABLE 8.3

WEIGHT AND ANTHROPOMETRIC CHANGES AND NITROGEN BALANCE DURING NUTRITIONAL THERAPY

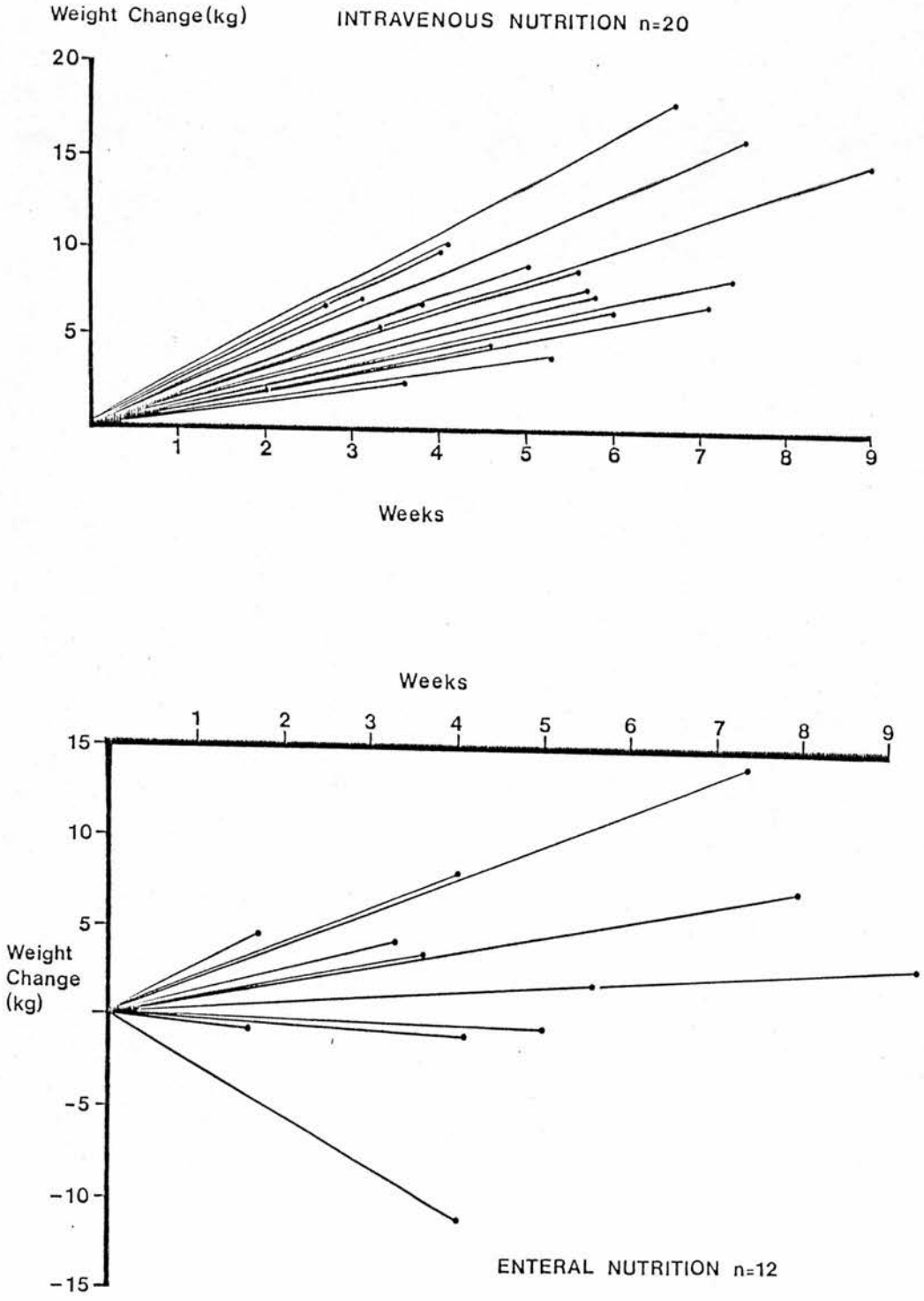
	E N		I V N	
	START	FINISH	START	FINISH
BODY				
WEIGHT Kg	47.1	49.9	43.8	51.9[3]
(S.E.M.)	(2.1)	(1.8)	(2.7)	(2.9)
% OF IDEAL (Mean)	80	85	75	89
SKINFOLD THICKNESS[1] mm	10.4	11.6	9.6	13.6[3]
(S.E.M.)	(1.6)	(1.1)	(1.0)	(0.8)
MUSCLE CIRCUMFERENCE[2] cm	18.7	19.4	16.9	18.7[3]
(S.E.M.)	(0.6)	(0.5)	(0.7)	(0.8)

	E N	I V N
ENERGY INTAKE(kcal/day)	3000	2413
(S.E.M)	116	100
(range)	2400-3600	1550-3390
NITROGEN INTAKE(g/day)	16.0	11.8
(S.E.M.)	0.5	0.5
(range)	12 - 18	9 - 17
NITROGEN BALANCE[4] (g/d)	+5.46	+2.16
(S.E.M)	0.68	0.46
(range)	+1.5 to +7.9	-0.7 to +7.0

Notes:
1 = Reference range for skinfold thickness: 12.5 - 16.5 mm
2 = Reference range for muscle circumference: 23.2 - 25.3 cm
3 = $p<0.05$ - Difference between start and finish
4 = Crude estimate based on product information data (intake) minus measured urine output and notional daily faecal nitrogen output of 2g.
+ = net retention of nitrogen
- = net loss of nitrogen

FIGURE 8.1

WEIGHT CHANGES DURING NUTRITIONAL THERAPY



The variability of weight change and duration of feeding are illustrated. Four patients on enteral nutrition lost weight

In six patients improvement in diarrhoea was considered to be a primary aim of NT. One of these (No 48) had periods of both IVN and EN separated by 7 months. Patient 52 had IVN immediately following failure of EN to relieve symptoms.

The role of EN

In patient 30 a combination of EN and corticosteroids resulted in sustained remission. Patient 48 had a sustained and dramatic improvement as a result of EN for 3½ weeks. As previously after IVN, he remained well after EN was stopped. In patient 52, treatment with EN was accompanied by a continuing rapid decline. It was therefore abandoned and IVN commenced after an infusion of albumin. In patient 54, EN resulted in no alteration in fistula consistency (watery) or quantity (Table 8.4).

In 3 of the patients with diarrhoea in which EN was employed, the elemental diet Vivonex was used as the sole food source. In the fourth EN fed patient No 30 (Table 8.4) Ensure was given as well as some oral food.

The role of IVN

IVN was used in four patients with varying degrees of 'bowel rest' with the restrictions on oral food and fluid intake indicated in Table 8.4.

In patient 48 (Table 8.4 and Appx 8.3) sustained success can be attributed to IVN with deprivation of oral food and restriction of fluid since there was no other change to his treatment and because IVN had been preceded by a prolonged period of ill health with constant severe diarrhoea. It seems that the crucial factor was a restriction of oral fluid intake. In patients 25 qnd 51 (Table 8.4 and Appendix 8.3), IVN had temporary benefit. In patient 52 total 'bowel rest' (nil by mouth) had no effect on his protein losing enteropathy but IVN did halt his nutritional decline and reversed his rapid weight loss while high dose intravenous corticosteroids resulted in remission of his diarrhoea within 48 hours (see Appendix 8.3).

b) Non-obstructive abdominal pain or rectal pain and sub-acute obstruction (Table 8.5)

TABLE 8.4

NUTRITIONAL THERAPY IN THE TREATMENT OF SEVERE DIARRHOEA

Patient Number	Type of NS	Duration w	Duration d	Drugs	ORAL food	ORAL fluid	COMMENTS
25	IVN	4	4	None	see text and below		Improvement in diarrhoea reversed when oral food restarted
30	EN	1	5	steroids	YES	YES	Improvement with EN and steroids
48	1, IVN	6	0	Cod, phos	see text and below		sustained success after IVN stopped
	2, EN	3	5	Cod, phos loperamide	NO	YES	Improved consistency and reduced volume of ileostomy output maintained after EN
51	IVN	5	4	Cod, phos	see text and below		Improvement during IVN not maintained
52	1, EN	4	0	see text	NO	YES	Failed, Patient deteriorated
	2, IVN	7	4	steroids	NO	see text	i.v. steroids probably responsible for dramatic improvement in diarrhoea
54	EN	8	0	Cod, phos loperamide	NO	YES	No alteration in fistula output or consistency (see details below)

CASE DETAILS

Patient 25 - IVN

	ORAL food	ORAL fluids	Bowel motions/ day
Baseline	soft	free	11,5
Week1	soft	free	7,8
2	soft	free	6,9
3	none	free	6,1
4	none	free	5,6
5	none	free	4,7
6	soft	free	6,2

Patient 48 - IVN

	ORAL food	ORAL fluids	Ileostomy Output (ml/day)
Baseline	soft	free	2300
Week1	none	free	2200
2	none	free	2400
3	none	<800	1500
4	none	<800	1000
5	none	<800	Formed
6	soft	free	Formed

Patient 51 - IVN

	ORAL food	ORAL fluids	Bowel motions/ day
Baseline	soft	free	>20
Week1	none	none	10,6
2	none	<500ml	3,9
3	none	free	1,6
4	none	free	5,1
5	soft	free	7
6	solid	free	5,3

Patient 54 - EN

	Fistula(ml/day)
Baseline	580
Week 1	525
2	356
3	572
4	590
5	489
6	604
7	575
8	603

The role of EN

patient 25 whose previous colectomy and ileorectal anastomosis was followed by a relapse with severe diarrhoea requiring IVN (Table 8.4) had several months of severe ano-rectal pain on defaecation. She quickly improved on EN and remained well for more than a year on a low-residue oral diet. In patient 48 EN without any other change in therapy was associated with a resolution of his obstructive symptoms and avoidance of surgery. He was still well 3 years later. In patients 19 and 53, EN was unsuccessful and had to be abandoned as described in the next paragraph.

The role of IVN

In patient 42, pain settled without other changes in therapy. Patients 49 and 51 had severe rectal symptoms, had undergone extensive previous surgical resections and further surgery was considered undesirable. While IVN was successful in correcting severe nutritional deficiencies, it had no effect even with 'bowel rest' in both cases on the anorectal symptoms and both patients underwent surgery during a period of IVN with a successful symptomatic outcome. All four with obstructive symptoms, patients 47, 49, 53 and 19 had undergone previous surgery. In all cases IVN was combined with deprivation of oral food and in 3 cases no fluid or only sips by mouth. In patients 47 and 49 symptoms quickly settled and immediate surgery was avoided. In both cases surgery was required later for new symptoms (Table 8.5). In the other two, patients 19 and 53 IVN followed immediately after EN had failed. In patient 19 symptoms were only partly relieved and recurred after oral food was re-introduced. Surgery resulted in a sustained remission. In patient 53 symptoms were partly relieved (vomiting but not abdominal pain)by IVN with 'bowel rest'. Her pregnancy proceeded to a successful conclusion and otherwise inevitable surgery was avoided. After the child was born her symptoms immediately improved and she was able to go home to look after her new offspring. However she required surgery several months later.

TABLE 8.5

NUTRITIONAL THERAPY (NT) IN THE TREATMENT OF PAIN AND SYMPTOMS OF SUB-ACUTE INTESTINAL OBSTRUCTION

Patient Number	SYMPTOMS	NT	w	d	Drugs	ORAL food	ORAL fluid	RESULTS AND COMMENTS
19	o	EN	1	6	None	NO	NO	EN poorly tolerated, Obstructive symptoms no better, EN abandoned + IVN,
	o	IVN	3	4	None	NO	NO	Temporary improvement in obstructive symptoms reversed by re-introduction of oral food, Subsequent surgery resulted in sustained remission
25	r	EN	5	4	None	NO	YES	Sustained improvement in anorectal pain, Remained well on low-residue diet, Resection of anorectal stricture 15 mo later, (No change in faecal output during EN),
42	a	IVN	5	5	SSZ	YES	YES	Was not on 'bowel rest', Symptoms improved without any other change in therapy, Surgery not required, Symptom free 9 months later
47	o	IVN	5	0	L	NO	NO	Abdominal pain and obstructive symptoms settled quickly with 'bowel rest', Remained well after IVN, Further surgery 12 months later (acute obstruction)
48	o	EN	3	5	CP L	NO	YES	Obstructive symptoms (and diarrhoea-Table 8,4) settled and he remained well after EN ceased Further surgery not required
49	o	IVN(2)7	3		SSZ	NO	YES	Obstructive symptoms quickly settled Further surgery avoided
	r	IVN(3)7	1		None	NO	YES	No improvement with IVN, Required surgical drainage of perirectal abscess, Then improved while IVN continued
51	r	IVN(1)5	4		CP	NO	YES	Because of extensive previous surgery, further op, was considered undesirable, She had severe anorectal
	r	IVN(2)2	5		None	NO	YES	disease and severe rectal pain requiring copious analgesics, While IVN corrected critical malnutrition
	r	IVN(3)5	0		None	NO	YES	but had no effect on her rectal symptoms, Had colectomy with sustained improvement 18 months later,
53	o	EN	5	0	S see text	NO	sips	Deteriorated with no alteration in symptoms Weight loss despite pregnancy proceeding,
	o	IVN	9	0		NO	sips	Successful outcome to pregnancy, Symptoms only partly relieved, Later required surgery,

SYMPTOMS; a = abdominal pain (constant often with local tenderness)
r = rectal/anal pain
o = symptoms of subacute obstruction (colicky pain, distension, vomiting confirmed by radiological features of intestinal obstruction

DRUGS; CP = codeine phosphate, L = loperamide, S = corticosteroids, SSZ = sulphasalazine

c)Abdominal or peri-anal fistulae (Table 8.6)

The role of EN

Various preparations were used in six patients for periods varying from 3 to 10 weeks and in all but one case oral food was withheld. Despite modest improvements in general nutritional state in all patients, only 2 of the six (Nos 27 and 28) had any temporary improvement in the external appearance or output from the fistula and in none did the fistula heal.

The role of IVN

IVN was used for this purpose in only one patient, a 34 year old man who can be regarded as having intestinal failure as described later. With regard to his entero-cutaneous fistula which followed a number of previous abdominal operations, IVN (without 'bowel rest') can be regarded as the factor responsible for healing his fistula as described in Table 8.6.

d)Treatment of Intestinal Failure

Four patients, numbers 49, 50, 51 and 62, described in Appendix 8.3, had features in common:

1. chronic diarrhoea unresponsive to anti-diarrhoeal drugs and courses of sulphasalazine and corticosteroids
2. Chronic malnutrition associated with severe fat malabsorption and body weight persistantly less than 80% of ideal for sex and height and associated nutrient depletion. Three of the four are depicted as having more than 5 laboratory abnormalities in the 'point prevalence' survey (see Table 3.2)
3. All had undergone previous bowel surgery which in two (49 and 51) resulted in extensive bowel resection (Table 8.7). Patient 50 retained most of his small bowel and half of his colon but had a chronic post-operative fistula and radiological evidence of diffuse disease in the remaining small bowel as did patient 62 who had a severe motility problems and severe malabsorption. Despite numerous laparotomies however, no bowel had been removed.
4. A requirement for recurrent NT

The three patients, numbers 49, 50 and 51 who received three or more

TABLE 8.6

NUTRITIONAL THERAPY IN THE TREATMENT OF FISTULAE

Patient Number	SITE OF FISTULA	NS	w	d	Drugs	ORAL food	ORAL fluid	RESULTS AND COMMENTS
2	ileo-rectal	EN (Ensure)	3	2	SSZ Metro	YES	YES	Discharge from fistula reduced but EN poorly tolerated. Fistula not healed
26	e-cut e-e, e-pelvic	EN (Vivonex)	4	1	Folate	NO	YES	Fistula remained unhealed. Further resection required.
27	r-vag	EN (Triosorbon)	10	0	Metro	NO	YES	By week 5, vaginal discharge had ceased. Recurred when oral food re-introduced, 9 months later diverting colostomy-healed.
28	e-cut	EN (Triosorbon)	7	3	Zinc	NO	YES	Wound fistula following colectomy. Part healing during EN. Left with small wound sinus. Would not accept further surgery
29	peri-anal	EN (Ensure)	4	0	SSZ, L	NO	YES	No alteration in fistula. Colectomy required
50	e-cut ?e-e	IVN(1)	4	1	CP Lom	YES	YES	The fistula followed multiple ops. During each period of IVN, fistula completely healed despite oral nurients
	Interval - 5 months							
		IVN(2)	3	2	CP Lom	YES	YES	which he would not forego, being taken throughout IVN. Although further IVN (see text) required, fistula remained healed
	Interval - 3 months							
		IVN(3)	6	6	CP Lom	YES	YES	
54	e-cut	EN (Vivonex)	8	0	CP, L	NO	YES	No healing. (No alteration in faecal effluent - see Table 8.4). Would not consider further surgery

SITE OF FISTULA: e-cut = enterocutaneous (to anterior abdomonal wall), e-e = entero-enteral, e-ves = entero-vesical, e-pelvic = communication between bowel and free pelvic cavity
r-ves = recto-vesical, r-vag = recto-vaginal

DRUGS: CP = codeine phosphate, L = loperamide, Lom = Lomotil, S = corticosteroids, SSZ = sulphasalazine, Metro = metronidazole

TABLE 8.7

NUTRITIONAL THERAPY IN INTESTINAL FAILURE

Pt	Bowel	Sm. bowel	Periods	Total IVN	Ideal	BEFORE INTERVAL				AFTER INTERVAL				Latest
No	Resect.	Remaining	of IVN	(weeks)	Wt(Kg)	Kg	%ideal	Yr	Mo	Kg	%ideal	Yr	Mo	Weight
49	2	200 cm	3	16	46[1]	35	75	3	2	44[2]	96	--	--	--
50	1	All but 150 cm	5	21	75	58	77	3	2	74	99	1	6	70[3] (96%)
51	1	100 cm	3	13	50	32	64	2	6	38	76[4]	2	0	37[5] (74%)

Notes:

1 Ideal weight rising throughout the period (puberty). Therefore weight after IVN (44Kg) probably much less than 96% of ideal

2 Subsequent sustained clinical improvement without requirement for further IVN followed resection of diseased rectum including an abscess

3 Continues on Enteral Nutrition at home

4 Came to emergency colectomy for fulminant colitis during third period of IVN

5 Remains chronically underweight but clinically well with an ileostomy

periods of IVN in our department are depicted in Figure 8.2 and Table 8.7. As Fig.8.2 indicates all three suffered rapid weight loss (usually to less than 80% of ideal weight) after gaining weight during IVN. In different ways their chronic nutritional problems have to some extent resolved.

Patients 49 and 51, who had undergone extensive previous resections (Table 8.7), had active disease in their distal colons. After further resections of the diseased bowel, their general health underwent a sustained improvement and patient 49 passed through a late but normal puberty. The other, while feeling well with an ileostomy which she previously would not have accepted, remained grossly underweight at less than 40Kg. A different strategy was adopted in patient 50. During his third admission for IVN it was decided to commence him on EN at home, as described in Appendix 8.3. Despite this regimen his weight fell but at a much slower rate (fig 8.2) and his fistula remained healed. After home EN was commenced he remained out of hospital for 16 months before having a 'top-up' period of IVN. He has continued on this EN regimen at home, and when reviewed 3 years and 5 months after EN had started, his weight was 70 Kg (97% Ideal). The success of this regimen is indicated by the continued absence of his fistula and by improved quality of life: before home EN he spent more than half of two years in hospital. After EN was started he spent only 2 months in hospital in 3½ years. Patient 62, described in Appendix 8.3, is illustrated in Fig 8.3. This 17 year old girl was the most severely malnourished of all. She had been ill for 10 years with diffuse and widespread disease, chronic diarrhoea, steatorrhoea, multiple deficiencies, especially of fat-soluble vitamins, and growth failure. She had received in the paediatric wards a number of courses of IVN resulting in increasing difficulty in gaining vascular access due to venous thrombosis. EN had been attempted but was not tolerated. Further IVN was given but was terminated by the development of superior vena cava obstruction which became chronic. Her next four years were characterised by recurrent episodes of non-mechanical intestinal obstruction, tetany due to Mg and Ca deficiency, night blindness

FIGURE 8.2

NUTRITIONAL THERAPY IN INTESTINAL FAILURE

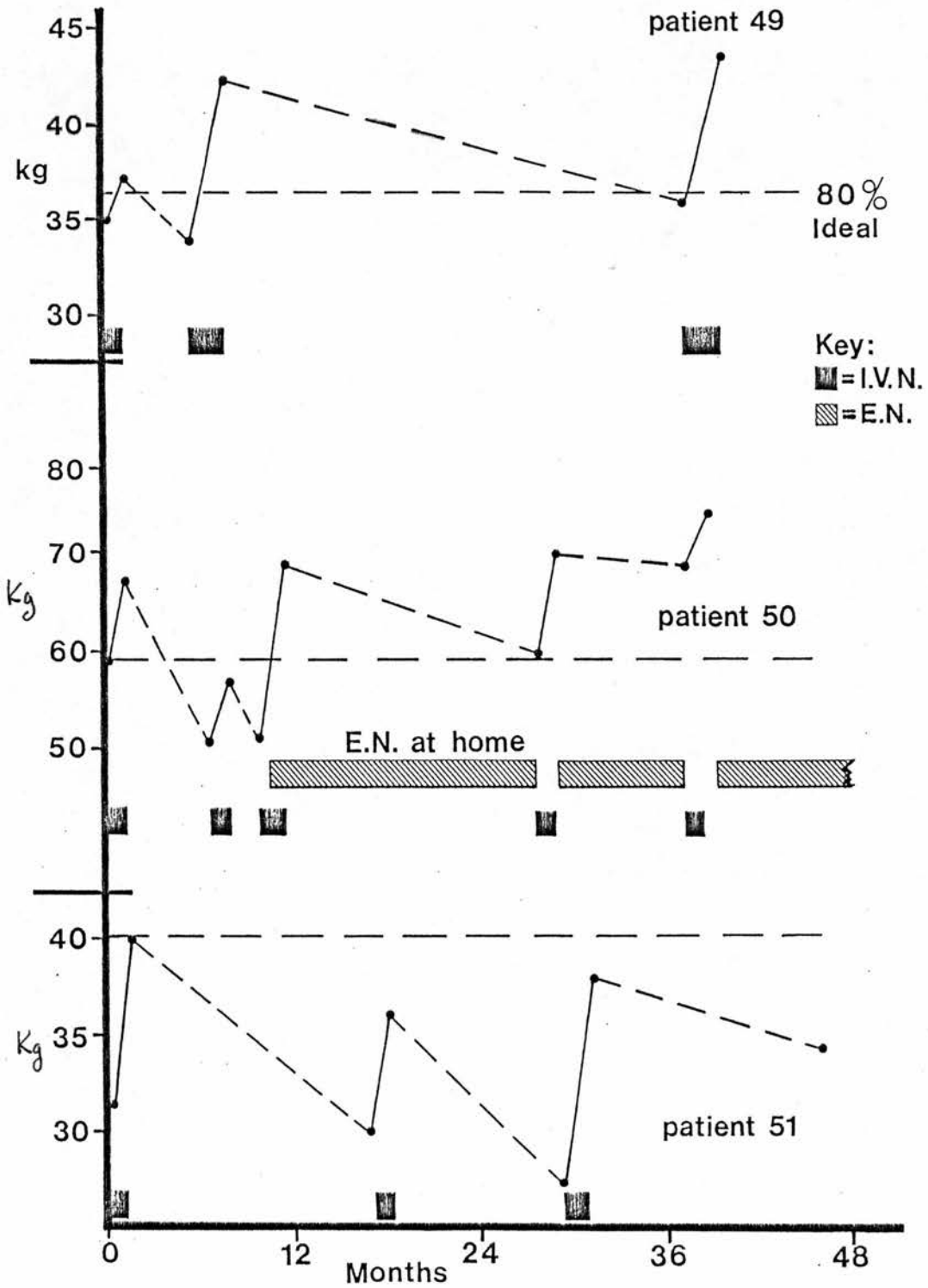
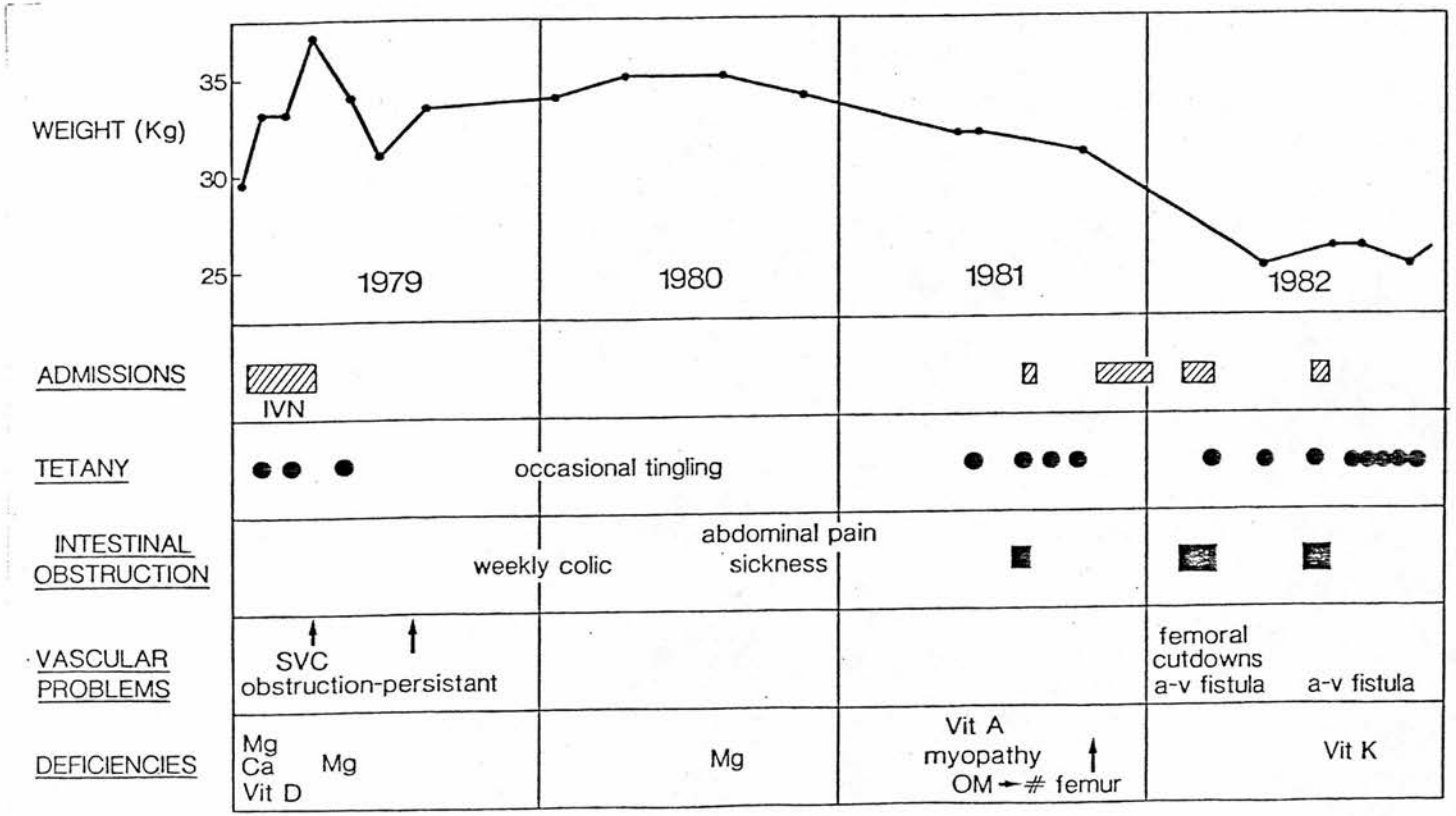


FIGURE 8.3

PROBLEMS ENCOUNTERED BY PATIENT 62



due to Vitamin A deficiency, a fractured femoral shaft due to osteomalacia and progressive difficulty in achieving vascular access including two unsuccessful attempts to create a permanent arterio-venous fistula. Eventually she died when the collateral venous supply to the right side of her heart (via the azygous system) failed.

e)Miscellaneous complications

(i)Failed puberty

Patient 49, described above and in Fig 8.2 (top diagram) was 18 years old before attending for investigation of failed puberty. The 80% estimate of ideal weight (36.5 Kg) was based on his height at the start of his hospital career and can be regarded as a gross underestimate. He had no secondary sexual characteristics during this period of chronic ill-health which followed emergency surgery and extensive bowel resection. Some pubic hair was observed in the Spring of 1980 (Age 21). It was not until after his final operation during his third period of IVN that his voice broke and subsequently with a weight sustained above 45 Kg his penis enlarged and he developed axillary hair. Patient 62 described earlier and illustrated in Fig 8.3 never had any secondary sexual characteristics up to her death at the age of 23.

(ii)Treatment of secondary amenorrhoea

Patient 42 A 36 year old woman (patient 42) with a six year history of colonic and terminal ileal disease and no previous surgery, had been well for 5 years. Despite sulphasalazine she relapsed with a five month history of vague abdominal pain and anorexia. Over the period her weight fell 10 Kg to 36 Kg (73% Ideal) associated with secondary amenorrhoea. She was unable to take food supplements and continued to lose weight. She had a tender rather ill defined mass in the right iliac fossa but surgery was not considered necessary. During IVN her abdominal pain improved (Table 8.5) and she gained weight and her appetite also improved. During the final week of IVN normal menstruation

returned. At review 9 months later she was well with regular menstrual periods.

(iii)Sustaining pregnancy

Patient 53 is described in Appendix 8.3 and fully discussed in the reprint of the case report which is enclosed in the thesis. Briefly, obstructive symptoms were worsening as her pregnancy proceeded and both EN and steroid therapy failed to relieve her symptoms. Only when IVN was introduced was weight loss reversed and pregnancy proceeded to term. I believe this is a unique achievement of IVN in Crohn's disease.

A summary of the achievement of these primary indications (major complications) is contained in Table 8.8.

SECONDARY INDICATIONS

1.CORRECTION OF DEFICIENCIES

a)Protein depletion

Of the 19 patients treated with NT, all but 3 had plasma levels of albumin below the reference range of 35g/l. In most cases plasma transferrin concentration was also low (<2g/l) (Table 8.2). Thus correction of low plasma albumin was considered an aim of nutritional therapy in most cases.

(i)Symptomatic protein depletion

Details of patients with symptomatic protein depletion (oedema) and in others with severe hypoalbuminaemia (<25g/l) are indicated in Table 8.9. Oedema was a significant clinical problem in 3 patients all of whom had plasma albumin concentrations less than 20g/l. In all 3 protein infusions or whole blood were given in addition to NT.

In patient 48 severe oedema did not resolve until the 4th week of IVN, 3 weeks after a blood transfusion (Table 8.8). Patient 50 had only transient resolution of his oedema during IVN. It is of interest that his oedema remained a minor problem during his prolonged treatment with EN at home. Patient 52 who was severely protein depleted before EN had no oedema until after EN was

TABLE 8.8

SUMMARY OF THE ACHIEVEMENTS OF NUTRITIONAL THERAPY
IN THE TREATMENT OF MAJOR COMPLICATIONS

	SUCCESS RATE		
COMPLICATION	E N	I V N	
Diarrhoea	1 / 4	1 / 4	Further 2: temporary improvement
Pain (non-obstructive)	1 / 1	0 / 6	Two patients each had IVN x 3
(obstructive)	1 / 3	2 / 4	
Fistula	0 / 6	3 / 3	Recurrent fistula 1 patient
Intestinal failure	1 / 1	11 / 12	In 3 out of 4 patients
Linear growth	---	0 / 4	IVN + surgery successful in one
Secondary amenorrhoea	---	1 / 1	
Sustaining pregnancy	0 / 1	1 / 1	
TOTAL SUCCESSES	4 / 16	19 / 35	

TABLE 8.9

NUTRITIONAL THERAPY IN THE TREATMENT OF SEVERE PROTEIN DEPLETION
(SERUM ALBUMIN LESS THAN 25 g/l)

Patient Number	NT	Duration w	d	Protein infusion	Serum Albumin (g/l) BEFORE	AFTER	Nitrogen Balance (g/d)	COMMENTS
19	EN	1	6	NONE	23	21	C	No oedema, EN poorly tolerated, IVN given
	IVN	3	4	90g albumin before IVN	21+47	37	+0,6	No oedema
47	IVN	5	2	NONE	24	25	+2,2	No oedema, Remission during IVN
48	IVN	6	0	3 0 whole blood-Wk 1	17	25	+1,4	Severe oedema resolved by week 4 Diarrhoea settled(see text)
	EN	3	5	NONE	24	25	+4,5	No oedema, Diarrhoea settled
49	IVN(3)7		1	135g albumin before IVN	17+28	36	+3,7	After initial protein infusion, se Alb 28, then steady fall till surgery during week 4(Appx 8,3), Then rapid rise in serum albumin, No oedema,
50	IVN(1)4		1	90g albumin before IVN	17+27	32	+3,9	Oedema appeared during refeeding and persisted
	IVN(2)3		2	90g albumin during IVN	16	25	+3,2	Oedema resolved during IVN
	IVN(3)6		6	6 0 PPPS in week 2	18	36	+2,6	Oedema resolved
	IVN(5)3		1	90g albumin during IVN	23	32	+5,2	Oedema improved but remained clinically evident after IVN and became a chronic minor problem despite maintenance of serum albumin at >30g/l
51	IVN(1)5		4	NONE	24	40	+1,0	No oedema
	IVN(3)5		0	NONE	25	20	C	Developed fulminant colitis requiring colectomy
52	EN	4	0	NONE	16	16	C	Dehydration at start, Oedema appeared during EN, 5g of N per day in copious faecal effluent,
	IVN	7	4	135g albumin before IVN	16+27	37	+3,9	Remission and resolution of oedema during IVN induced by steroid therapy
53	IVN	9	0	NONE	22	25	+3,8	No oedema, Successful outcome to pregnancy,

N, Balance = IV or enteral N, intake less Urine N + arbitrary faecal N of 2g/d
C = Urine samples contaminated with faeces or incomplete (<2 complete 24 hour collections per week)
PPPS = purified plasma protein solution

commenced. The oedema remained until mid-way through his subsequent period of IVN after his severe protein losing diarrhoea was controlled by intravenous steroid therapy.

Thus NT alone was not tested as a cure for oedema and the fluid stress of NT in association with protein depletion on occasions made matters worse.

(ii)Effects of NT on plasma protein concentrations

To assess the overall effects of NS on protein levels, patients who received infusions of blood or protein were excluded from analysis. Thus 15 out of the 20 IVN periods and 10 of 12 EN periods were examined.

EN. (Mean duration 5 weeks)

Serum albumin concentrations did not rise during EN although similar starting values to IVN were observed. Before-32.3±5.4: after-33.6±5.0 g/l (Mean ± standard deviation). Neither was there a significant rise in transferrin levels: 2.2±0.6 to 2.7±0.6. Transferrin levels were however significantly higher before EN than before IVN ($p<0.05$).

IVN. (Mean duration 5 weeks)

There was a significant rise in serum albumin concentration from 32.8±8.1 to 35.7±7.8 g/l ($p<0.05$) and in serum transferrin concentration from 1.5±0.8 to 2.5±1.0 ($p<0.01$)

b)Other deficiencies Table 8.10

Depletion of plasma magnesium

Plasma magnesium concentration was low (<0.7 mmol/l) in 5 patients before IVN. Two patients had tetany associated with combined calcium and magnesium depletion and were given electrolyte infusions to treat these symptoms before commencement of IVN. Chapter 4 gives more detailed consideration to magnesium status, and chapter 9 examines in greater depth the requirements for magnesium supplementation during IVN.

Depletion of plasma zinc

Plasma zinc concentration was low (<10.0 µmol/l) before 6 periods of

TABLE 8.10

NUTRITIONAL THERAPY IN THE TREATMENT OF OTHER DEFICIENCIES

MAGNESIUM DEPLETION (plasma concentration < 0.7 mmol/l)

Patient Number	IVN w	d	Supplement per day (mmol)	Plasma conc, (mmol/l) BEFORE	AFTER	COMMENTS
47	5	2	12,8	0,61	0,82	No symptoms of Mg deficiency
48	6	0	15,0	0,40	0,70	Developed tetany before IVN, Also calcium depleted (text)
50(1)	4	1	13,5	0,38	0,59	No symptoms, Plasma concentration remained low,
(2)	3	2	6,3	0,55	0,66	No symptoms, Plasma concentration remained low,
(3)	6	6	14,6	0,58	0,70	Supplement only just sufficient to raise plasma level to normal
52(2)	7	4	11,5	0,63	0,74	No symptoms
62	3	6	6,5	0,59	0,99	Many episodes of tetany see text and Fig 8,3, Calcium and Mg depletion were constantly present despite supplements

ZINC DEPLETION (plasma concentration < 10.0 µmol/l)

Patient Number	IVN w	d	Supplement per day (µmol)	Plasma conc, (µmol/l) BEFORE	AFTER	COMMENTS
1	5	6	120	7,9	11,4	
42	5	5	112	6,4	16,6	Rapid weight loss and abdominal mass ? abscess
47	5	2	125	7,2	10,9	Very ill before IVN, Vomiting and abdominal distension
48	6	0	120	7,7	9,9	Severe diarrhoea low serum albumin and tetany (see above)
50(2)	3	2	109	5,4	11,3	Fistula, severe malnutrition including low serum albumin
(3)	6	6	108	9,8	9,2	

TETANY AND PLASMA CALCIUM LEVELS BEFORE IVN
(Normal range - 2.2-2.6 mmol/l)

Patient Number	Plasma calcium (mmol/l)	plasma albumin (g/l)	'adjusted' pl, calcium* (mmol/l)	
48	1,50	17	2,06	* - Plasma Ca + [0,02x(45-pl alb)]
49(2)	1,65	40	1,75	
50(6)	1,70	44	1,72	

IVN (5 patients). None had symptoms of zinc deficiency. Associated plasma protein depletion was characteristic. Chapter 9 examines zinc status and intravenous requirements during IVN.

Symptomatic calcium depletion

Tetany occurred in 3 patients before IVN. Plasma calcium levels, adjusted for plasma albumin were low (< 2.2 mmol/l). Patient 48 also had severe magnesium depletion. It is of interest that only one of these patients was protein depleted when tetany occurred. All patients were given calcium infusion for symptomatic treatment and maintained on calcium supplements during IVN.

Symptomatic vitamin A deficiency

Patient 50 developed severe night blindness in association with other deficiencies. The influence of IVN which included vitamin A supplements is illustrated in Figs 6.2 and 6.3.

2. REDUCTION IN DISEASE ACTIVITY

The Simplified Crohn's Disease Activity Index (CDAI) shown in Table 1.2 (Harvey 1980) was used to judge the overall clinical effect of NT in association with bed or chair rest. Details of other therapy are contained in Appendix 8.1. In the majority of patients other treatment was unaltered during NT except, as indicated in Appendix 8.1, in three circumstances:

(i) 4 patients required a short course of antibiotics during IVN.

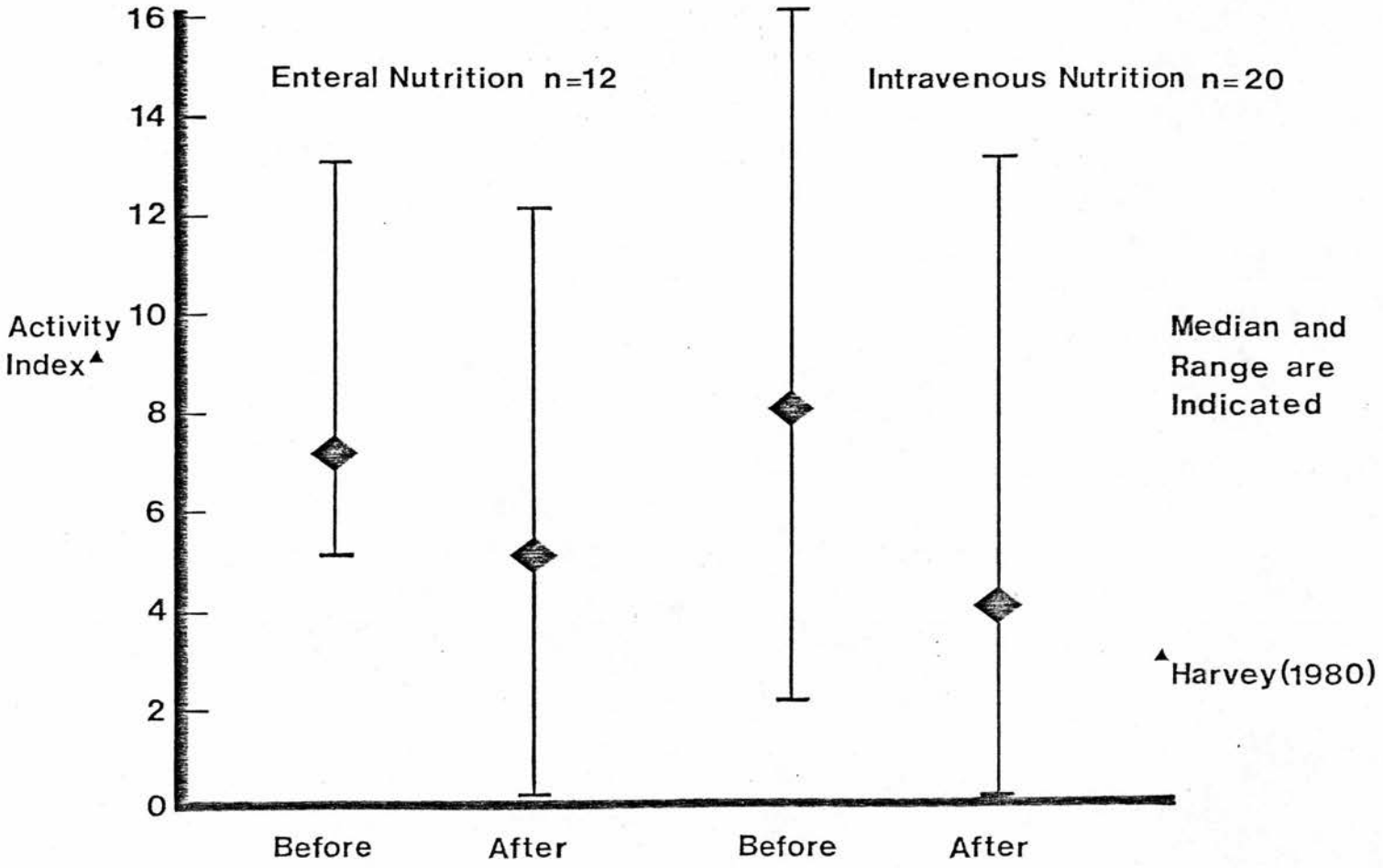
(ii) Change in specific therapy: Intravenous corticosteroids were commenced during IVN in patient 52, and oral prednisolone during EN in patient 53 (See Fig 8.4).

(iii) Change in anti-diarrhoeal drugs: in patient 42, loperamide was commenced during week 3 and in patient 51, codeine phosphate was stopped during the third week of IVN.

There was an improvement in CDAI during both EN (Median score (7 to 5) and IVN (Median score 8 to 4) as depicted in Figure 8.4. With EN, the score fell during 10 of the 12 periods. In 1 it remained the same and in 1 there was a slight rise from 11 to 12. CDAI was lower after 17 of the 20 periods of IVN. In 2 the CDAI remained the same and in

FIGURE 8.4

EFFECTS OF NUTRITIONAL THERAPY ON DISEASE ACTIVITY



the third a rise from 11 to 13 was followed by emergency colonic surgery. Changes in CDAI cannot therefore in this uncontrolled observation be attributed necessarily to the effects of NT alone. For example in patient 53 who received corticosteroids went into remission while his CDAI fell from 7 to 0.

The achievements of NT (and other changes in therapy) in respect of disease activity can at best be regarded as modest: Only 5 of the 12 EN periods and 8 of the 20 IVN periods resulted in inactive disease (CDAI < 5).

8.5 COMPLICATIONS OF NUTRITIONAL THERAPY

ENTERAL NUTRITION (Table 8.11)

Complications directly related to EN were uncommon. In only 2 of the 12 was EN abandoned because of feeding complications (one requiring IVN). An additional 2 patients continued to deteriorate despite EN and required IVN.

INTRAVENOUS NUTRITION (Tables 8.12 and 8.13)

Although a detailed study of complications of IVN was undertaken many of the issues are not peculiar to Crohn's disease. However an overall impression of the impact and severity of complications is essential in a balanced appraisal of the worth of IVN in Crohn's disease. This is especially true when complications can compromise possible benefits of therapy (or may even be life-threatening) and in circumstances when a major symptom such as pyrexia causes difficulties in management since it may be due to either cannula related infection or to the disease itself or its complications. For the purposes of this thesis, investigation was confined to problems of safe delivery of intravenous nutrients to the patient and to the causes and investigation of pyrexia during IVN.

Premature stopping of IVN - Table 8.12

This occurred in 6 out of the 20 periods of IVN. In 2 cases the patient required urgent surgery for complications of severe disease. In one patient (No 62) the life threatening complication of superior

TABLE 8.11

COMPLICATIONS OF ENTERAL NUTRITION

Patient Number	Duration w	Duration d	Stopped prematurely	COMPLICATIONS
2	3	2	YES	Bloating and poor tolerance of naso-gastric tube
19(1)	1	6	YES	Vomiting++. Poorly tolerated and abandoned.
25(2)	5	4	NO	NONE
26	4	1	NO	NONE
27	10	0	NO	NONE
28	7	3	NO	NONE
29	4	0	NO	NONE
30	1	5	NO	NONE
48(2)	3	5	NO	NONE
52(1)	4	0	YES	NONE, but severe diarrhoea continued with decline in weight. EN abandoned
53(1)	5	0	YES	NONE, but pre-EN vomiting and abdominal pain did not settle. EN abandoned
54	8	0	NO	NONE

TABLE 8.12

COMPLICATIONS OF INTRAVENOUS NUTRITION

A. PREMATURE STOPPING OF IVN in 6 out of 20 periods

	Patient
(i)Complications of IVN - Proven I.V cannula infection -	50(2)
- Recurrent pyrexia ? cause -	49(1)
(settled after IVN stopped) -	51(2)
- Superior vena cava obstruction -	62(1)
(ii)Complications of Crohn's disease	
- Fulminating colitis requiring emergency surgery -	51(3)
- Arterial bleeding from diseased rectum req. surgery-	49(3)

B. PROBLEMS RELATING TO INTRAVENOUS CANNULAE

Studied in 15 of the 20 IVN periods (insuff. data in 5)

(i)No of cannulae per IVN period. 4 IVN periods: 1 cannula
6 IVN periods: 2 cannulae
TOTAL 32 cannulae. 4 IVN periods: 3 cannulae
1 IVN period: 4 cannulae

(ii)Reasons for removing 32 catheters (more than one in 5 cases).

	Number
Intended termination of IVN	11
Cannula infection	6
Cannula block (gravity feed)	5
Cannula fell out	3
Pyrexia of uncertain cause	3
Pneumothorax after insertion	2
Superior vena cava obstruction	1
Pulmonary embolus	1
Other reasons (leakage, catheter breakage, local phlebitis, cannula in jugular vein, routine change)	5

(iii)Impact of technical improvements in nutrient delivery

	Number of cannulae	Feeding Days	Mean duration of cannula (days)
TOTAL	32	587	18
GRAVITY FEED WITH 500 ml BOTTLES	24	366	15
PUMP FEED WITH 3000 ml BAGS	8	221	28

vena cava obstruction occurred. Before coming under my care she had undergone several periods of IVN as a child and had previous problems with venous access. In the remaining 3, cannula infection was probably responsible.

Problems relating to intravenous cannulae - Table 8.12

The reasons for removing 32 cannulae: intended termination of IVN in 11 cases, cannula or feed-delivery problems in 11 (infection 6; blockage 5). In the earlier part of the study when nutrients were delivered by gravity feed, 3 bottle changes were required each day. When electrical peristaltic pumps (IVAC UK) and 3 litre feed receptacles were introduced there was a marked improvement in cannula 'life' from 15 to 28 days.

Problems relating to pyrexia - Table 8.13

Pyrexia (>37°C) was extremely common accounting for 47% of days of IVN (257 out of 546 days). The main diagnostic problem was whether this generally sick group of patients were suffering from the effects of the disease or complications of IVN. No formal comparison was made between the prevalence of pyrexia on and off IVN but low grade pyrexia was generally common in our hospitalised Crohn's patients. However when pyrexia was sustained above 38°C the cause was much easier to determine. There were 15 such major episodes. and the explanations were usually forthcoming (Table 8.13). The commonest cause was cannula related infection in 9 cases.

Routine swabs from the cannula site gave a low yield of positive cultures (Table 8.12) and even in the 13% which were positive there were frequently no local or systemic signs of infection. However culture of the tips of 10 cannulae was more helpful. 7 out of 10 yielded positive results and all 3 patients with sustained pyrexia >38°C yielded organisms considered responsible for the infection. Nevertheless removal was the only therapy required. Only 5 out of 43 'drawback' blood cultures (12%) were positive but 4 of the 5 positive results were associated with major pyrexia >38°C (Table 8.13), 2 cannula related and 2 associated with intra-abdominal sepsis.

TABLE 8.13

COMPLICATIONS OF INTRAVENOUS NUTRITION (continued)

C. PROBLEMS WITH PYREXIA DURING IVN

Studied in 15 of the 20 IVN periods (insufficient data in 5)

Patient (IVN)	TEMP >37°C Days/Total*	SUSTAINED PYREXIA >38°C - Explanation	EVIDENCE FOR CANNULA RELATED INFECTION† Cann. site	Cann. tip	Blood culture
1(1)	27 / 42	Active disease ? abscess	-	-	-
25(1)	11 / 33	Cannula infected (pus at site)	+	o	-
42	9 / 38	Catheter blocked (? infected)	-	-	-
47(1)	2 / 35	NONE	o	o	o
48(1)	27 / 41	1, Active disease+chest inf, 2, Cannula block/infected	- +	o +	o o
49(1)	2 / 14	Cannula infection (temp settled when cann. out)	-	-	+(S.epid.)
49(2)	21 / 54	1, Cannula infection 2, abdo. abscess+septicaemia	+ -	+ -	o +
50(1)	20 / 29	Abdominal abscess	o	o	+(S.aureus)
50(2)	19 / 23	Cannula infected/blocked	+	-	+
50(3)	29 / 39	NONE	-	-	-
51(1)	9 / 40	NONE	o	o	o
51(2)	25 / 29	1, Cannula infection 2, Rectal abscess	- -	+ -	- -
52(2)	27 / 62	1, PTE ? cannula infection 2, ? cannula infection	- -	- -	- -
53(2)	4 / 63	NONE	o	o	o
62(1)	25 / 40	Superior vena cava obstruction	-	-	-

Abbrieviations:S.=Staphylococcus, PTE=pulmonary thrombo-embolism

‡ = discrepancies between this total and duration of IVN are due to either short periods without cannulae during period of IVN (TOTAL < IVN) or times when cannula is used for purposes other than IVN (TOTAL > IVN).

† = The search for catheter related infection involved bacteriological culture of swabs from the site of entry through the skin of the I.V. cannula (Cann. site), culture of the tip of a removed cannula (Cann. tip) and blood culture. + = positive culture, - = negative culture, o = culture not done. (Blood culture was a 'drawback' sample from the catheter hub)

TABLE 8.13 (continued)

C. PROBLEMS WITH PYREXIA DURING IVN

SUMMARY

Causes of 15 episodes of sustained pyrexia >38°C

CANNULA RELATED INFECTION - Definite*	6
- probable	3
ACTIVE CROHN'S OR COMPLICATIONS	5
Superior vena cava obstruction	1
Pulmonary thromboembolism	1
Chest infection	1

(More than one cause in 2 patients)

* = Cannula related infection considered define when pyrexia was associated with positive culture from cannula site and/or removed cannula tip or in one case when S. epidermidis was cultured from the blood. Probable infection was the combination of pyrexia with red or infected looking cannula site but in the absence of positive cultures

Yield from routine bacteriological investigations

	NUMBER	POSITIVE		ORGANISMS		
		No	%	S. epid.	S. aureus.	Other
Swab from cannula site (Every 2-3 days)	248	32	13	15	8	9
Cannula tip (if pyrexial)	10	7	70	4	-	3
'Drawback' Blood culture (if pyrexial)	43	5	12	3	-	2

S. epid. = Staphylococcus epidermidis
S. aureus = Staphylococcus aureus

8.6 SUMMARY

Nineteen patients with severe Crohn's disease were given NT in the form of EN (58 patient weeks; 12 periods; average duration 5 weeks) or IVN (102 patient-weeks; 20 periods; average duration 5 weeks). Assessment was based on the achievements of predetermined primary aims: changes in body weight (and other anthropometric measurements) or successful resolution of severe unresponsive symptoms or complications. During EN, weight increased by an average of only 0.6 Kg per patient per week, with no overall significant improvement and weight loss in 4 patients. Of the complication episodes it achieved success in only 4 of 16. During IVN, weight and other anthropometric measurements rose significantly with a mean weight rise of 1.6 Kg per week. Of 35 complication episodes, greatest success was achieved in the intermittent management of intestinal failure: successful in 11 out of 12 episodes. Secondary aims were also identified: correction of deficiencies and reduction in disease activity using a simple global clinical score. EN resulted in no significant improvement in plasma proteins Mean serum Alb: before-32.3; after 33.6; TF: before-2.2; after-2.7 g/l. There was a modest reduction of disease activity (score 7 to 5). In contrast during IVN, a significant rise in albumin (32.8 to 35.7 g/l) and in TF (1.5 to 2.5 g/l) was observed with a fall in activity score from 8 to 4. Complications of EN limiting its use occurred in 2 out of 12 cases. Problems with IVN were more serious and resulted in premature stopping of IVN in 4 periods and premature removal of 11 out of 32 intravenous cannulae. The most serious was superior vena cava obstruction. The other main problem was pyrexia. Of 15 major episodes, cannula related infection was responsible for nine (60%). The other main cause was active disease or intra-abdominal abscess. New technology (electrical pumps and 3 litre feed receptacles) improved cannula life from 15 to 28 days

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 9

MAGNESIUM AND ZINC REQUIREMENTS DURING INTRAVENOUS NUTRITION

9.1 AIMS

1. To determine daily intravenous magnesium (Mg) requirements during intravenous nutrition (IVN) by relating intravenous intake to serum and urine Mg levels.
2. To determine intravenous zinc (Zn) requirements by relating the results of Zn measurements to the quantity of Zn given, clinical progress and changes in various nutritional indices. Serum and urine Zn measurements were considered in relation to serum protein changes, body weight, skinfold thickness and muscle circumference and an estimate of nitrogen (N) balance.

9.2 PATIENT SELECTION

Ten of the nineteen patients described in Chapter 8 were studied. They received 14 periods of IVN for 64 complete weeks. The reasons for IVN and their general clinical progress are described in Chapter 8. One patient had disease confined to the small bowel, one had large bowel disease and the remaining eight had large and small bowel involvement. Thus they were predominantly patients with widespread disease.

9.3 METHODS

Magnesium.

Methods of measuring Mg in serum and urine are described in Chapter 2 and criteria for determining Mg status were the same as in Chapter 4. Data were available for 60 of the 64 patient-weeks of IVN.
Intravenous Mg was supplied from 3 sources: Amino acid Solution:5 mmol/l (Synthamin-Travenol Laboratories); Trace mineral solution: 1.5mmol/vial (Addamel-KabiVitrum); Mg sulphate solution(50%): 2mmol/ml. Total Mg intake was calculated as a daily average for each patient-week of IVN and weekly serum and urine values were the average of two measurements. It was thus possible to relate IV Mg intake to Mg status during IVN and to assess the minimum amount of Mg required to maintain normal Mg status during IVN. Statistical comparisons between the intake groups were by Fisher's modification of Yates's Chi-squared test.

Zinc.

Serum and urine Zn measurements were carried out as described in Chapter 2. Out of the 64 complete patient-weeks of IVN, data are available for 57 weeks for serum Zn concentration and 59 weeks for urine Zn output.

Intravenous Zn was from two sources: Trace metal solution: 20μmol/vial (Addamel-Kabi-Vitrum) and Zn sulphate solution: 100 μmol (6.5mg)/vial. Daily Zn supply, and weekly serum and urine Zn levels were measured as for magnesium. Control groups are described in Chapter 2. Serum albumin and serum Zn values were also compared in the following groups:

(i)50 fasting patients about to undergo minor orthopaedic operations (controls).

(ii)21 patients in hospital with active inflammatory bowel disease.

(iii)all 10 patients throughout their IVN.

Statistical comparisons were by a Mann-Whitney test, but in addition, mean values and standard errors (SEM) are quoted. Relationships between serum albumin and serum Zn were examined by linear regression analysis.

Provision of IVN followed the principles described in Chapters 2 and 8 and its nutritional monitoring is described in Chapter 2.

9.4 RESULTS

Pre-IVN status (Table 9.1)

All but two patients were 80% or less of standard weight for height. Pre-IVN Mg status was examined in Chapter 4. Serum Zn values (mean±SEM μmol/1) in the 10 Crohn's patients (9.9±1.0) were less than in the 36 controls (13.2±0.3; $p<0.01$). Urine values (mean±SEM μmol/24h) for eight of the Crohn's group (3.3±0.6) were less than in 12 controls (7.0±0.8; $p<0.01$). No patients had clinical signs of Zn deficiency.

Progress on IVN

The nutritional state of all patients improved with increases in body

TABLE 9.1

BASELINE NUTRITIONAL STATE AND PROGRESS ON IVN

IVN				Baseline and weekly			Baseline and total Change (Δ) during IVN						N. balance	Mean daily
No	Per.	w	d	weight	change Kg	%ID* Δ	Se Albumin g/l	Δ	Se T.ferrin g/l	Δ	Se zinc µmol/l	Δ	+ = retention - = loss (g/day)	Zinc supply µmol/day
1	1	5	6	35	69	+1,6	29	+2	2,0	+0,4	7,9	+3,5	+0,3**	120
25	1	4	4	58	103	+0,9	44	+0	3,2	+0,3	13,5	+0,1	+1,6	42
42	1	5	5	35	72	+1,4	33	+6	2,5	+0,6	6,4	+5,9	-0,7**	111
47	1	5	2	46	83	+0,8	24	+1	1,1	+0,8	7,2	+3,7	+2,2	126
48	1	6	0	54	80	+1,1	17	+8†	n/a	n/a	7,7	+2,2	+1,4	120
49	1	2	0	35	74	+1,1	39	+6	n/a	n/a	13,1	-0,6	-0,6	57
	2	7	3	34	72	+1,1	40	+0	2,4	+1,5	11,5	-2,0	+0,6	39
50	1	4	1	58	78	+2,5	27	+5†	1,3	+0,5	15,3	-3,0	+3,9	100
	2	3	2	51	70	+1,6	16	+9†	0,1	+1,2	5,4	+5,9	+3,2**	109
	3	6	6	51	70	+2,6	18	+18†	0,9	+1,2	9,8	-0,6	+2,6**	108
51	1	5	4	32	64	+1,5	24	+16	1,0	+1,7	10,1	+4,6	+1,0	89
	2	2	5	30	60	+2,3	37	-2	2,0	-0,2	10,1	+0,2	+1,6**	120
52	1	7	4	45	63	+2,1	27	+10	1,0	+2,2	11,0	-3,2	+3,9	70
62	1	3	6	30	54	+1,2	33	+13	2,3	+2,6	10,8	+0,7	+2,8**	120

Notes:
Per. = period of IVN

* = percentage of ideal body weight for height (see Chapter 2)

** = Small amounts of oral food given

† = Intravenous protein or blood given during IVN

weight as shown in Table 9.1 and increases also in skinfold thickness (mean 1 mm a week) and mid-arm muscle circumference (Mean 0.36 cm a week). This was accompanied by positive nitrogen (N) balance and increases in serum transferrin concentrations in most patients. Increases in albumin concentrations occurred during 12 of the 14 periods of IVN. Patients 48 and 50 also received intravenous protein or blood. Severe diarrhoea, likely to increase Zn loss, occurred in patients 48, 50, 52 and 62. Systemic sepsis occurred only in patient 49. Minor local sepsis related to the intravenous cannula occurred in several patients as described in Chapter 8.

Magnesium status and iv requirements during IVN

Table 9.2 is the serum and urine data during IVN. Combined low serum and urine levels indicating definite Mg depletion occurred in 3 of 60 patient-weeks all associated with a Mg intake of less than 5 mmol/day. The difference in incidence of Mg depletion between this low intake group and each of the other two groups was significant. These results indicate that 5-10 mmol of Mg are required daily if Mg depletion is to be prevented.

Individual low serum or urine levels occurred in 16 of 60 patient-weeks. Five low results occurred sporadically in different patients, but 11 low levels occurred in 2 patients.

Patient 48 who had a very low pre-IVN Mg status, suffered from severe diarrhoea throughout the early part of IVN. When the IVN line became temporarily blocked, he developed frank tetany which resolved quickly when the IVN was restarted with a solution containing Mg. The serum Mg level remained low until the fourth week of IVN despite an intake of more than 10 mmol/day.

Patient 49 had multiple nutritional deficits, but was not initially Mg depleted. Difficulty was encountered in establishing IVN, and during a period of inadequate intake associated with rapid weight loss he developed biochemical Mg deficiency and clinical tetany not due to hypocalcaemia.

None of the other patients developed symptoms to suggest Mg deficiency during IVN.

TABLE 9.2

MAGNESIUM STATUS DURING 60 PATIENT-WEEKS OF IVN RELATED TO Mg INTAKE

IV Mg intake (mmol/day)	Low serum Mg*	Low Urine Mg*	Low serum and urine Mg
<5	5 / 8	3 / 8	3 / 8
5-10	2 / 16	0 / 16	0 / 16
>10	4 / 36	2 / 36	0 / 36
Totals	11 / 60	5 / 60	3 / 60

p<0.01† p<0.05†

* The left hand number of each pair is the no of patient-weeks in which a low level was recorded. The right hand number is the total number of patient weeks

† Each of the higher intake groups is compared with the lowest intake group (< 5mmol/day)

Serum Zn levels

The improvement in nutritional state in all patients was not accompanied by a predictable overall change in serum Zn levels, which increased during nine periods of IVN and decreased during the remaining five (Table 9.1). Serum Zn levels in patients with diarrhoea (nos.28, 50, 52 and 62) were not different from those without diarrhoea. There was no relationship between the mean daily Zn supply and the overall changes in serum Zn concentration. Nor had the level of Zn supply an influence on serum Zn concentrations (Fig.9.1). The serum Zn concentrations (mean ± SEM μmol/l) in the low intake group (9.4±1.0) and the two higher zn intake groups (11.0±0.8; 10.5±0.4) were not significantly different from baseline values, and were less than controls ($p < 0.01$ for each group). No patient received more than 220 μmol of Zn per day.

Patient 52 whose period of IVN is illustrated in Fig. 9.2, was the only patient to show a fall in serum Zn concentration (13.0 to 7.8 μmol/l) after his serum proteins had risen and his body weight increased 8 kg in only two weeks. His Zn intake was 70 μmol/day.

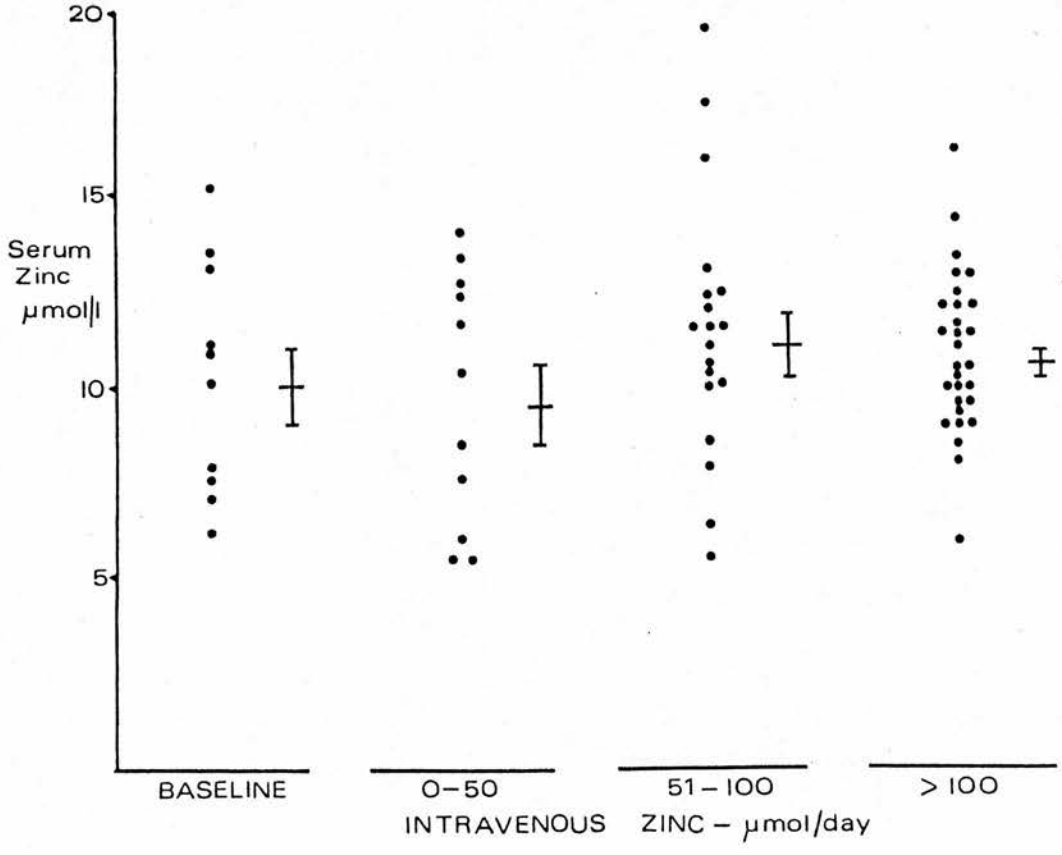
The relationship between serum albumin and serum Zn is shown in Table 9.3. Serum albumin was lower in the inflammatory bowel disease group ($p<0.001$) and IVN group ($p<0.001$) than in controls. Serum Zn, similarly, was lower in the inflammatory bowel disease ($p<0.001$) and IVN ($p<0.001$) groups than in controls. There was a significant correlation between serum albumin and serum Zn only in the combined group and in the inflammatory bowel disease group.

Urine Zn excretion

As illustrated in Fig.9.3, all levels of intravenous Zn supply were associated with a rise in urine Zn excretion above baseline values. The difference between each of the intake groups and the baseline values were significant. Urine Zn excretion in the two highest groups was greater than when the Zn supply was less than 50 μmol/day ($p<0.005$; $p<0.01$). When urine Zn excretion was expressed as a percentage of intake for each intake group (Table 9.4), however, there was no difference in the mean percentage of intake excreted between the intake groups, a wide range being present in each group.

FIGURE 9.1

SERUM ZINC CONCENTRATION AND ZINC SUPPLY



Serum zinc concentrations before intravenous nutrition (baseline) and during each of 59 patient-weeks of intravenous nutrition, separated according to the quantity of zinc supplied. Bars indicate the mean and standard error for each group.

FIGURE 9.2

INTRAVENOUS NUTRITION IN PATIENT 52

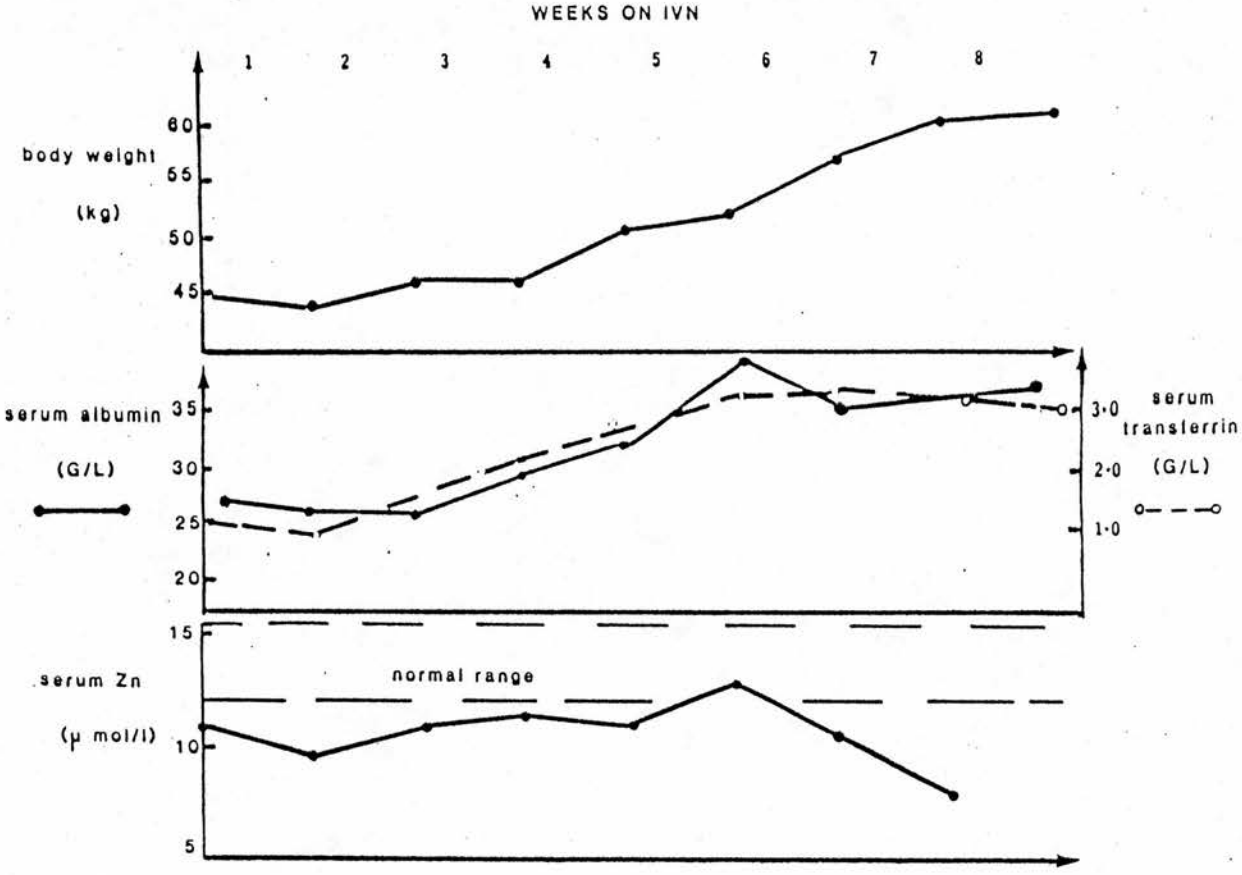


TABLE 9.3

RELATIONSHIP BETWEEN SERUM ALBUMIN AND SERUM ZINC

	No of Values	Serum albumin (g/l) Mean	S.E.M.	Serum zinc (μmol/l) Mean	S.E.M.	Correlation between se albumin and se zinc *r*	*p*
Controls	50	43.1	0.5	13.8	0.3	+0.22	NS
IBD*	21	27.4	1.6	9.6	0.7	+0.48	<0.05
IVN†	57	31.1	0.9	10.8	0.3	+0.20	NS
Combined	128	35.1	0.8	11.8	0.3	+0.55	<0.001

* inflammatory bowel disease group
† intravenous nutrition (individual patient-weeks)

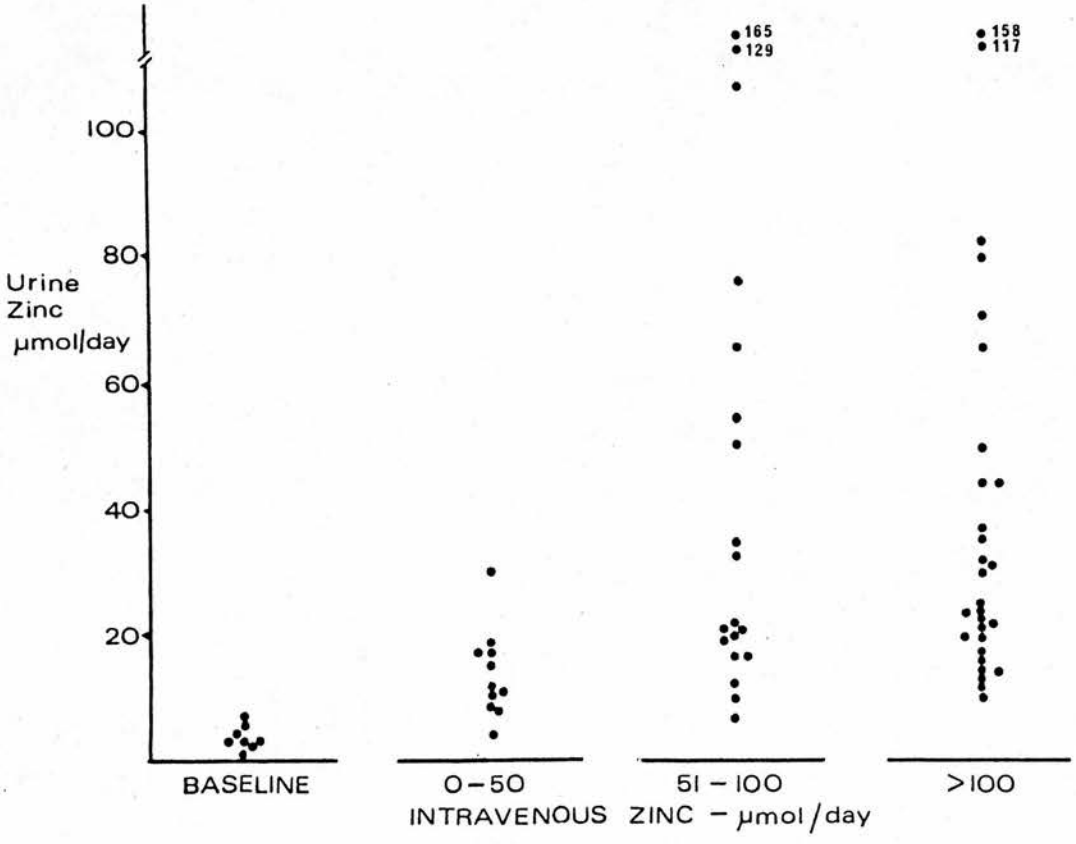
TABLE 9.4

URINE ZINC EXCRETION AS A PERCENTAGE OF INTRAVENOUS INTAKE

iv zinc intake (μmol/day)	Urine zinc excretion (% of intake) Mean	Standard deviation	Range
0 - 50	38	23	19 - 85
51 - 100	54	28	14 - 165
101 - 220	33	30	9 - 132

FIGURE 9.3

URINE ZINC EXCRETION AND ZINC SUPPLY



Daily urine zinc excretion before intravenous nutrition (baseline) and during each of 59 patient-weeks of intravenous nutrition separated according to zinc supply.

Low urine Zn excretion (mean±SEM) (3.3±0.06 μmol/24h) was observed before IVN. During the first week of feeding a rise in urine output was observed in all patients varying from a 1.3 to a 53-fold increase, the mean increase being 11 times the value before IVN.

In patient 50, urine Zn losses diminished markedly after albumin (93g) was given intravenously during the second week of intravenous nutrition (Fig.9.4), while serum Zn levels remained low (<10 μmol/l) throughout.

Patient 48 showed a similar drop in urine Zn output (158 to 18 μmol/24h) after a transfusion of blood was given. No other patients received protein during IVN.

9.5 SUMMARY

Magnesium

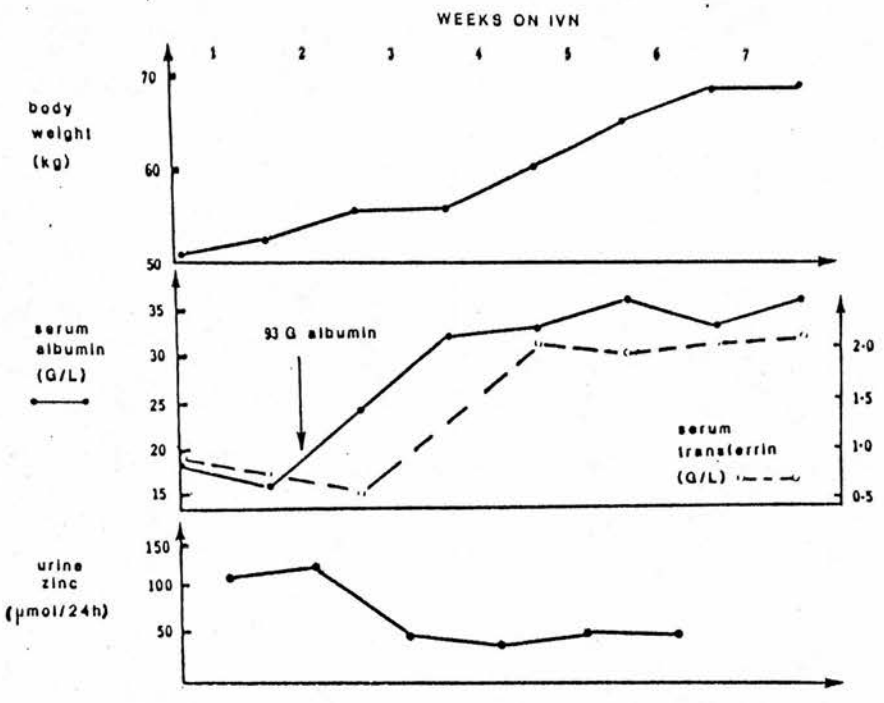
Intravenous Mg requirements have been studied in 10 patients during 14 periods of IVN (total 60 patient-weeks of IVN). Using combined serum and Urine Mg as indicators of Mg depletion, Five to 10 mmol of Mg were required daily during IVN to prevent Mg depletion during IVN. Our observations would suggest that patients with severe Mg depletion before IVN should be given more than 10 mmol of Mg a day.

Zinc

Serum Zn concentrations and urine Zn excretion have been studied in the same patients before and during 59 patient-weeks of IVN. Before IVN serum Zn concentrations (9.9±1.0 μmol/1: mean ± SEM) and urine Zn excretion (3.3 ± 0.6 umol/24h) were less than controls ($p<0.01$). No patients had clinical signs of Zn deficiency before IVN and none developed signs during it. There were no overall changes in serum Zn concentrations, despite nutritional improvements in all patients, and increased serum albumin and serum transferrin concentrations during all but two periods of IVN. Nor was there any relationship between serum Zn concentrations and Zn intake (up to 220 μmol/day), serum Zn concentrations remaining significantly lower than control levels. Urine Zn excretion during the first week of IVN showed a 1.2 to 53-fold increase (mean 11-fold) over pre-IVN levels, and a positive relationship was demonstrated between Zn intake and urine Zn

FIGURE 9.4

THIRD PERIOD OF INTRAVENOUS NUTRITION IN PATIENT 50



Weight gain during the first two weeks of intravenous nutrition was attributable to the accumulation of oedema fluid which rapidly disappeared after the infusion of 93g of albumin during the second week

excretion. It is suggested that Zn supplied by the intravenous route is inefficiently transported to the tissues, and that some is excreted in the form of small molecular weight chelates into urine. Based on the findings the following recommendations of Mg and Zn supply during IVN in Crohn's disease are offered: Mg: 5 - 10 mmol/day (more if Mg depletion is present before IVN); Zn: 100 - 200 µmol/day adjusted according to levels of Zn excretion in urine.

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 10

CONTROLLED STUDY OF THE COMPARATIVE EFFECTS OF ENTERAL LIQUID DIETS ON NUTRITIONAL EFFICIENCY AND FAECAL RESIDUE IN INTACT RATS

10.1 AIMS

1. To compare 2 defined formula diets (DFD) and 3 polymeric diets (PD) with respect to nutritional efficiency: growth, body composition whole body nitrogen and nitrogen (N) balance.
2. To examine their effects on faecal residue (dry weight, bacterial composition).

10.2 METHODS

Practical aspects

36 Sprague-Dawley rats of similar age and weight were caged individually in metabolic cages designed to allow separate collection of urine and faeces. This was achieved using a mesh floor through which both faeces and urine passed. Below this was a finer mesh on which faeces were deposited and beneath this a funnel collected urine into a conical flask. The feeds apart from the control diet were in liquid form from a bowl secured inside the cage to prevent spillage. The animals were allowed free access to water from a water bottle. Cages were in a temperature and humidity controlled animal house with fluorescent lighting night and day. Before the experiments began the rats were on ad libitum feeding with the control diet (Oxoid 41B) and they were not starved before the experiments began. In order to achieve a wash-out effect, all measurements apart from daily weighing, were delayed until the third and fourth week of the experiments. In almost all cases the feed was completely consumed but some spillage of the Oxoid diet occurred for which an arbitrary 10% allowance was made in the calculation of daily provision.

Experimental design

36 rats were each fed for 28 days on a single test diet for the whole period. Thus, each of the six diets was fed for 28 days to six rats. In clinical practice, liquid diets are usually given based on a calorie target and the rats were therefore fed in isocaloric amounts. After a test period on the control diet with rats of medium weight, it was found that 70.3 kilocalories intake per rat per day was achieved and all the rats were successfully fed this amount throughout.

The test diets

There were six test diets including the control rat chow (Oxoid 41B) (O), two DFDs, Vivonex (V) and Vivonex HN (VHN) (Eaton Laboratories), and the PD, Flexical (F) (Mead Johnson), Ensure (E) (Abbott Laboratories) and Clinifeed Iso (C) (Roussel Laboratories). The composition of these diets is shown in Table 10.1 and some differences between them are worth noting. The principal difference was in N source, being aminoacids in the DFDs and hydrolysed or whole protein in the remaining diets. The carbohydrate source was also different and fat composition varied considerably. Another difference was the kilocalorie to nitrogen ratio. Since the rats were fed the same number of calories [70.3 kCal(295 kJ) a day], a small ratio in Oxoid, Vivonex HN and Ensure indicate a relatively high nitrogen intake compared with the remaining diets. N intake (mmol/day) was as follows:

Oxoid 43.6; Vivonex 16.4; Vivonex HN 31.8; Flexical 19.3; Ensure 27.6 Clinifeed Iso 23.2.

Laboratory measurements

Body weight was measured daily before the day's feed was provided. N balance was measured during the second half of the feeding period to allow adaptation to the diets. It was the difference between nitrogen intake and the sum of urine and faecal nitrogen output measured by a microkjeldahl technique (Fleck 1965) on aliquots of each diet and on the excreta. At the end of the 28d feeding period the rats were killed and deep frozen. They were then submitted for measurement of whole body nitrogen (WBN) by Neutron Activation analysis (NAA) in a 14 MeV NAA facility at the Scottish Universities Reactor Centre (Williams 1978) using method adapted for small animals and validated by demonstrating close similiarity between WBN by this method and by direct measurement after Kjeldahl digestion (Preston 1985). Nitrogen wastage was an arbitrary measure of the efficiency of nitrogen assimilation from the various diets: the N excretion (faeces plus urine) expressed as a percentage of N intake over the second half of the feeding period. Faecal analysis: all faeces passed during days 15-28 were collected, dried and weighed. Results were expressed as

TABLE 10.1

COMPOSITION OF TEST FEEDS

PRODUCT	N SOURCE	CARBOHYDRATE SOURCE	RATIO OF kCAL TO g OF N	% CALORIC CONTRIBUTION BY FAT
Oxoid 41B (O) (Control diet)	Wheat, oats, fish meal, milk	Milk + ?	115:1	Not known
Vivonex Standard (V)	Amino acids	Glucose and oligosacch.	300:1	1.3
Vivonex High Nitrogen (VHN)	Amino acids	Glucose and oligosacch.	150:1	0.78
Flexical (F)	Hydrolysed casein + 3 amino acids	Sucrose, dextrin tapioca starch	285:1	30
Ensure (E)	Hydrolysed casein and soy protein	Corn syrup poly-saccharides 74% sucrose 26%	154:1	33
Clinifeed ISO (C)	Milk, whey proteins	Milk, malto-dextrin	200:1	37

the mean daily faecal weight over this 14d period. Aliquots were submitted for N estimation and the remaining faeces from each diet group were pooled and thoroughly mixed. Samples of each diet were submitted for further analysis of bacterial content by slightly adapting the method of Stephen (1980).

Statistical Methods

The results for each diet group are expressed as median and range. Statistical comparisons between diet groups were by the non-parametric Wilcoxon's sum of ranks test.

10.3 RESULTS

Nutritional efficiency

Weight gain (Table 10.2): the control (Oxoid-fed) rats appeared to fare best but there were no statistically significant differences, even between V and controls. Whole body N (Table 10.2) achieved after 28 days was less with V than with F ($p<0.01$), C ($p<0.05$) and controls ($p<0.05$). Ensure-fed rats also achieved less WBN than controls ($p = 0.05$). N balance (Table 10.3) appeared best in control animals but the difference was not significant. the calculation of N wastage suggested that F (48% wastage) was the most efficiently utilised, being better than E ($p<0.01$) and controls ($p<0.01$). V was the next most efficient (54%). Of course, the N intake varied considerably since isocaloric feeding was given and it can be seen that the diets with highest N intake (control (O), VHN and E) were associated with the highest N wastage and although apparently less efficient they achieved levels of N retention similar to the other diets. V and VHN can be directly compared since the only difference in their composition is in N content which is greater in VHN. From the results in Table 10.3, it can be seen that much of the excess N appeared in the urine but that the N retention overall was similar with the two diets

Faecal composition - Table 10.4

Faecal weight was much less (<8%) with all the test diets when compared with controls (O), indicating that they were all of

TABLE 10.2

WEIGHT GAIN AND NITROGEN ACCRETION
expressed as median (range)

PRODUCT	INITIAL WEIGHT (grams)	WEIGHT GAIN (% of initial weight)	WHOLE BODY N (g)
OXOID n=5*	203 (168-217)	55 (36-94)	10.03 (6.78-11.50)
VIVONEX n=6	195 (166-233)	37 (19-48)	8.48 (8.17-9.33)
VIVONEX HN n=6	196 (163-250)	44 (23-67)	9.13 (8.55-10.60)
FLEXICAL n=6	199 (169-239)	46 (27-75)	9.54 (8.99-10.05)
ENSURE n=6	194 (160-206)	52 (24-78)	9.05 (8.41-9.63)
CLINIFEED ISO n=5*	191 (163-211)	63 (35-72)	9.15 (8.99-10.72)

* one rat discounted because of sickness

TABLE 10.3

NITROGEN BALANCE
expressed as median (range)

PRODUCT	N INTAKE* (mmol/day)	N OUTPUT (mmol/day) FAECES	URINE	N RETENTION (mmol/day)	N WASTAGE (output-% of intake)
OXOID	43.6	15.0 (12.3-18.1)	18.5 (12.4-21.8)	12.8 (4.9-15.4)	73 (62-89)
VIVONEX	16.4	1.1 (1.0-1.3)	7.1 (6.3-9.4)	7.8 (5.9-9.0)	53 (45-64)
VIVONEX H N	31.8	1.2 (0.7-1.8)	20.9 (13.6-25.0)	9.9 (6.1-6.4)	61 (46-82)
FLEXICAL	19.3	1.8 (1.2-2.0)	7.5 (4.9-9.0)	10.0 (8.6-13.1)	48 (31-56)
ENSURE	27.6	2.0 (1.6-2.4)	16.6 (15.0-19.6)	8.6 (5.9-10.5)	70 (62-79)
CLINIFEED ISO	23.2	2.5 (2.0-4.3)	11.2 (7.9-12.9)	9.3 (7.0-13.0)	60 (44-70)

* Intake based on measured N in aliqouts of feeds and arbitrary 10% allowance for spillage in the control group (Oxoid)

TABLE 10.4

FAECAL COMPOSITION

PRODUCT GIVEN	FAECAL DRY WEIGHT (mg/d/rat) Median	Range	% OF BACTERIA IN FAECES*
OXOID	7057	6100-8671	26
VIVONEX	236	198-251	47
VIVONEX HIGH NITROGEN	197	107-257	46
FLEXICAL	426	299-484	58
ENSURE	387	309-511	57
CLINIFEED ISO	547	404-803	64

** = Single pooled sample from each dietary group*

comparatively low residue. However, the DFDs, V and VHN induced significantly lower faecal weight than the PD F, E and C (all comparisons $p<0.01$). Bacterial content of the faeces (Table 10.4) contributed about a quarter of the faecal bulk of the control diet and absolute qualities of bacteria were much higher in control faeces than the test diets. Because only a single pooled sample of faeces from each dietary group was analysed, it was not possible to subject the comparative results to statistical analysis but it seemed that the lower faecal weight observed with V and VHN was associated with a lower faecal bacterial content than with the other diets.

10.4 SUMMARY

This study has compared in experimental animals the effect of five commonly used enteral liquid defined-formula diets on efficiency of N utilisation (weight gain, whole body N, N balance, N wastage) and has compared their influence on faecal residue (faecal weight and faecal bacterial content).

Vivonex, Vivonex Nitrogen, Flexical, Ensure, Clinifeed Iso and control rat pellet feed (Oxoid 41B) were fed to 36 rats (6 rats each diet) for 28 days in isocaloric amounts (70.3 Kcal (295 kJ per rat per day). Median weight gain (% of starting weight) varied from 37 (Vivonex) to 63 (Clinifeed) but there were no significant differences from controls (55). N balance was positive in all cases but no significant differences were observed. Whole body N (neutron activation analysis) (g) after 28d feeding was, however, less with Vivonex (8.48 (8.17-9.33)) (Median (range)) than Flexical (9.54 (8.99-10.05); $p<0.01$) or Clinifeed (9.15 (8.99-10.72); $p<0.05$). N wastage was highest in the feeds with a high N content. Faecal residue (daily dry weight) was less with Vivonex and Vivonex High Nitrogen (236 (198-251) and (197 (107-257) respectively) than Flexical (426 (299-484); $p<0.01$), Ensure (387 (309-511); $p<0.01$) and Clinifeed (547 (404-803); $p<0.01$). All were less than 8% of the high residue control diet. Faecal bacterial content in rats fed the various tests diets varied from 46% (Vivonex HN) to 64% (Clinifeed).

DISCUSSION AND CONCLUSIONS - CHAPTER 11.

CHAPTER 11

DISCUSSION

11.1 DISCUSSION CHAPTER BY CHAPTER

11.2 MALNUTRITION IN CROHN'S DISEASE. AN OVERVIEW

11.3 NUTRITIONAL THERAPY IN CROHN'S DISEASE. AN OVERVIEW

Each of the studies will be discussed chapter by chapter including a discussion of the methods used. This will be followed by an overview of the results and the contribution they make to increasing knowledge of malnutrition and the role of nutritional therapy in Crohn's disease

11.1 DISCUSSION OF INDIVIDUAL STUDIES CHAPTERS 3 to 10

DISCUSSION OF CHAPTER 3.
A SURVEY OF CLINICAL AND LABORATORY ABNORMALITIES

This survey of an unselected group of 65 patients with Crohn's disease has revealed that half the patients were underweight and nearly one third were severely underweight. Significant abnormalities of all laboratory measurements were discovered varying between 11% (serum Na) and 40 % (serum Alb concentration). Severe depletion however was less prevalent. Certain abnormalities were more common in patients with widespread bowel involvement. Those severely underweight (<80% ideal) were more likely to be protein depleted and to have low calcium and vitamin A levels than those with normal weight. Patients with small and large bowel involvement had more abnormalites than those with disease confined to the small or large bowel. Patients with multiple abnormalities were characterised as being underweight, having active disease usually of long duration and requiring nutritional therapy.

INDIVIDUAL ABNORMALITIES

Anaemia

Anaemia in Crohn's disease has been extensively investigated but mainly in patients receiving treatment in hospital giving a prevalence of between 50 and 70% (Van Patter 1954; Krause 1971; Dyer 1972; Beeken 1975). The prevalence in my patients was slightly lower at 32%, reflecting perhaps the more general nature of the patients (in- and out-patients) and that some were already on treatment. Severe anaemia was present in only 21% of my patients. The commonest type of anaemia reported in the above investigations is iron

deficiency which was indeed the commonest in my series (7 out of 13 of those with severe anaemia). Only one patient had severe anaemia due to folic acid deficiency but in this 'point prevalence' study, many of the patients studied had been successfully treated for previously identified folic acid deficiency which occurs in about one third of untreated patients (Dyer 1972; Beeken 1975; Eade 1972). Of interest were the five patients with a 'secondary' anaemia (normal MCV and no response to iron or other therapy). This type of anaemia may reflect the inflammatory process, sepsis or severe malabsorption but has not been investigated further here.

Electrolyte abnormalities

These were less prevalent and readily correctible. The prevalence of hyponatraemia (11%) is similar to the 10% reported by Beeken (1975). The only patient in my series who had severe hyponatraemia had severe diarrhoea due to active large bowel disease. The prevalence of potassium depletion as measured by serum K concentration (15% in this series) is hard to find in the literature but true K depletion may be even more common since body K levels may not be accurately reflected by serum K measurements (Lehr 1982).

Calcium, magnesium and zinc

These minerals and the relationship between the general survey and more detailed investigations are discussed in Chapters 5, 4 and 9 respectively.

Protein depletion

Depletion of serum albumin (Alb) was the most prevalent abnormality in these patients (40%) and compares with a reported prevalence varying from 20 - 80% in patients in the series indicated in Table 1.4. In my patients, of the 26 patients in whom serum Alb was low two thirds had moderate or severe depletion (serum Alb < 30g/l). In some, mild depletion occurred without bowel symptoms (inactive disease), an observation also noted by Cobb (1969). However hypoalbuminaemia was a serious clinical problem, associated with oedema in a number of patients discussed in Chapter 8 in relation to nutritional therapy.

Associated transferrin depletion was the rule. This fast turnover protein is widely used as an indicator of protein status and may be more sensitive to acute changes (either depletion or repletion) than Alb. However like Alb its blood levels may be influenced by factors other than nutritional deficiency which are relevant in Crohn's disease. These are sepsis and protein loss (Jeejeebhoy 1981).

Vitamins A and E

The high prevalence (23% each) of depletion of these fat-soluble vitamins is a new finding since systematic studies in Crohn's disease are lacking. The significance of these results and further studies are reported in Chapters 6 and 7.

THE CLINICAL CONTEXT

To identify patients at high risk of one or more abnormalities three conventional and easily obtained clinical classifications have been used supplemented by an examination of patients with multiple abnormalities. This approach has not been adopted previously to my knowledge. In respect of the site of disease it showed an association between low plasma Zn, TF vitamin E and abnormal activity of alk phos in patients with widespread bowel disease compared with patients whose disease was confined to the small bowel. A similar 3 group division by body weight again revealed an association between protein depletion (Alb and TF) as well as Ca and vitamin A in patients severely underweight compared with normal weight. The binary division of disease activity into active or inactive failed to reveal differences either because it was truly a poor guide to nutrient depletion or the 'middle ground' contained similar patients in both active and inactive groups sufficient to swamp differences in the extreme patients. Other differences might be present but may not have emerged for the the following reasons. Firstly the apparent significance of differences in prevalence between groups using conventional statistical methods depends crucially on the overall prevalence which was relatively low for the majority of measurements. It was not surprising therefore that albumin, transferrin were most frequently 'significantly' different in the various groups since they

were most frequently abnormal in the whole group. With a larger group of patients, other differences would probably have emerged (see Appendix 3.1). Secondly, cluster analysis to identify groups of clinical features which together would indicate a high risk (prevalence) of abnormalities may have failed to show differences because of small numbers. This approach and its relationship to prognosis has been used in surgical patients (Dionigi 1983). In this exploratory investigation with relatively small numbers, univariate analysis was used for the most part. Multivariate techniques were not considered appropriate but would be useful in future research with larger numbers of subjects. The finding of more than four abnormalities per patient with small and large bowel disease is of some interest when compared with around two abnormalities in those with only small bowel involvement. Slightly surprising was the finding of more abnormalities in those with large bowel disease than with small bowel involved. perhaps indicating that badly diseased large bowel can be the source of considerable losses. There was no characteristic pattern of abnormalities in the three groups.

This study has offered a new approach to the examination of malnutrition in Crohn's disease by attempting to place in some sort of clinical perspective the large array of laboratory abnormalities which were found. In addition new findings or symptoms worthy of deeper investigation have been identified.

DISCUSSION OF CHAPTER 4
MAGNESIUM DEFICIENCY

There was a high prevalence of biochemical Mg depletion in patients with Crohn's disease requiring admission to hospital. In a few patients with severe disease Mg depletion caused symptoms and required urgent treatment. In some cases of severe malabsorption, Mg deficiency was a long-term problem. The level of Mg supplementation is most conveniently based on regular measurements of serum magnesium concentrations. Patients with Mg concentrations less than 0.6 mmol/l

appeared to be at high risk of symptoms. Oral supplements of between 30 and 60 mmol of Mg a day appeared to be sufficient.

The prevalence of Mg depletion in patients with severe Crohn's disease in this study is much higher than in Beeken's series, in which he used serum Mg levels alone as an index of deficiency (Beeken 1975). This difference is explained by my use of urine as well as serum measurements and the selection in my study of hospital in-patients with predominantly extensive disease. In these patients poor intake increased loss and failure of absorption of Mg may coexist. Symptoms occurred in the two patients who had serum Mg concentrations of 0.40 and 0.59 mmol/l. The third patient who had the lowest serum Mg level of 0.38 did not have tetany but had severe generalised weakness for which Mg deficiency may have been partly responsible. These findings concur with the suggestion that muscular symptoms and tetany are likely to occur when the serum levels drop below 0.5 mmol/l (Paymaster 1976). Calcium deficiency may also cause paresthesia and tetany, and may have been an associated problem in this study. However serum calcium levels, when adjusted for low albumin were normal at the time of the study.

Is my method of judging Mg status justified?

The assessment of Mg status, as with other predominantly intracellular substances, poses problems. Studies of Mg kinetics have been hampered by the relatively short half-life of radioative ^{28}Mg (Watson 1979), but ^{26}Mg, a stable isotope has received some attention (Schwartz 1978). Measurement of tissue biopsy levels may not reflect total body reserves (Alfrey 1974). Early observations of serum Mg levels showed that levels were maintained within a narrow range (Wacker 1964; Alcock 1960; Briscoe 1966). The mechanism is complex and would appear to be regulated at the cellular level (Williams 1967), in the kidney and in the intestine. Parathyroid hormone is an important regulator of serum Mg levels, although other factors may play a part. The net effect is Mg conservation by the kidney in response to lowered serum Mg levels, so that in conditions of Mg depletion, Mg almost disappears from the urine. Thus, low urine

Mg levels are the earliest indicator of Mg depletion and have been used as an indicator of early deficiency (Heaton FW 1969). Serum Mg levels fall later. Measurements of serum and urine Mg levels therefore provide the fairly sensitive and practical way of measuring Mg status used in this study and in the examination of Mg requirements during intravenous nutrition reported in Chapter 9.

Chronic magnesium deficiency

Long-term follow-up has indicated chronic Mg deficiency in several patients. Oral Mg supplements are available as liquid suspensions. Mg chloride mixture is available in three strengths (8, 10, and 25 mmol Mg/10 ml). It is probably the preparation of choice but in larger doses may have a purgative action. In patients who cannot tolerate it, Mg hydroxide (BPC) containing 13.6 mmol/10ml may be used. A combination of aluminium hydroxide and Mg hydroxide (Maalox-Pharmax) may reduce the purgative effect. Mg sulphate BPC containing 21 mmol Mg/10ml is normally used as a bowel evacuant and is poorly absorbed. It may be reserved for patients who cannot tolerate the other preparations.

DISCUSSION OF CHAPTER 5

DIAGNOSIS AND TREATMENT OF OSTEOMALACIA

Can osteomalacia be diagnosed without recourse to bone biopsy?

This study has characterised the Crohn's patient with severe osteomalacia as being underweight (<90% ideal) having active disease with diarrhoea and steatorrhoea and having characteristic musculoskeletal symptoms. The lack of osteoporosis in these patients is surprising (Driscoll 1982). The study has also shown that the search for osteomalacia cannot be restricted to patients with small bowel resection as in the studies of Compston (1978) and Driscoll (1982). Although all my patients had radiological signs (strictures or skip lesions) or indirect evidence (steatorrhoea) of extensive small bowel disease, 4 of the 6 with osteomalacia had less than 100cm resected and one of these had an intact small bowel. If the presence of severe rather than mild osteomalacia is considered the indication for therapy then the diagnosis without bone biopsy is fairly easy.

The findings of a high bony alkaline phosphatase (in this study an elevated total alkaline phosphatase in association with a normal γ-GT) in the clinical context described above is sufficient for therapy to be justified for presumed osteomalacia. This would agree with the findings of Peach (1982), that plasma alkaline phosphatase is a sensitive predictor of bone histology.

However, it is also important to identify patients with mild osteomalacia so that early treatment can be given before symptoms become severe. The difficulty of making such a diagnosis in patients who may be asymptomatic and have normal serum biochemistry is recognised in resected Crohn's disease (Compston 1978; Driscoll 1982) and in other disease states, (Melvin 1970; Chalmers 1967) and is well illustrated by the only patient in this study who had mild osteomalacia with normal serum biochemistry including alkaline phosphatase. However, she was distinguishable from the non-OM patients by having a plasma 25 (OH)D level (4 nmol/l much lower than the lowest non-OM patient (14 nmol/l) and a high WBR of Tc-99m HEDP (Figure 5.1 - 42.1%). Is it not possible to draw firm conclusions from a single case but Vitamin D status and WBR of Tc-99m HEDP deserve further consideration as means of identifying or excluding mild osteomalacia.

Vitamin D Status and diagnosis of osteomalacia

Vitamin D malabsorption is well recognised in small bowel disease (Davies 1980; Compston 1977; Batchelor 1982), and Vitamin D deficiency (low plasma 25(OH)D) is common in Crohn's disease (Driscoll 1982; Compston 1977) occurring in 65% of Driscoll's patients and in 38% of a previous sample of 47 Crohn's patients in our Unit. In the histological study (Table 5.1), the lowest 25 (OH)D level in a non-OM patient was 14 nmol/l. Furthermore, in the majority of our Crohn's patients in a previous study, these winter levels did not rise to normal as would be expected in late summer (Compston 1977). Thus a normal 25(OH)D level (winter >16 nmol/l; summer >25 nmol/l) possibly excludes osteomalacia while a very low 25(OH)D level may imply a high risk of osteomalacia.

Whole Body Retention of Tc-99m HEDP in the diagnosis of osteomalacia

HEDP is a diphosphonate (Editorial 1981) which is thought to be taken up, like pyrophosphate, by calcifying osteoid. When the compound is labelled with radioactive technetium, the 24 hour retention of the isotope is thought to reflect the total amount of osteoid being calcified and is increased in any condition associated with hyperosteoidosis including osteomalacia and other diseases associated with high bone turnover (Fogelman 1978). In the context of this study, the technique might be expected to detect early osteomalacia since increased bone turnover may precede the development of histological osteomalacia (Frame 1978), when an increase in the absolute amount of osteoid is present but before the percentage which is calcified is decreased (the main criterion for defining osteomalacia histologically). Our data would fit with these concepts, whole body retention of diphosphonate being increased in mild as well as severe osteomalacia. It was also increased in 3 patients on treatment with healing osteomalacia on a second biopsy and who despite having a normal percentage of calcifying osteoid (>60%) still had an increased total osteoid surface. This discrepancy may represent a sampling problem inherent in bone biopsies but remains largely unexplained. Our results suggest that the technique is slightly oversensitive but is unlikely to miss even mild osteomalacia. Despite being relatively easy to perform and non-invasive with a low dose of radioactivity, it is not widely available. Nevertheless it may be a useful screening test, a normal WBR excluding osteomalacia. An abnormal result should lead to a search for causes of metabolic bone disease, one of which is osteomalacia.

Treatment of osteomalacia in Crohn's disease

This poses potential problems since orally administered vitamin and mineral supplements might not be adequately absorbed. In the 5 patients treated (Table 5.3), 3 responded to: 1-alpha hydroxyvitamin D (1 alpha - Leo Laboratories) and calcium supplements. This drug is potent and patients must be monitored for signs of toxicity due to the resulting hypercalcaemia. The dosage requirement in this study

was between 1 and 5 μg per day. Magnesium deficiency was present in 2 and is a cause of osteomalacia resistant to conventional therapy (Frame 1978) and a relatively common finding in severe Crohn's disease (Chapters 3 and 4). The only patient who did not respond to oral therapy may have been suffering from phosphate depletion, a further cause of resistant osteomalacia (Frame 1978). Following a period of intravenous nutrition which included phosphate, her serum phosphate level rose and her waddling, due to a proximal limb myopathy, markedly improved.

DISCUSSION OF CHAPTER 6
VITAMIN A DEPLETION AND NIGHT BLINDNESS

This study has shown that vitamin A deficiency is a significant clinical problem in severe Crohn's disease and has identified the clinical and biochemical accompaniments of the condition. Plasma retinol concentration has proved useful as a means of identifying patients at high risk of developing night blindness. The study has also shown that treatment is effective either orally or during intravenous nutrition in association with improvements in protein nutrition.

Previous studies of Vitamin A deficiency

In developed countries, vitamin A deficiency is unlikely to occur for dietary reasons alone and the search for clinical evidence of vitamin A deficiency has therefore centred on patients with liver disease (Russell RM 1978; Vahlquist 1978; Carney 1980) and various gastrointestinal diseases (Russell RM 1973; Vahlquist 1978; Carney 1980) among which some patients with Crohn's disease have been included. Chapter 6 (and associated publication) is the first systematic examination of Vitamin A deficiency in Crohn's disease

Protein depletion and fat malabsorption in the pathogenesis of Vitamin A deficiency

Patients with severe Crohn's disease may be protein depleted as this study has shown. Indeed, RBP and PA which have a relatively short

half-life are more sensitive to protein or energy deprivation than albumin or transferrin (Shetty 1979). Plasma concentrations of RBP and PA fall rapidly in protein malnutrition and rise on feeding (Coward 1981). The expected close relationship between retinol, RBP and PA in plasma (Goodman DS 1974 and 1976) has been confirmed in our patients with Crohn's disease and emphasises the importance of adequate protein nutrition for transport of retinol to its target tissues, principally the retina. If protein malnutrition is not corrected, plasma retinol and RBP levels may remain low despite adequate intake of vitamin A (Smith FR 1973). Fat malabsorption was a significant problem in some patients, and might be expected to result in vitamin A deprivation, which in animal experiments has been shown to inhibit release of hepatic RBP into the circulation (Mato 1972). Repletion of vitamin A results in a fall in hepatic RBP and a rise in serum RBP (Smith JE 1979). Assessment of the relative importance of protein depletion and fat malabsorption in the pathogenesis of xerophthalmia in our patients was difficult because only three had impaired dark adaptation. All three, however, were protein depleted and two had fat malabsorption. Vahlquist (1978) in various gastrointestinal diseases, showed an association between steatorrhoea and low plasma RBP levels, and between very low RBP levels and impaired dark adaptation. No direct relationship between steatorrhoea and impaired dark adaptation, however, was suggested.

Can zinc deficiency cause Vitamin A deficiency?
This possibility has received some attention in animals (Smith JC Jr 1973; Smith JE 1974) and in humans (Bates 1981) The effect is probably because of the depression of protein synthesis and in particular impaired synthesis of PA (Bates 1981) and RBP (Smith JE 1974). Serum zinc levels were not significantly different in the two groups (Table 6.3). However as discussed in a Chapter 9, zinc levels alone are not good indicators of zinc nutrition.

What is the clinical context of Vitamin A deficiency in Crohn's disease?
Impaired dark adaptation, the earliest clinical sign of vitamin A

deficiency, was present in three in-patients two of whom complained of night blindness. These patients had extensive small bowel disease, very low plasma retinol concentrations, and depletion of plasma proteins, especially retinol binding protein (RBP) and prealbumin (PA). Two patients had in addition impaired fat absorption and severe steatorrhoea. It was not possible to predict from the extent of small bowel disease alone which patients were at risk from vitamin A deficiency. The presence of only localised disease did not exclude low plasma retinol levels. Conversely, extensive disease was compatible with normal plasma retinol levels. None of the five patients with very low levels of retinol (<1.0 µmol/l), however, had localised disease and it may be that patients with localised disease are unlikely to develop clinical signs of vitamin A deficiency. Body weight measurement may be more useful. The out-patient group seemed at lower risk than the in-patients. All had plasma retinol levels >1.0 µmol/l (28.6 µg%) and weighed >80% of ideal body weight. In contrast the five who had plasma retinol levels <1.0 µmol/l were all in-patients admitted with exacerbations or complications. All five, including the three with impaired dark adaptation, weighed <80% of ideal weight (Table 6.4).

Is plasma retinol concentration a reasonable screening test?
Among the various methods of assessing vitamin A status recently reviewed by Pitt (1981), concentration of vitamin A in liver tissue is the most sensitive guide to body status, as vitamin A is stored almost entirely in the liver. There may be, however, an uneven distribution of vitamin A in liver (McLaren 1979). Plasma retinol levels only fall when liver reserves are exhausted and therefore are relatively insensitive guides to vitamin stores (Pitt 1981). Retinol concentration in plasma, however is a reasonable screening test as clinical signs of vitamin A deficiency (impaired dark adaptation) do not appear to occur when plasma retinol levels are greater than 1.4 µmol/l (40 µg%)(Carney 1980). Despite differences between our method of measuring plasma retinol and that of Carney (1980), we felt it was reasonable to define our 'high risk' patients (Table 6.3) as those with plasma retinol <1.4 µmol/l, and to undertake dark adaptation

testing only on these patients. Furthermore, very low plasma retinol levels are useful in the clinical situation: Carney (1980) in a study of patients with a variety of diseases, reported that 15 out of 21 patients with plasma retinol <1.05 μmol/l (<30 μg%) had abnormal dark adaptation testing. In this study three out of four patients with plasma retinol <0.8 μmol/l (< 23 μg%) had abnormal dark adaptation testing whereas dark adaptation was normal in all the patients with plasma retinol >0.8 μmol/l. It could be argued that night blindness is readily reversible and tests could therefore be reserved for those patients who admit to the symptom on direct questioning. One of the three patients with impaired dark adaptation testing, however, was asymptomatic and direct questioning may not be completely reliable in the detection of retinal impairment. Furthermore, protein depletion, which has adverse effects unrelated to vitamin A deficiency, may be far advanced before night blindness develops. It seems reasonable, therefore, to improve protein status before night blindness occurs.

What new information is gained from this study?
The data suggest that patients with extensive small bowel Crohn's disease who weigh less <80% of ideal body weight should have biochemical tests performed including measurement of plasma retinol and plasma proteins. The data presented here suggest that patients with plasma retinol <0.8 μmol/l(23μg%) run a high risk of developing night blindness which may be sub-clinical. If dark adaptation testing is not possible, Vitamin A supplements should be given. Protein depletion which is likely to be present should also be corrected. Both oral and intravenous therapy have been effective in resolving symptoms and improving impaired tests of dark adaptation.

DISCUSSION OF CHAPTER 7
VITAMIN E AND SELENIUM STATUS

This study in 25 patients with predominantly widespread Crohn's disease and a high prevalence of fat malabsorption has demonstrated evidence of depletion of Vitamin E and selenium in plasma, reduced activity of Red cell GSH-Px activity and a high prevalence of *in*

vitro RBC membrane instability to oxidative stress. However there is no convincing evidence of any associated haematological disease. There seemed no justification to test the effects of Vitamin E therapy.

What is known about Vitamin E deficiency in adults?

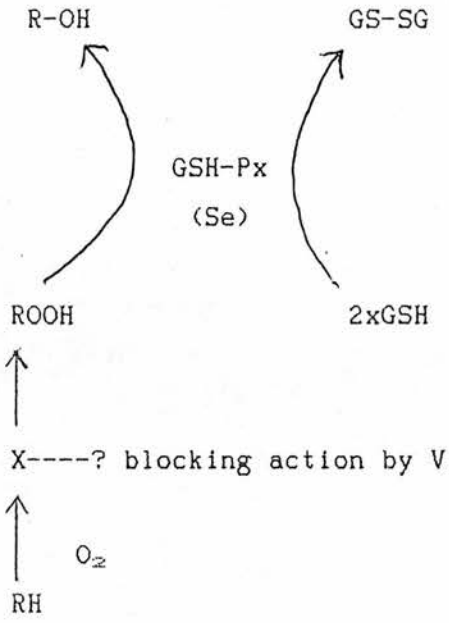
Information is sparse. The case report of Brin (1985) is described in Chapter 1. Goransson in a clinical survey of patients with low plasma tocopherol (Vitamin E) concentrations, described the clinical diagnoses of 29 patients with gastrointestinal disorders of whom only 3 had Crohn's disease (Goransson 1973). Leonard's study (1971) was of 8 patients with gastrointestinal or liver disease or alcoholism with evidence of reduced hydrogen peroxide stability of erythrocytes but none had Crohn's disease. Other reports of Vitamin E deficiency in adults were in sprue (Darby 1946) and in chronic pancreatitis (Braunstein 1961). The study reported in Chapter 7 is thus the first study of the haematological consequences of Vitamin E depletion in Crohn's disease. Binder (1965) in a study of 55 patients with various gastrointestinal diseases (5 with Crohn's disease), discovered 17 (31%) with Vitamin E depletion all of whom had steatorrhoea. However as in this study he found no evidence of abnormal erythropoesis (RBC formation or destruction) despite a similarly high prevalence of impaired hydrogen peroxide stability (13 out of 17). Binder found a direct relationship between plasma Vitamin E levels and hydrogen peroxide stability as has been shown in my study. A causative relationship between Vitamin E depletion and RBC stability <u>in vivo</u> is also suggested by Leonard's study (1971) in which an improvement in impaired RBC survival was demonstrated after Vitamin E therapy in Vitamin E depleted patients.

Discussion of the methods used

In the early 1920s, a fat-soluble dietary factor was discovered in wheat germ and lettuce the lack of which resulted in foetal death and resorption in the laboratory rat (Evans 1922). Its discovery came just after the anti-rachitic factor known as Vitamin D and so it was called Vitamin E. Tocopherol esters in the diet are hydrolysed by

pancreatic lipase and incorporated into micelles. Thus for adequate digestion, intact bile (bile salts and phospholipid) is required as well as adequate pancreatic function. Micelles incorporating free tocopherols are absorbed across the intestinal mucosal cell in to lymphatics in the chylomicra closely associated with very low density lipoproteins (VLDL) but distributed also throughout the lipoprotein with no specific plasma carrier protein. In blood there is a rapid exchange between plasma and erythrocytes, the tocopherol being concentrated in the red cell membrane. In the tissues Vitamin E is concentrated in all membrane containing structures such as cell walls, mitochondria, microsomes and the cell nucleus. It was not until the late 1930s that a unifying hypothesis was developed to explain a wide variety of apparently disparate syndromes. Here was the first hint that Vitamin E was an anti-oxidant in which it was considered to have a function in protecting cellular and sub-cellular membranes from damage by a number of stresses especially from free oxygen radicals. In relation to RBCs, this property is the basis of the hydrogen peroxide stability test used in this thesis. However Binder's results (1965) and mine suggest that this in vitro test in no way mimicks the oxidative stresses to the RBC in vivo. and the test would appear to be over-sensitive. Nevertheless a real influence of Vitamin E on red-cell survival in man is likely as discussed earlier. However we did not test the influence of vitamin E supplementation on RBC stability to hydrogen peroxide.

The role of selenium. The possible importance of selenium in the human is a much more recent discovery again based on earlier animal work. In 1973, Rotruck demonstrated that this trace metal was an essential component of a membrane-located enzyme glutathione peroxidase (GSH-Px), a selenoprotein containing 4 atoms of selenium per molecule (Rotruck 1973). However as with Vitamin E depletion, it is hard to demonstrate any clinical detriment of selenium depletion or benefit from therapy as indicated in a previous report from our group in patient No 50 from this thesis (Fell 1979). The simplified inter-relationships between Vitamin E, selenium, and GSH-Px are indicated in the diagram below relating to activities on the red cell membrane.



R-OH = Reduced fatty acid (FA)
ROOH = FA peroxide
GSH = Glutathione

It is suggested that the presence of Vitamin E on the RBC membrane blocks the production of membrane damaging FA peroxides (ROOH) and that GSH-Px with its essential co-factor selenium(Se), facilitates reduction of ROOH to inert FA (R-OH) by a reaction linked to the oxidation of glutathione (GSH). Thus depletion of Vitamin E, selenium or reduced activity of Red cell GSH-Px would be expected to render the RBC membrane liable to damage by the unchecked action of ROOH especially in oxygen rich tissues such as lung in which GSH-Px is especially plentiful.

Conclusions

Since only one patient had minor RBC abnormalities on microscopy and none had evidence of haemolysis or failed erythropoesis, there was no way in which any clinically relevant improvement in Vitamin E metabolism could have been tested by giving patients Vitamin E. Tappel (1973) was of the opinion:

> "The more research is done on the substance the more intriguing it appears. There is a nagging suspicion that there is a very important use for the Vitamin and we are not smart enough to see it".

Nevertheless important consequences do occur in circumstances of severe depletion described in Chapter 1 in which Vitamin E in blood

may be undetectable, but not in adults with Crohn's disease in whom the depletion, although demonstrable biochemically is less severe.

DISCUSSION OF CHAPTER 8
NUTRITIONAL THERAPY

Observation of the achievements of short term nutritional therapy of mean duration 5 weeks in Crohn's disease has indicated that enteral nutrition was largely unsuccessful. It failed to improve nutritional state overall and largely failed in the treatment of complications of Crohn's disease. Its only notable success has been in the long-term maintenance along with intermittent intravenous nutrition of one patient with intestinal failure. Short-term intravenous nutrition succeeded in improving the overall nutritional state, in healing a recurrent intestinal fistula, and assisted with the successful conclusion of a pregnancy. However its main achievement has been the intermittent management of intestinal failure. Complications however were more serious with intravenous than with enteral nutrition.

What was the main aim?

Underlying this detailed and time-consuming clinical audit was the desire to determine which of the complications of Crohn's disease were most likely to respond to nutritional therapy.

What do my observations add to what is known about the rôle of nutritional therapy in Crohn's disease?

Restoration of Body weight

The morbidity associated with nutritional depletion described elsewhere makes artificial feeding rational if oral supplements fail. Improvement in body weight and other anthropometric measurements are the most consistently reported aim successfully achieved in Crohn's disease (see Table 1.5). Enteral Nutrition: despite no significant overall improvement in weight during short term feeding there was marked individual variation, greater than with IVN. During EN average weight gain was 7% and overall only about 2% per week. But of those

who actually gained weight, mean weekly weight gain was 2.5% of pre-EN weight. Four patients, (one third of the EN fed group) failed to gain or lost weight. The circumstances associated with this were sub-acute intestinal obstruction (2), an enterocutaneous fistula(1) and severe protein-losing diarrhoea(1) (all discussed later). Voitk(1973) treated 7 patients with severe Crohn's disease with the elemental diet Flexical and states that they all gained weight without stating how much. Rocchio (1974) treated 25 patients with severe Crohn's disease using Enteral Nutrition. The 5 with disease confined to the small bowel appeared to do best, 4 of the 5 gaining weight, while in the other weight was maintained. Details of actual weight gain are not stated. Goode(1976) used oral instead of tube feeding of an elemental diet in 8 patients with Crohn's disease and reported in long-term feeding, restoration of lost weight varying from 10% per month in 3 pre-operative patients to 18.5% in patients following successful surgery. Ó'Moráin et al (1984) in a controlled study comparing EN with steroid therapy, treated 11 patients with acute Crohn's disease with the elemental diet Vivonex at libitum mostly by mouth without additional food achieved an average weight gain of just over 1 Kg in a four week treatment period. However, although on average this weight gain was sustained two months after EN was stopped, judging by the large standard error in his graph, in some patients weight must have dropped to less than pre-EN values. In a previous study, Ó'Moráin (1979), fed 24 patients using a similar EN regime. They failed to gain weight significantly over a four week treatment period. Intravenous Nutrition. In contrast to EN, weight gain occurred in all 20 periods of IVN. Longer term effects have not been assessed since the natural course of the disease, changes in subsequent drug treatment and surgical intervention in some cases make any contribution of IVN to long term maintenance of weight impossible to assess, except in the patients with intestinal failure discussed later. The only comparable series in which patients with Crohn's disease are distinguishable from others is that of Lochs (1983). In a study of 20 patients, fed for a mean duration of 28 days, weight gain was almost identical to this series with a mean weight change from 76 to 89 percent of ideal weight compared with 75

to 89 percent in my patients fed however for slightly longer (35 days). Greenberg (1976) recorded average weight gain of 1.09kg/week compared with 1.6 Kg in my patients.
In summary, short term IVN consistently improves weight while EN is less predictable. This would suggest that if weight loss is severe and its reversal considered important, IVN is to be preferred to EN.

Treatment of Diarrhoea
Only one of six patients achieved sustained relief of diarrhoea attributable to nutritional therapy. He required restriction of oral intake to achieve improvement during both IVN and EN. In some others 'bowel rest' seemed to have a temporary benefit. This notion that 'bowel rest' (deprivation to varying degrees of oral food and fluids) might induce a remission of Crohn's disease including the improvement of diarrhoea has received some attention in the literature in relation to EN (Ó'Moráin 1979 and 1984) and IVN (Greenberg 1976). Greenberg's was an uncontrolled study reporting clinical remission including relief of diarrhoea in 33 out of 43 patients treated with IVN and bowel rest in whom previous therapy had failed. the results were regarded as a success for the combination of IVN and bowel rest. In contrast Lochs and his colleagues(1983) in a controlled study demonstrated equal benefit (reduction in CDAI and weight gain) in patients treated with IVN with and without bowel rest. The symptom of diarrhoea however was not singled out for attention. The method used in my studies has been the stepwise introduction of bowel rest (restriction of food and /or fluids). This approach was acceptable to patients unwilling initially to be deprived of oral intake. The results were overall disappointing in relation to treatment of diarrhoea.

Treatment of abdominal pain and bowel obstruction
Non-obstructive abdominal pain (constant rather than colicky in character) resolved with IVN without bowel rest in one patient. The success of EN and partial bowel rest (deprivation of oral food but not fluids) in the treatment of a painful bowel stricture in patient 25 can be contrasted with the failure of IVN and bowel rest to

relieve the pain of confluent active rectal disease. The difference in the aetiology of the rectal symptoms may have been the crucial factor.

Sub-acute intestinal obstruction Nutritional Therapy with bowel rest was used for relief of obstructive symptoms in five patients. All had undergone previous surgery and there was a desire to avoid further operations if possible. Mixed success is reported in my patients. Voigt (1973) reported success with EN in one of two patients, while Russell RI (1979) using Vivonex as a source of EN, noted improvement in 2 patients but in both surgery was required later. Reilly (1976) while noting nutritional benefit in three patients who received IVN was not able to avoid surgery. Eisenberg (1974) treated 8 obstructed patients but was unable to avoid subsequent surgery. My experience added to other anecdotal evidence would suggest that nutritional therapy as EN or IVN does not usually avoid the necessity for surgery but may improve nutritional state prior to operation. Whether nutritional improvement alters the outcome of surgery in this context remains unproven.

Treatment of fistulae

EN for 36 weeks in 6 patients was unsuccessful and none healed. Only in patient 50, in whom prolonged EN at home was added to 'top-up' periods of IVN, did a recurrent fistula remaining healed. In searching the literature one is constantly frustrated by the difficulty in distinguishing the results of nutritional therapy in sub-groups with specific complications such as fistulae submerged in larger series. The healing rates of fistulae in Crohn's disease in the literature in which fistulae are discernible from other complications is summarised in Table 11.1. Overall EN is disappointing as I found while IVN appears to afford a better healing rate if only in the short term. A patient described by Strobel (1970) seems very similar to our patient whose fistula remained unhealed except during repeated courses of IVN. While surgery gives the best chance of healing (McIntyre 1984), the patients studied here had all had previous resections so that they and we were hoping to avoid further surgery. Of the six treated unsuccessfully with EN, surgery

TABLE 11.1

NUTRITIONAL THERAPY IN THE TREATMENT OF FISTULAE IN CROHN'S DISEASE

ENTERAL NUTRITION

SERIES	DURATION OF EN (weeks)	FISTULAE TREATED Total	Healed	SURGERY
THIS SERIES	6	6	0	3/6
Voitk (1973)	ns	1	0	1/1
Rocchio (1974)	ns	1	0	ns
Axelsson (1977b)	3½	5	2*	2/5
	TOTAL	13	2	15% healed

Notes:
* Prednisolone added in 1 patient
ns = not stated

INTRAVENOUS NUTRITION

SERIES	DURATION OF IVN Mean (weeks)	FISTULAE TREATED Total	Healed	
THIS SERIES	5	1[1]	1	
Strobel (1970)[2]	25	4[3]	4	
Meng (1971)	5	1	0	
Greenberg (1976)	3½	14	7[4]	
Eisenberg (1974)	ns	18	5	
Rault (1977)[2]	ns	2	1	
	TOTAL	40	18	45% healed[5]

Notes: 1 Recurred each time IVN stopped (see text)
2 Prolonged IVN at home
3 In 2 of 4, fistula recurred when IVN stopped
4 6 of the 7 required additional prednisolone
5 Only 33% if patients given additional prednisolone excluded

in three was successful in the short term at least in healing the fistulae. Surgery in Eisenberg's patients enhanced the fistula healing rate from 5 out of 18 (IVN alone) to 16 out of 18 (IVN combined with surgery)(Eisenberg 1974). The role of IVN in these patients is doubtful.

Treatment of intestinal failure

There can be little doubt that IVN was of great value in three of the four patients with severe malabsorption described in Chapter 8. The fourth patient although requiring repeated nutritional support over the years died partly as a result of the complications of IVN. I have used the term intestinal failure to describe patients who were unable to sustain an adequate nutritional state without recourse to artificial feeding. Only two of the four however had resections substantial enough to fulfil the definition of 'short bowel syndrome' suggested by Jeejeebhoy (1983) - resection of more than 50% of the bowel. In Crohn's disease a combination of resections and impaired function of diseased residual bowel may result in permanent intestinal failure. This was the case in our four patients. An additional problem for the clinician is illustrated by patients 49 and 51 who had only 200 and 100 cm respectively of small bowel remaining. They both had new and active disease in unresected colon (pain and bleeding) which had defied medical treatment. IVN with bowel rest while improving their general nutritional state did nothing to improve their severe colonic symptoms. Neither patient understandably wished further surgery but surgery was required as an emergency in both cases (severe rectal arterial bleeding and fulminant colitis) and both did well although the second patient has remained chronically underweight. With hindsight perhaps surgery would have been safer earlier. In a review of the therapy of short bowel syndrome (SBS), Jeejeebhoy (1983) suggests a stepwise approach to its management, progressing from the use of anti-diarrhoeal agents to specially formulated easily absorbed oral or tube fed enteral diets. All our patients had progressed beyond this stage with chronic diarrhoea, steatorrhoea and weight loss despite oral drugs and nutritional supplements. As Jeejeebhoy recommends they were given

oral food (or EN in the case of patient 50) combined with periods of IVN. As with the patients with SBS described by Ladefoged (1978), we failed to persuade our patients to restrict food or fluid intake to aid control of their diarrhoea. An alternative method of long-term management pioneered by Broviac (1974) is prolonged IVN at home saving the cost of a hospital bed and potentially enhancing the general quality of life of the patient. We did not employ this technique but by providing EN at home, pump-fed overnight 5 or 6 nights a week, patient 50 was able to walk his dog, look after a small garden allotment and he became a keen amateur photographer! Two of the other three after their final operations were able to obtain part-time jobs. Two out of three Crohn's patients with massive bowel resections described by Jeejeebhoy (1976) and receiving IVN at home were described as socially active housewives. In contrast 7 such patients described by Rault (1977) were unable to work. The social toll of severe intestinal failure in the fourth patient was great. During her time with us she managed to obtain a clerk's job, but after a month she fractured her femur in a trivial fall because of severe osteomalacia and was never in sufficiently good health to work again.

Miscellaneous complications

The successful treatment of growth failure and promotion of puberty in patient 49 can be attributed to a combination of IVN and surgery. The use of both EN (Ó'Moráin 1979) and IVN (Layden 1976; Strobel (1970) has been successful in promoting both linear growth and puberty in children with severe Crohn's disease. I believe our use of IVN to sustain pregnancy in Crohn's disease is unique.

Correction of protein depletion

Improvements in serum albumin levels and those of transferrin occurred during IVN but not EN. Yet as with weight gain, improvements in some patients were masked by deterioration in 3. Certainly EN, using the elemental diet Vivonex, has been shown to reduce intestinal protein loss in Crohn's disease (Logan 1981) and to induce a rise in serum albumin concentration (Logan 1981: Ó' Moráin 1984). However

using a different method of measuring protein loss, Axelsson (1977a) found no change in albumin degradation and by implication no change in protein loss in patients with inflammatory bowel disease (mostly ulcerative colitis). With respect to IVN, the average rise in serum albumin of 3g/l in my patients fed for 35 days compares with a higher gain of 4g/l for a 25 day feeding period in Crohn's patients reported by Greenberg (1976). In contrast, Lochs (1983) in a study of 20 Crohn's patients receiving IVN found no significant increase in albumin but average pre-IVN albumin levels were higher than in my patients. Using prealbumin concentration as a more sensitive indicator of changes in protein nutrition, Lochs noted a significant rise after IVN. I have used transferrin levels for this purpose which in the absence of iron deficiency are a useful marker of changes in protein status.

Reduction in disease activity

The disease activity index (Harvey 1980) is simply a global clinical assessment of progress taking into account general well-being and a number of complications analysed separately in earlier sections. Taking nutritional therapy as a whole, activity fell in the majority of patients but inactive disease was achieved in only 40%. Furthermore occasional other changes in therapy may have contributed to these modest improvements. That improvement was simply due to the passage of time or bedrest is possible and a valid criticism of any uncontrolled therapeutic study. However this is unlikely since the majority of the patients had been in hospital, largely on bed-rest and yet were deteriorating clinically before nutritional therapy was commenced.

Enteral Nutrition Ó'Moráin (1979) using erythrocyte sedimentation rate (ESR) in an uncontrolled investigation of EN showed a significant fall in ESR during a four week course of treatment. In his subsequent controlled investigation (Vivonex v steroids) using the same activity index as in my studies, a steady fall in activity was observed in both treatment groups and was maintained at 3 months, 2 months after oral food had been re-introduced. Other studies in mixed inflammatory bowel diseases have shown a reduction in activity

for example that of Axelsson (1977b). The less dramatic reduction overall in my patients was due partly to the deterioration in three patients and may also have been a difference in beneficial effect of the various enteral diets used. Furthermore we were not able to persuade all of the patients to give up taking oral food. The relative value of different enteral diets has not been investigated in Crohn's disease but is examined in the controlled experiments in rats reported in Chapter 10.

Intravenous Nutrition A better reduction in activity score was achieved with IVN (Mean fall from 8 to 4). Strobel (1979) recorded ESR and measured protein loss as a means of assessing progress in children with Crohn's disease receiving long term IVN. Those whose albumin excretion was low appeared to remain in remission after IVN was stopped in contrast to those who were losing protein. Greenberg (1976) reported clinical remission (relief of diarrhoea, abdominal pain and well-being) in 33 of 43 patients treated with IVN and bowel rest. Lochs (1983) found a significant reduction in activity in patients on IVN using a different numerical index (Best 1976). His study compared IVN and oral food with IVN and bowel rest but he he found that no extra benefit was achieved with bowel rest. Our patients were not deprived of oral food except when severe diarrhoea or obstructive symptoms were being treated. Overall, my experience and that of others would suggest that a modest reduction of disease activity can be expected with both EN and IVN. It was possible to judge whether nutritional therapy had any benefit in the longer term except in patients who had several courses of treatment.

Complications of nutritional therapy in Crohn's disease

Enteral Nutrition The possible complications of EN are indicated in Table 11.2 which is a combination of personal experience and a recent review by Bastow (1986). The preventive measures routinely employed in our department are also indicated in the Table. The main problem in Crohn's disease in relation to EN is distinguishing between the symptoms of active disease (for which EN is being given) and the gastrointestinal side-effects of EN. Despite carefully controlled slow flow 'starter regimes' and continuous pump feeding two patients

TABLE 11.2

COMPLICATIONS OF ENTERAL NUTRITION[1] AND THEIR PREVENTION

PROBLEM	PREVENTIVE MEASURES (routinely employed in this series)
1. MECHANICAL/FEED DELIVERY	
Wide-bore (eg Ryle) tube	
irritation and inflammation of oesophagus. Reflux into the oesophagus	Not used at all
Fine-bore tubes (preferred)	
Coiling in oropharynx or entering trachea	Position checked before commencing feed.
Tube tip may ride up into Oesophagus	Weighted tip can be used
Blockage with viscous feed	Regular flushing with water. Routine use of electrical pump Continuous not bolus feeding
2. GASTROINTESTINAL (over 25%) (See Bastow 1986)	
Nausea and vomiting	Low flow dilute feeds increasing flow and strength over 4 days up to 2 - 3 litres/day
Diarrhoea due to bolus feeding	Continuous feeding. Also 'starter' regime as above
Diarrhoea due to high osmolarity	Start with dilute feed to allow adaptation. Use of iso-osmolar feeds See Chapter 10
Diarrhoea due to bacterial contamination	Use freshly prepared feed and avoid rewarming of feeds
3. METABOLIC	
Dehydration, hyperglycaemia, electrolyte abnormalities, vitamin and trace metal deficiency	Correct delivery and formulation of enteral diets
4. RESPIRATORY	
Aspiration of feed (more likely in inconscious patients)	Regular check of tube position Nocturnal feeding semi-supine

1 Bastow (1986) - Review

(16%) were unable to tolerate EN due to poor tolerance of the naso-gastric tube and bloating in one and actual vomiting in the other. In the second patient obstructive symptoms already present were actually made worse by EN and it was abandoned in favour of IVN. In the other two in whom EN was prematurely stopped the reason was a failure of the treatment to improve the patients' symptoms. In the first severe diarrhoea continued and he lost weight. In the other obstructive symptoms did not improve and she was losing weight despite the progression of her pregnancy. In both IVN was commenced. Thus two of three patients with symptoms of intestinal obstruction actually deteriorated during EN and perhaps EN should not be given in this circumstance.

Intravenous Nutrition Possible complications and measures taken in our patients to try and prevent and combat problems are shown in Table 11.3. Overall feeding complications serious enough to terminate IVN prematurely occurred in only 4 cases (20%). In one, this was a result of an accumulation of repeated central vein trauma over the years and she eventually died as a result of central vein blockage. This serious complication has been reported by several authors in patients on long-term IVN including 17 occurences in 9 patients described by Ladefoged (1978). As in our patient several of his had a persistant total occlusion many months after IVN. In the other three probable or definite cannula infection was responsible. Removal of 32 cannulae was premature in more than half (Table 8.12) most commonly due to cannula infection or blockage. It was gratifying however to observe a marked improvement in cannula life after the introduction of pumps and 3 litre receptacles for the feeds and less frequent interruptions to feed flow with no other changes in nursing technique. The interpretation of pyrexia, which occurred in nearly half of the days of IVN, was difficult. Bacteriological swabs from the insertion site gave a low yield. Colonisation of the catheter hub was not investigated but has been suggested as the commonest cause of cannula sepsis during IVN (Liñares 1985). The results did indicate however the relative importance of active Crohn's disease and complications of IVN and its delivery as causes of pyrexia. Cannula

TABLE 11.3

COMPLICATIONS OF INTRAVENOUS NUTRITION[1] AND THEIR PREVENTION

PROBLEM	PREVENTIVE/COMBATIVE MEASURES (routinely employed in this series)
1. MECHANICAL/FEED DELIVERY	
Cannula sepsis - local or systemic	Scrupulous aseptic technique during insertion and changing of dressings Avoid disturbing crust at insertion site. Bacteriological swab from site of cannula and 'draw-back' blood culture. Consider cannula removal or antibiotics
Cannula blockage	Continuous feeding by pump. Use of 3 litre containers (once a day) rather than 2x500ml (3 times a day) Prevention of sepsis.
Traumatic complications: Pneumothorax	Good technique. Less likely with infraclavicular rather than supra-clavicular route of insertion
Venous thrombosis often due to combination of repeated insertion and local sepsis	Vary site of insertion. Aseptic technique. Avoidance or repeated insertion. Large central vein always used
2. METABOLIC / DEFICIENCIES	
Hyperglycaemia and osmotic diuresis	Avoidance of high glucose concentration with use of fat as part of the energy source. Use of continuous rather than bolus feeding
Liver disturbance	Usually minor and transient. Settles when IVN ceases
Electrolyte disturbances	Careful monitoring of blood levels and adjustment of electrolyte content
Trace metal and vitamin deficiencies	Biochemical monitoring and routine supplementation of trace metals and vitamins (see Chapter 2)
Fluid overload especially in patients with hypoalbuminaemia	Temporary reduction in iv volume Occasional intravenous albumin infusion

1 Various sources eg Cetrullo (1976)

related infection was roughly twice as common as active Crohn's disease or its complications. Bacteriological culture of a removed cannula tip and a search for intra-abdominal abscess were the most fruitful ways of achieving a definite diagnosis.

Are controlled trials the best method of evaluating nutritional therapy in Crohn's disease?

In the evolution of any new therapy, attention is drawn to it firstly by the pioneers of the therapy extolling its virtues illustrated by a description of a few highly selected patients not chosen to emphasise any failings of the therapy! Experience of the therapy spreads bringing with it a more balanced appraisal of the treatment's worth often emphasising the drawbacks. Then the scientific community demands controlled therapeutic studies and many eminent writers will ignore all others. Such an evolution has occurred with nutritional therapy in relation to Crohn's disease and only a few controlled studies have appeared as described earlier. Why is this?. In addition to the trial design difficulties described in Chapter 1 in relation to drug therapy, the evaluation of nutritional therapy is hampered by:

1. The technical difficulties, hazards and high cost of medical and nursing manpower materials and monitoring.
2. Small numbers of patients thus available in any one hospital suitable for treatment coupled with:
3. The large numbers of patients and long periods which were necessary to demonstrate even marginal significant clinical improvement in the studies of drug therapy; hence the need for multi-centre studies with the problems of differing standards and protocols.
3. The ethical difficulties in stopping other therapy which would be desirable for the purposes of adequate scientific design. (Ó'Moráin (1984) in his controlled comparison of EN with steroids was refused ethical approval to test EN against placebo despite the controversy which still surrounds the efficacy of steroid therapy; personal communication)
4. The necessity, because of small numbers, of artificially

homogenising the patients at entry using numerical indices such as those of Best (1976) and Harvey (1980). This gives the false impression that patients with the same activity score have similar symptoms or complications. The patient (and his doctor) wish to know whether a fistula will heal not whether an activity score will be reduced!

Is my study design justified?

This study can be regarded as an appraisal of the contribution of nutritional therapy to the management of a highly selected and atypical group of Crohn's patients: highly selected largely because of failure of other therapy and atypical of the overall Crohn's 'population' in that there was a greater predominance of patients with extensive or very active disease. The only sense in which nutritional therapy is compared with other more standard therapy is that in many cases standard therapy had failed to relieve symptoms, successfully treat complications or halt a decline in nutritional state. Thus it is not a controlled therapeutic trial and its effects cannot be extricated from the effects of the passage of time (especially in a disease with such an unpredictable clinical course) or indeed from the effects of putting a patient to bed! Nevertheless I believe that valid conclusions about nutritional treatment can be drawn when:

a) it appears to have no benefit since it is an expensive unpleasant and potentially hazardous form of therapy.
b) Complications appear to limit its safety or usefulness.
c) It appears to alter the clinical state in patients in a stable chronically ill state.
d) used repeatedly it appears to halt otherwise inevitable decline. In this circumstance the patient can be regarded as his own control.

I believe that my uncontrolled but carefully observed clinical practice is of great value in attempting to answer what I consider to be the important questions about treatment, those I have chosen to call the Primary Aims of therapy. A standardised approach such as I have adopted assessing the success or otherwise of achieving predefined individual aims in the context of other therapy seems to

me the only way of giving useful clinical guidance. When combined with others' experience it gives a useful consensus for an important complication which would be impossible in any of the controlled studies which fail to recognise the wide clinical disparity between patients. For example my experience added to others would indicate that short term EN is unlikely to result in healing of abdominal fistulae. I therefore consider the global assessment of disease activity as embodied in the CDAI of Harvey (1980) of lesser interest and have observed it as a secondary aim.

Methods of monitoring progress of nutritional therapy
(Anthropometry and protein state)
The use of body weight related to standards for height and sex is widely used (Van Patter 1954; Mekhjian 1979). Triceps skinfold thickness and the derived mid-arm muscle circumference were also measured and as in studies by Harries (1982), the 3 anthropometric measurements correlated well. I have therefore emphasised only body weight. Only simple assessments of protein status have been employed and it was not possible to examine the pathogenesis of protein depletion in these studies. The use of serum albumin is not ideal since temporary changes in serum concentrations occur in circumstances other than protein depletion, such as sepsis (lower) and dehydration (higher), circumstances not uncommon in severe Crohn's disease. Furthermore the metabolic turover of albumin is relatively slow and serum albumin is not very sensitive to rapid changes in protein nutrition. Yet it is widely used and I have compared my results with others. A number of faster turnover proteins are available including transferrin and offer a more sensitive indicator of protein malnutrition (Jeejeebhoy 1981: Reeds 1976). My experience in calculating dietary intake in a pilot study of 20 patients indicated such unreliability in dietary recall especially of intake before the recent exacerbation of disease and considerable inter-observer variation in calculation of energy and protein intake from dietary histories by dietitians. I was unable to assess the contribution of poor food intake to the malnutrition before

nutritional therapy. However many patients were anorexic or avoided food because it exacerbated their symptoms.

DISCUSSION OF CHAPTER 9
MAGNESIUM AND ZINC REQUIREMENTS DURING INTRAVENOUS NUTRITION

Routine monitoring of Blood and urine Mg and Zn levels has been useful in determining safe levels of Mg and Zn provision during IVN and has provided some insight into the determinants of serum Zn concentrations and urine Zn excretion during IVN in patients with severe Crohn's disease. Recommendations were made for the supply of intravenous Mg based on monitoring serum and urine Mg levels: 5-10 mmol Mg a day (more if Mg depletion is present before IVN). Zn provision of 100-200 μmol daily may require to be adjusted based on monitoring urine Zn excretion in individual patients.

Magnesium provision during intravenous nutrition

The rationale for IV Mg recommendations during IVN is seldom clear from the literature and recommendations have varied from 2-21 mmol/day (Chapter 1). In the early days of IVN, Dudrick (1969) based his recommendations on work in infants with severe congential anomalies. In later patients, Dudrick (1971) as well as Meng (1971) aimed intravenous Mg supply at maintaining serum levels in the normal range. Jeejeebhoy (1976) based his Mg provision on measurements of urine, stoma, and faecal losses before IVN and adjusted the intake according to serum Mg levels during IVN. Driscoll's recommendations (1978) were for a group of patients similar to our own. More recently, Shenkin and Wretlind (1978) have offered guidelines for different types of patients-0.04 mmol/kg/day as a basal recommendation to cover minimal requirements, a moderate amount (0.15-0.2 mmol/kg/day) for depleted patients or those with increased losses, and high supply (0.3-0.4 mmol/kg/day) for patients during or subsequent to a period of severe catabolism. Our patients probably fall into the middle category, but Mg needs may be higher in individual cases. IVN solutions available in Britain contain variable amounts of Mg:

Amino acid / protein hydrolysate solutions		
Synthamin 9, 14 an 17 (Travenol Laboratories)		5 mmol/litre
Vamin (with glucose or fructose) (KabiVitrum Ltd)		1.5 mmol/litre
Aminofusin (Pfrimmer and Co)		5 mmol/litre
Glucose Sources (with electrolytes)		
Glucoplex 1000 and 1600 (Geistlich Sons Ltd)		2.5 mmol/litre
Electrolyte/Trace metal solutions		
Solution A	(Travenol Laboratories)	14 mmol/vial
Addamel	(KabiVitrum)	1.5 mmol/10 ml

Therefore Mg requires to be added in some cases. Addamel (KabiVitrum) contains only 1.5 mmol/vial and is insufficient by itself to provide Mg needs; 50% Mg sulphate solution (2 mmol/ml) is a suitable intravenous preparation for addition to amino acid and glucose solutions.

Zinc provision

Is serum Zinc level of any help in determining zinc requirements?

This study has demonstrated low serum zinc levels in severe Crohn's disease and confirms the findings of other workers (Solomons 1977; McClain 1980; Storniolo 1980). Despite nutritional improvement in all patients, low serum zinc levels were not changed during intravenous nutrition despite zinc supply up to 220 µmol/day. Fleming (1976) suggested that persistently low serum zinc concentrations during IVN in the absence of disease associated with hypozincaemia might indicate zinc deficiency. The three patients he described, had conditions which might be associated with depression of serum zinc concentration (abscess, alcoholism with pancreatitis, short bowel syndrome). However, the only proof of zinc deficiency is the emergence of clinical signs rapidly corrected by supplying zinc alone. Serum zinc levels do not give a direct guide to intracellular zinc content (Golden 1981), and can be moderately depressed by a variety of factors unrelated to tissue depletion. Zinc in serum bound to α-2 macroglobulin does not appear to be exchangeable (Sturniolo 1980) and albumin is the principal zinc transporting protein. Increased production of ACTH or administration of high dose

corticosteroids lowers the albumin-bound zinc fraction, (Flynn 1971; Falchuk 1977) as does altered pituitary activity in stress and infection (Wannemacher 1975). These factors may be partly responsible for depressed plasma zinc levels in Crohn's disease. That hormonal infleunces probably play a part in regulating serum zinc levels is suggested by the diurnal rhythm in normal subjects (Morrison 1979). Leucocyte endogenous mediator (LEM) lowers total plasma zinc levels in infection (Wannemacher 1975) and in Crohn's disease (Solomons 1978). It has been suggested that low serum zinc in Crohn's disease simply reflects reduction in serum albumin (Sturniolo 1980). This view is not entirely supported by our data. Although there was a good correlation between serum albumin and serum zinc in our combined group, this did not hold true for the patients receiving IVN during which serum albumin levels tended to rise while zinc levels did not. Wolman (1979) was able to show a positive relationship between plasma zinc and the amount of zinc infused during intravenous nutrition. In that study, zinc was infused in quantities up to almost 400 µmol/day and the patients with diarrhoea achieved positive zinc balance with 185 µmol (12mg) a day. In my study, patients with severe diarrhoea received less than this (Table 9.1) and it is possible that a positive relationship between zinc supply and plasma zinc would have been achieved by increasing zinc supply in these patients. In patient 52 serum zinc level fell during a period of rapid anabolism. This single observation clearly needs further documentation, but Kay (1976) considered anabolism in the absence of adequate zinc supply to be responsible for profound falls in plasma zinc levels to less than 5 µmol/l preceding clinical signs of zinc deficiency. In the present study, serum zinc concentrations remained low throughout IVN, despite substantial increases in serum albumin in several patients. Clearly serum zinc levels gave no guide to zinc requirements.

Is urine zinc excretion helpful?

In this study low urine zinc levels before IVN were found in severe Crohn's disease in contrast to a previous report (Mills 1979). Low urine zinc has been considered to reflect tissue zinc depletion, (Sandstead 1975) but may also be due to raised levels of LEM as this

substance, released from white blood cells, stimulates liver uptake of amino acids (Beisel 1976) and might lower the ultrafilterable amino acid-bound zinc fraction and therefore the amount of zinc available for urinary excretion. Thus low urine zinc might have been in part due to factors other than zinc depletion. The results suggest there may be inefficient retention of zinc supplied by the intravenous route. When the three intake groups were compared we found a relationship between intravenous zinc supply and urine zinc excretion but there was wide variation in the proportion of infused zinc excreted in urine within each of intake groups and during the course of IVN in individual patients. We also observed a rapid increase in urine zinc excretion during the first week of IVN. These findings might be explained by a difference in chelation of zinc with other nutrients in the premixed feed and differing availability of zinc binding sites in plasma. Increasing the serum zinc ultrafilterable fraction would result in urinary losses. Van Rij (1979) showed a six-fold increase in urine zinc excretion when amino acids and zinc were given intravenously. Freeman (1975) attributed a similar rise in urine zinc excretion to the formation of amino sugar-zinc complexes. Reduction in urine zinc excretion was seen in two patients who received plasma proteins intravenously during intravenous nutrition. This suggests that the retention of intravenous zinc may be improved by increasing zinc binding proteins, principally albumin, thereby perhaps reducing the ultrafilterable zinc fraction. The variability of zinc excretion during IVN makes firm recommendations about additional zinc supply difficult. Nonetheless, monitoring of urine zinc excretion may help in the management of individual patients when losses are high.

Recommendations for zinc provision

As a general rule we have found that the provision of 100 µmol (6 mg) of zinc/day is adequate to prevent the syndrome of zinc deficiency during IVN. Low urine zinc excretion before IVN (<2 µmol zinc/day) can be expected when the patient is zinc depleted but not catabolic. During IVN low excretion can be expected when blood or albumin is given. It is suggested that 24 hour urine zinc excretion should be

measured several times during the first two weeks of IVN. If urinary zinc excretion is persistently high (>80 μmol/day) or even exceeds input, the clinician should suspect either catabolism or poorly utilised zinc supply. In these circumstances, it might be reasonable to increase zinc supply to 200 μmol/day, especially if the patient subsequently becomes anabolic.

DISCUSSION OF CHAPTER 10
COMPARATIVE EFFECTS OF ENTERAL DIETS IN RATS

This controlled study in a monogastric animal has shown that the defined formula diets (DFD), Vivonex and Vivonex HN are no better with respect to efficient utilisation of the ingested feed than the cheaper and more palatable polymeric diets (PD), Ensure and Clinifeed and Flexical when fed isocalorically. Indeed, the DFD may be inferior in some respects especially in relation to nitrogen (N) wastage. The DFDs produce a slightly lower faecal residue which might be advantageous clinically.

Weight gain and nitrogen accretion

Failure to demonstrate any significant differences in weight gain was a little surprising when one compares for example a median weight gain of 37% for Vivonex with 63% for Clinifeed. Why should this be? Although the median initial weight was very similar in the six diet groups (Table 10.2), the spread in each group was quite large and the slightly larger rats grew less perhaps because of differential calorie deprivation with the constant calorie intake provided as the basis of the feeding regime. Being equally spread through the groups their presence may have obscured real differences between the diets. However this problem did not obscure differences in terms of whole body nitrogen which was low in Vivonex fed rats probably reflecting comparatively low N intake.

Nitrogen balance and utilisation

However, high N intake did not imply better N retention and the highest N wastage was with the diets of highest N content. Least N

wastage was with Flexical. The reasons for efficient utilisation of this latter diet are uncertain but it has a very different composition from Vivonex (V) and Vivonex High Nitrogen (VHN). N wastage with VHN was mainly by urinary loss and when V and VHN (identical apart from N content) were compared, much of the excess N in VHN was excreted in urine. This accords with the findings of Smith JL (1982) in human balance studies. Comparisons of V and VHN shows that the principal difference is the high content of glutamine and glycine in VHN which are converted largely to urea instead of protein (Smith JL 1982). Indeed the diets differ not only in composition (Table 10.1) but in the degree of carbohydrate polymerisation and it is not possible to say which element was more important. That would require artificial synthesis of diets varying one constituent at a time. Our aim was to look at commonly used commercial diets in these experiments. Differences in diet composition may also affect intestinal absorptive function as Nelson (1981) and Young (1981) have previously demonstrated in rats. These effects on absorption might affect the nutritional efficiency of the diets.

Faecal residue

All the test diets induced a low faecal residue but in contrast to their nutritional achievements, the DFD, V and VHN were superior to PD in this respect. Why might these differences occur? A possible explanation may lie in the composition of the diets and in particular to the carbohydrate composition. In the DFD, V and VHN, carbohydrate was in the form of oligosaccharides and glucose and was presumably largely absorbed in the small gut. However, the other diets contained more complex sugars and, in the case of Clinifeed, the principal protein source, milk, may also have contributed complex polysaccharides to the luminal contents. In monogastric animals, of which the rat and human are two examples, non-starch polysaccharide, which is the main component of dietary fibre, is thought to be fermented by anaerobic bacteria (Nyman 1982) to produce various gases which are expelled, and short-chain fatty acids to provide energy for the proliferation of bacteria (Cummings 1981). It seems likely that

the provision of fibre in the form of non-starch polysaccharide determines the number of bacteria which can be supported in the colonic environment. Thus, the high fibre control diet produced a very high bacterial content possibly a result of the high fermentable-fibre content of the diet as well as a very high residue of non-fermentable fibre. In the test diets, reduced fermentable fibre would provide less energy for microbial growth. At the same time, a low quantity of non-fermentable fibre was present. Both these factors would contribute to a very low faecal bulk. In fact, the non-bacterial constituents of the faeces in the test diets were partly due to animal hair which could not be separated from the faeces. This accentuates the contribution that bacteria make and suggests that the lowest faecal bulk produced by V and VHN was principally due to lower bacterial content. We had the impression that nitrogen output correlated quite closely with bacterial output. However, because only pooled faeces from each example were analysed, we were not able to subject the results to correlation analysis. It seems likely, however, that most of the faecal N is derived from bacteria. The method of measuring faecal bacterial content and other contituents of the faeces (Stephen 1980) is a direct one and may have advantages over previous methods which rely on the culture of faecal bacteria and bacterial counting techniques. The variable effect on bacterial content of faeces (Koretz 1980) by these methods may be due to differences in methods of culturing (Winitz 1970; Allenbury 1972). Moreover it is difficult to extrapolate accurately from in vitro faecal bacterial counts to the contribution bacteria make to faecal bulk in vivo.

We used intact animals rather than an experimental disease model of Crohn's disease. Nevertheless the differences between the diets which have emerged deserve further study in humans especially those with impaired bowel function. The methods used including serial measurements of whole body N are applicable to human subjects.

11.2 MALNUTRITION IN CROHN'S DISEASE - AN OVERVIEW

Malnutrition in perspective

Although I have emphasised some serious consequences of nutritional depletion, many of the patients were normal or relatively mildly depleted. Table 11.4 attempts to place nutritional deficiency in perspective by showing that relatively few patients had what I have described in the various Chapters as 'severe' abnormalities:
(i) very low blood levels or numerous abnormalities (Chapter 3).
(ii) clinical symptoms associated with objective evidence of deficiency (Chapter 4-6).

Small bowel disease (SB)

Only 6 (25%) had severe abnormalities and only 2 (8%) had more than one.

Large bowel disease (LB)

Four (24%) had severe abnormalities (one each).

Small and large bowel disease (SB+LB)

In contrast, 13 (54%) had serious abnormalities and in all but one patient the small bowel involvement was widespread. All but two had more than one problem. All the patients with symptomatic deficiency (Chapter 4,5 and 6) had widespread disease and more than one symptomatic deficit.

Thus severe nutritional deficits were present in only 35% of the whole patient sample and all the problems causing symptoms were in a small group with both large bowel and widespread small bowel involvement.

What do these studies of malnutrition in Crohn's disease add to current knowledge?

I have offered a new approach to the examination of malnutrition in Crohn's disease by attempting to place in some sort of clinical perspective the large array of laboratory abnormalities which were found. While abnormalities were common severe abnormalities occurred in a few patients with widespread disease who were underweight. In

TABLE 11.4

NUTRITIONAL DEFICIENCY IN PERSPECTIVE
Patients with severe abnormalities

Pat No	Site	CHAPTER 3: anaemia (Hb <10 g/l) n=13	CHAPTER 3: low alb (< 25 g/l) n=8	CHAPTER 3: > five abnorm. n=11	Chap 4 (Mg) Tetany n=3	Chap 5 Osteo-malacia n=6	Chap 6 Impaired DAT* n=3
1	SB-TI	●		●			
3	SB-TI	●					
15	SB-TI	●					
19	SB-W		●				
20	SB-W	●	●	●			
21	SB-W	●					
27	LB			●			
29	LB	●					
31	LB	●					
41	LB		●				
44	SB+LB-TI	●					
47	SB+LB-W		●	●		●	
48	SB+LB-W		●	●	●	●	
49	SB+LB-W					●	●
50	SB+LB-W			●	●	●	●
51	SB+LB-W	●	●	●		●	
52	SB+LB-W		●	●			
53	SB+LB-W	●		●			
56	SB+LB-W	●					
58	SB+LB-W	●		●			
59	SB+LB-W					●	
62	SB+LB-W			●	●		●
65	SB+LB-W	●	●				

Notes:
* = Dark adaptation testing
SB = small bowel, LB = large bowel, SB+LB = small and large bowel
TI = terminal ileum W = widespread small bowel involvement

addition symptoms worthy of deeper investigation have been identified. These were symptomatic magnesium deficiency, osteomalacia not confined to patients with bowel resection or widespread small bowel disease, and night blindness. Attempts have been made to identify patients at risk, to provide simple screening tests and to assess the effectiveness of therapy. This first systematic study of Vitamin E has been useful in showing that Vitamin E depletion is of little clinical consequence in Crohn's disease.

11.3 NUTRITIONAL THERAPY IN CROHN'S DISEASE - AN OVERVIEW

Is Nutritional therapy ever likely to become first-line treatment in acute Crohn's disease?

Enteral nutrition My results were disappointing although 'primary therapy' was not a specific aim. I am surprised that Ó'Moráin (1984) managed to persuade so many patients to take Vivonex by mouth. It is expensive, unpleasant to smell and taste even with flavourings and unless (as was not shown in his study) EN proves superior to short term steroid therapy it is hard to imagine it being used as first line therapy. Patients frequently will not accept deprivation of oral food and our method of tube-feeding even with a fine bore tube was objectionable to some and limited the duration of feeding. Nevertheless it may be useful when corticosteroids or other drugs fail or are contraindicated. EN seems unlikely to benefit the patient who wishes to regain lost weight fairly quickly. Intravenous nutrition. While nutritional improvements can be expected the role of bowel rest as 'primary therapy' is less certain as discussed earlier and again corticosteroids would be preferred. IVN is expensive and potentially hazardous. In the current state of knowledge including the data presented here, IVN is not justified as first choice for primary therapy (bowel rest) in acute exacerbations of Crohn's disease.

Nutritional therapy for the complications of Crohn's disease

I believe that useful information has been gained to assist the practicing clinician faced with a patient who is losing weight and

who may have complications of Crohn's disease. Short term Enteral Nutrition (average 5 weeks duration) was largely unsuccessful. It failed to improve body weight or protein nutrition produced only a modest reduction in clinical disease activity and of the sixteen specific complication episodes considered as primary aims it was successful without other changes in therapy in treating only 4. Its only major success has been the long-term maintainance of of intestinal failure. Intravenous Nutrition of the same average duration as EN was more successful with improvements in anthropometric and protein status. In the treatment of complication episodes it was especially useful in the intermittent management of intestinal failure, achieved some success in the sustained resolution of sub-acute obstruction and the healing of a recurrent fistula but failed in 3 of 4 cases to assist severe diarrhoea. Notable was its unique contribution to the successful outcome of a pregnancy. Whether pre-operative IVN has any advantage over simple fluid replacement in patients requiring surgery in Crohn's disease remains to be proved but would seem unlikely unless the patient is severely malnourished.

Defined formula versus polymeric diets

Whether the polymeric diets such as the ones examined in my rat experiments and used in some patients are better than the defined formula diets remains to be proved. It is possible that the theoretical disadvantage that they may contain harmful food antigens may be outweighed by superior nutritional efficiency, lower cost and greater patient acceptability. Whether small differences in faecal residue will make any difference in Crohn's disease seems unlikely but remains to be tested.

CHAPTER 12

SUMMARY

This thesis examines aspects of malnutrition in Crohn's disease (CD) and evaluates nutritional therapy in Crohn's disease and in animal experiments. Chapters 1 and 2 are the introduction and methods.

Section 1 (Chapters 3-7)

The prevalence of malnutrition and depletion of various nutrients in 65 CD patients was followed by investigation of the clinical significance of some of the abnormalities found and an evaluation of treatment.

Chapter 3

Of 65 patients only 52% were of normal weight and 29% were severely underweight. In 15 laboratory measurements, abnormalities (mostly reduced blood levels) included albumin(40%), calcium (35%), transferrin(34%), haemoglobin(32%), alkaline phosphatase(30%), zinc(27%), vitamin A(23%), vitamin E(23%) and magnesium(11%). Abnormalities were commonest in patients with extensive bowel involvement (average 4.3) and those severely underweight (< 80% of ideal weight) were more likely to be protein depleted and to have low levels of calcium and vitamin A. Eleven (17%) had 6 or more abnormalites. Most were underweight with active disease.

Chapter 4

Fifteen out of 17 in-patients were found to have magnesium (Mg) depletion as judged by serum and urine Mg measurements. In three all with serum Mg levels < 0.60 mmol/l, symptoms (tetany) occurred. They all had extensive disease and severe malabsorption. Only these three proved to have chronic Mg deficiency. Their requirements for long-term oral therapy based on serial serum Mg measurements were 30 to 60 mmol of Mg a day.

Chapter 5

Osteomalacia (OM) was investigated in patients with varying extent of bowel involvement by the use of bone biopsies in 24 patients.

Clinical and biochemical features were compared between those with OM and those without. The six (25%) with OM weighed less and had more active disease than those without OM but in only 2 had more than 200 cm of small bowel been resected. All with OM had steatorrhoea. Abnormal bony alkaline phosphatase activity readily detected severe OM. In milder cases, when alk phos may be normal, the use of a radiolabelled diphosphonate and serial measurements of Vitamin D levels in blood are suggested as screening tests. It is suggested that OM can be diagnosed in Crohn's disease without the need for bone biopsy.

Chapter 6

Vitamin A deficiency was investigated in 52 of the 65 patients. Plasma retinol levels (low in 21%) were very low (< 1.0 µmol/l) in 5. They weighed less than 80% of ideal, were protein depleted and 3 of 4 had steatorrhoea. 3 of the 5 (the only ones with retinol <0.8 µmol/l) had impaired dark adaptation (DA) and two complained of night blindness. Correction of protein depletion and vitamin A supplements relieved the symptoms and DA improved. Plasma retinol is suggested as a useful screening test.

Chapter 7

The significance of abnormal vitamin E levels was examined in 25 patients by searching for evidence of red cell membrane instability. While *in vitro* instability (haemolysis during incubation with hydrogen peroxide) was present in 19 (76%), there was no *in vivo* haemolysis and no adverse effects of vitamin E depletion were found.

<u>Section 2</u> (Chapters 8 and 9)

The author's experience over 5 years of nutritional therapy with enteral (tube-fed) nutrition (EN) and intravenous nutrition (IVN) was examined in 19 Crohn's patients fed in total for approximately 3 patient-years (20 periods of IVN - total 102 patient-weeks and 12 periods of EN - total 58 weeks). The feeding was short term (mean 5 weeks) but several patients had more than one period and one patient has been sustained at home for more than three years.

Chapter 8

The main criteria for success of the therapy were the outcome of predetermined primary aims: the treatment of weight loss together with one or more complications of Crohn's disease. Short term EN largely failed with no overall improvement in weight and only 4 of 16 complication episodes successfully treated: diarrhoea(1), abdominal pain(2) and in maintenance treatment of intestinal failure at home(1). Amongst the failures were 6 fistulae treated for a total of 36 weeks and severe diarrhoea in 3 out of 4. There was no significant overall improvement in protein nutrition and two patients required IVN. IVN was successful in improving weight (mean 1.6Kg/week) and protein depletion and was successful in 19 out of 35 complication episodes notably in the intermittent treatment of intestinal failure. It was also helpful in relieving intestinal obstruction and allowed one pregnancy to proceed to term.

Chapter 9

Based on biochemical monitoring of serum and urine during IVN, recommendations for provision of Mg (10mmol or more a day) and zinc (100-200µmol/day) are made for Crohn's patients receiving IVN.

<u>Section 3</u> (Chap 10)

The aim was to investigate various commercially available enteral liquid diets with respect to their comparative nutritional efficiency and effects on faecal residue to determine which might be best in patients with impaired gut function.

Chapter 10

In a controlled experiment in intact rats the comparative efficacy of two defined formula diets, (DFD) Vivonex and Vivonex High Nitrogen and three polymeric (PD) Flexical, Ensure and Clinifeed Iso were compared. Each of the diets was fed to 6 rats for 28 days. The diets were given isocalorically and progress judged by observing growth, nitrogen (N) balance and faecal residue. No differences in growth (weight gain) or N balance emerged although Vivonex resulted in less

N accretion as judged by whole body N measurement than Flexical or Clinifeed. N excretion was highest in the feeds with high N content. Faecal residue was less with the two DFDs (Vivonex and Vivonex HN) than with the PD, Flexical, Clinifeed and Ensure. Faecal bacterial content varied from 46% with Vivonex to 64% with Clinifeed. It is suggested that these differences may be due to differences in the carbohydrate composition of the diets and availability to colonic bacteria of fermentable polysaccharides for their proliferation.

Section 4 (Chaps 11,12)

Chapter 11

A full discussion chapter by Chapter is followed by an overview of malnutrition and nutritional therapy in Crohn's disease including the contribution that the studies in this thesis make to the state of current knowledge.

Chapter 12

A summary of the main findings.

APPENDICES

APPENDIX 2.1

CLINICAL DETAILS OF 65 PATIENTS

THESIS NO	SITE	AGE	SEX	DURATION OF DISEASE (years)	RESECTIONS	THESIS NO	SITE	AGE	SEX	DURATION OF DISEASE (years)	RESECTIONS
1	SB	16	F	3	NO	34	LB	21	F	0,75	NO
2	SB	27	F	1	NO	35	LB	31	F	5	NO
3	SB	45	F	3	NO	36	LB	71	F	18	Colectomy
4	SB	36	F	1	TI+Caecum	37	LB	76	M	3	NO
5	SB	40	F	12	TI+Caecum	38	LB	67	M	2	Colectomy
6	SB	57	M	8	TI+Caecum	39	LB	47	M	7	NO
7	SB	26	F	10	TI+Caecum	40	LB	56	F	6	R hemi-col,
8	SB	46	F	1	NO	41	LB	39	M	?	NO
9	SB	48	F	21	TI+Caecum						
10	SB	63	F	5	NO	42	SB+LB	36	F	10	NO
11	SB	38	F	2,5	NO	43	SB+LB	30	M	2	Trans col,+TI
12	SB	29	F	7	NO	44	SB+LB	73	F	9	NO
13	SB	36	F	11	TI+Caecum	45	SB+LB	36	F	3	SB- ? amount
14	SB	47	F	1,5	TI+Caecum	46	SB+LB	27	F	2	NO
15	SB	43	F	6	TI+Caecum	47	SB+LB*	60	F	7	R hemi-col,
16	SB	30	M	?	TI+Caecum	48	SB+LB*	48	M	14	Colectomy
17	SB	53	F	14	TI+Caecum	49	SB+LB*	16	M	8	½ colon, >½ SB
18	SB	19	F	4	NO	50	SB+LB*	34	M	14	R hemi-col,+TI
19	SB*	27	F	8	TI+Caecum	51	SB+LB*	18	F	10	> ½ of SB
20	SB*	25	F	0,5	TI	52	SB+LB*	18	M	10	NO
21	SB*	29	F	2,5	TI	53	SB+LB*	24	F	2	Colect, + TI
22	SB*	64	F	22	++ resections	54	SB+LB*	26	F	10	Colect, + TI
23	SB*	33	M	10	200cm left	55	SB+LB*	33	F	6	Colectomy
24	SB*	33	M	11	TI	56	SB+LB*	61	M	11	NO
						57	SB+LB*	49	F	15	R hemi-col,+SB
25	LB	22	F	?	Colectomy	58	SB+LB*	31	M	8	SB ++ ? amount
26	LB	52	M	1	NO	59	SB+LB*	54	F	14	Colect, + TI
27	LB	73	F	10	Colostomy	60	SB+LB*	23	F	9	>½ col, + TI
28	LB	45	F	?	Colectomy	61	SB+LB*	35	M	27	½ colon, >½ SB
29	LB	27	F	3	NO	62	SB+LB*	19	F	12	NO
30	LB	22	M	0,25	NO	63	SB+LB*	64	F	?	NO
31	LB	32	F	6	NO	64	SB+LB*	23	M	2	NO
32	LB	20	F	0,5	NO	65	SB+LB*	67	M	?	NO
33	LB	22	F	1	NO						

Abbreviations: SB = Small bowel, LB = Large bowel (colon), SB+LB = small and large bowel
* = small bowel involvement is widespread (disease or resections not confined to the terminal 60 cm of small bowel (terminal ileum)
TI = Terminal Ileum
Colect, = colectomy
Transcol, = transverse colectomy
R hemi-col, = right hemicolectomy

APPENDIX 2.2

SELECTION OF PATIENTS FOR CLINICAL STUDIES

THESIS NO	SITE	CHAPTER 4	5	6	7	8	9	THESIS NO	SITE	CHAPTER 4	5	6	7	8	9
1	SB	●		●		●	●	34	LB			●			
2	SB			●	●	●		35	LB		●	●			
3	SB		●	●	●			36	LB			●			
4	SB							37	LB			●			
5	SB			●				38	LB			●			
6	SB		●					39	LB		●	●			
7	SB			●				40	LB						
8	SB		●	●				41	LB				●		
9	SB			●											
10	SB			●	●			42	SB+LB	●		●		●	●
11	SB			●				43	SB+LB			●			
12	SB			●				44	SB+LB						
13	SB			●				45	SB+LB		●	●	●		
14	SB			●				46	SB+LB		●	●	●		
15	SB			●				47	SB+LB*	●	●	●	●	●	●
16	SB			●				48	SB+LB*	●	●	●	●	●	●
17	SB		●	●	●			49	SB+LB*	●	●	●	●	●	●
18	SB							50	SB+LB*	●	●	●	●	●	●
19	SB*	●	●	●	●	●		51	SB+LB*	●	●	●	●	●	●
20	SB*	●						52	SB+LB*	●	●	●	●	●	●
21	SB*		●	●	●			53	SB+LB*			●		●	
22	SB*		●	●	●			54	SB+LB*			●	●	●	
23	SB*		●	●	●			55	SB+LB*	●		●			
24	SB*		●	●	●			56	SB+LB*			●			
								57	SB+LB*						
25	LB	●				●	●	58	SB+LB*	●		●			
26	LB			●		●		59	SB+LB*		●	●	●		
27	LB	●	●	●	●	●		60	SB+LB*		●	●	●		
28	LB			●		●		61	SB+LB*		●	●	●		
29	LB			●		●		62	SB+LB*	●		●	●	●	●
30	LB			●		●		63	SB+LB*	●					
31	LB							64	SB+LB*	●					
32	LB							65	SB+LB*			●			
33	LB		●	●	●										

SB = Small bowel. LB = Large bowel (colon). SB+LB = small and large bowel

● = included in the study

* = widespread small bowel involvement (disease or resections not confined to the distal 60 cm of small bowel (terminal ileum)

APPENDIX 2.3

INTRAVENOUS TRACE METAL AND VITAMIN SOLUTIONS

ADDAMEL (KabiVitrum) - 10 ml vial added daily to aminoacid/glucose solution. Contents per 10 ml (expressed as anions (+) or cation(-) in chloride solution and sorbitol)

Calcium (Ca^{++}) 5 mmol	Magnesium (Mg^{++}) 1.5 mmol
Iron (Fe^{+++}) 50 µmol	Zinc (Zn^{++}) 20 µmol
Manganese (Mn^{++}) 40 µmol	Copper (Cu^{++}) 5 µmol
Fluoride (F^{-}) 50 µmol	Iodide (I^{-}) 1 µmol

Sorbitol containing chloride (Cl^{-}) 13.3 mmol

VITLIPID (KabiVitrum) - 10 ml vial added daily to fat emulsion (Intralipid). Contents per 10 ml

Retinol 750µg Calciferol 3 µg Phytomendione 150µg
Fractionated soy -bean oil 1g

(Vitamins A, D, K and E)

SOLIVITO (KaiVitrum) - Powder added to sterile water and to aminoacid/glucose solution
Daily provision
Vit B_1 1.2 mg Vit B_2 1.8 mg Nicotinamide 10mg Pyridoxine 2 mg
Pantothenic acid 10 mg Vit C 30 mg Biotin 0.3 mg Folic acid 0.2 mg
Cyanocobalamin 2 µg Glycine 100mg

APPENDIX 2.4

COMPOSITION OF TUBE-FED ENTERAL DIETS

PRODUCT*	CARBOHYDRATE SOURCE	FAT SOURCE	PROTEIN SOURCE	ENERGY PROVISION	PROTEIN
Vivonex (Eaton Labs)	Glucose+ Oligosacch.	Ess. fatty acids	Amino acids	300 kcal (1 packet)	6 g
Triosorbon MCT (BDH Pharm.)	Mono- oligo- poly-sacch.	MCT**	Whey caseinate	400 kcal (1 packet)	16 g
Ensure	sucrose corn syrup polysacch	corn oil	Soy casein	240 kcal (1 bottle)	9 g
Isocal (Mead Johnson)	Corn syrup oligosacch	Soy oil MCT**	Soy caseinate	375 kcal (1 can)	12 g
Caloreen (Roussel)	Glucose polymer	NONE	NONE	400 kcal/ 100g	NONE

Notes

* In addition all contain vitamins and minerals apart from Caloreen which is purely a source of extra calories and not a 'complete' diet as the others are described

** MCT = medium chain triglycerides

I.V. NUTRITION
SHEET 1
BACKGROUND DATA
BASELINE CLINICAL DATA

NAME:

ADDRESS:

UNIT NO:
SEX:
D.O.B.:
PRINCIPAL DIAGNOSIS:
DATE OF DIAGNOSIS:
BASIS OF DIAGNOSIS

PAST HISTORY

A. OTHER ILLNESSES 1
2
3
4

BASELINE (PRETREATMENT) SKINFOLD THICKNESS:
TRICEPS MUSCLE CIRCUM:

Ideal Weight: Kg

	HEIGHT	WEIGHT (x3)	1	2
DATE TAKEN				

B. HOSPITAL ADMISSIONS

DATE	REASON FOR ADMISSION	SURGERY

C. COMPLICATIONS OF PRINCIPAL DIAGNOSIS:

PRESENT PROBLEM: Symptoms (Nature and Duration) EXAMINATION FINDINGS

REASON FOR ADMISSION TO I.V. NUTRITION TRIAL:

I.V. NUTRITION
SHEET 2
WEEKLY PROGRESS

NAME:

UNIT NO

WEEK NO FROM / / TO / /

SKINFOLD THICKNESS cm DATE

TRICEPS MUSCLE CIRCUMFERENCE cm

A. CLINICAL DATA	DAY	1	2	3	4	5	6	7
	DATE							
PHYSICAL (incl appetite diarrhoea, vomiting, unusual tastes)								
1 SYMPTOMS								
PSYCHOLOGICAL								
2 EXAMINATION FINDINGS								
3 DRUGS								
DAILY CLINICAL DATA	WEIGHT							
	% of Ideal Weight							
	BOWEL MOTIONS							
	MAX TEMP							
	MAX PULSE							
	GLYCOSURIA							
	(BL GLUCOSE)							
	OTHER							
FLUID BALANCE	IN ORAL							
	IN I.V.							
	OUT							
	BALANCE					CUMULATIVE BALANCE		

I.V. NUTRITION
SHEET 3
WEEKLY PROGRESS
B I.V. REGIME AND COMPLICATIONS

NAME UNIT NO

WEEK NO _____ FROM / / TO / /

DAY	1		2		3		4		5		6		7	
DATE														
I.V. REGIME (BASIS SOLUTIONS)	Solution	Vol	SOL.	VOL	SOL.	VOL.	SOL.	VOL.	SOL.	VOL.	SOL.	VOL.	SOL.	VOL
ADDITIVES														
DISCREPANCIES REASON														
DISCREPANCIES AMOUNT														
COMPLICATIONS														
ACTION TAKEN														

I.V. NUTRTION
SHEET 4
CANNULA AND SUMMARY
OF COMPLICATIONS

NAME:

UNIT NO:

I.V. FEEDING FROM TO

REASON FOR STOPPING I.V. NUTRITION (CIRCLE ITEM) :

PATIENT NON-COMPLIANCE
ATTAINMENT OF ADEQUATE NUTRITION
COMPLETION OF _____ WEEKS
COMPLICATION:

A. CANNULA

TYPE	SITE	FROM	TO	REASON FOR CHANGE/STOPPING

B. COMPLICATIONS

	DATE	DETAILS	ACTION TAKEN
CANNULA Local Infection, Pneumothorax, Septic Thrombo-phlebitis			
PYREXIA			
HYPERGLYCAEMIA			
ACIDOSIS			
LIVER DISTURBANCE			
OTHER (including mineral and vitamin deficiency)			

APPENDIX 3.1

NUMERICAL LABORATORY DATA AND PREVALENCE OF ABNORMAL VALUES

1. S I T E O F D I S E A S E

	Small Bowel (1-24)					Large Bowel (25-41)					Small and Large Bowel(42-65)				
	Numerical data			Abnormalities		Numerical data			Abnormalities		Numerical data			Abnormalities	
	n	Mean	SD	No	(%)	n	Mean	SD	No	(%)	n	Mean	SD	No	(%)
Hb	24	12,5	2,4	7	(29)	17	12,7	2,0	4	(24)	22	11,3	2,6	8	(36)
MCV	21	87,3	10,0	6	(29)	14	87,1	4,3	0	(0)	21	86,7	11,6	3	(14)
Na	18	138	2,6	2	(11)	13	138	3	2	(15)	22	136	3,5	2	(9)
K	18	4,1	0,6	2	(11)	13	4,3	0,5	1	(8)	22	4,1	0,8	5	(23)
Urea	18	3,7	1,9	5	(28)	13	5,0	3,1	3	(23)	22	5,0	4,1	6	(27)
Ca	24	2,16	0,30	6	(25)	17	2,27	0,14	5	(29)	24	2,08	0,32	12	(50)
Mg	23	0,79	0,05	1	(4)	16	0,82	0,09	0	(0)	24	0,71	0,13	6	(25)
Zn	13	11,2	2,5	1	(8)	11	15,3	5,3	1	(9)	21	10,7	3,4	8	(38)
Alb	24	37,4	7,1	7	(29)	17	35,8	6,7	7	(41)	24	32,4	8,2	11	(42)
TF	21	2,9	0,8	4	(19)	14	2,5	0,7	4	(29)	23	2,3	1,0	12	(52)
PA	19	251	89	2	(11)	9	252	104	2	(22)	9	239	84	3	(33)
RBP	19	42,9	12,6	4	(21)	9	42,6	15,3	1	(11)	9	40,4	14,5	1	(11)
Alk P	23	235	79	3	(13)	16	396	370	6	(38)	24	358	386	10	(42)
Vit A	23	1,67	0,59	3	(13)	15	1,44	0,61	7	(29)	24	1,58	0,89	7	(29)
Vit E	22	24,0	10,01	1	(5)	15	16,7	8,6	3	(20)	23	16,8	11,2	10	(43)

Notes

1. For units of measurement and reference ranges see Chapter 2 and Table 3.1
2. Differences in numerical values and in the prevalence of abnormalities between groups discussed in text

APPENDIX 3.2

NUMERICAL LABORATORY DATA AND PREVALENCE OF ABNORMAL VALUES

2. B O D Y W E I G H T

	≥ 90 % IDEAL				80-89 % IDEAL				< 80 % IDEAL			
	Numerical data			Abnormalities	Numerical data			Abnormalities	Numerical data			Abnormalities
	n	Mean	SD	No (%)	n	Mean	SD	No (%)	n	Mean	SD	No (%)
Hb	32	12,4	2,5	8 (25)	13	12,5	2,1	3 (23)	17	11,3	2,4	9 (53)
MCV	27	88,1	9,7	2 (7)	13	91,5	8,8	3 (23)	15	82,7	8,3	3 (20)
Na	21	137	3	2 (10)	13	137	3,4	3 (23)	17	137	3,2	3 (18)
K	21	4,2	0,8	2 (10)	13	4,0	0,5	1 (8)	17	4,2	0,6	2 (11)
Urea	21	4,6	2,7	3 (14)	13	5,3	4,5	2 (15)	17	4,1	3,0	7 (39)
Ca	32	2,23	0,27	8 (25)	13	2,11	0,30	5 (38)	18	2,06	0,31	10 (56)
Mg	30	0,78	0,08	2 (7)	13	0,71	0,13	4 (31)	18	0,76	0,14	2 (11)
Zn	14	12,7	3,0	Insuff	12	10,4	3,3	6 (50)	18	12,6	5,2	5 (28)
Alb	32	38,7	6,6	7 (22)	13	33,5	8,8	5 (38)	18	30,4	5,9	14 (78)
Tf	25	3,0	0,7	4 (16)	13	2,4	0,9	5 (38)	18	2,0	0,8	9 (50)
PA	26	262	77	3 (12)	4	Insuff	-	- -	6	Insuff	-	- -
RBP	26	44,4	12,7	3 (12)	4	Insuff	-	- -	6	Insuff	-	- -
Alk P,	31	229	103	5 (16)	12	265	107	5 (42)	18	518	511	7 (39)
Vit A	30	1,75	0,81	7 (23)	12	1,6	0,56	2 (17)	18	1,3	0,6	6 (33)
Vit E	30	21,3	10,1	6 (20)	12	16,3	11,4	5 (42)	17	18,0	11,0	4 (22)

Notes
1. For units of measurement and reference ranges see Chapter 2 and Table 3.1
2. Differences in numerical values and in the prevalence of abnormalities between groups discussed in text

APPENDIX 3.3

NUMERICAL LABORATORY DATA AND PREVALENCE OF ABNORMAL VALUES

3. A C T I V I T Y O F D I S E A S E

	INACTIVE DISEASE (CDAI < 5)*					ACTIVE DISEASE (CDAI ≥ 5)				
	Numerical data			Abnormalities		Numerical data			Abnormalities	
	n	Mean	SD	No	(%)	n	Mean	SD	No	(%)
Hb	24	12.0	2.4	8	(33)	38	12.2	2.5	14	(37)
MCV	22	88.1	11.5	6	(27)	33	86.6	8.0	3	(9)
Na	18	138	3.05	2	(11)	32	137	3	4	(13)
K	18	4.1	0.6	2	(11)	32	4.2	0.7	3	(9)
Urea	18	3.7	1.56	3	(17)	32	4.6	2.9	9	(28)
Ca	24	2.22	0.28	4	(17)	38	2.11	0.29	18	(47)
Mg	23	0.77	0.05	1	(4)	37	0.76	0.14	5	(14)
Zn	12	11.1	3.03	4	(33)	30	12.3	4.6	9	(30)
Alb	24	37.5	5.7	6	(25)	38	33.7	8.5	19	(50)
TF	21	2.6	0.7	5	(24)	34	2.5	1.0	13	(38)
PA	18	254	83	1	(6)	19	242	97	5	(26)
RBP	18	43.1	13.7	2	(11)	19	41.4	13.4	5	(28)
Alk P	23	303	252	6	(65)	37	336	351	11	(29)
Ret	23	1.63	0.52	2	(9)	36	1.52	0.83	13	(36)
Vit E	22	23.0	8.3	3	(14)	36	17.3	11.4	11	(31)

* = See Harvey (1980)

Notes

1. For units of measurement and reference ranges see Chapter 2 and Table 3.1
2. Differences in numerical values and in the prevalence of abnormalities between groups discussed in text

APPENDIX 8.1

SELECTION OF PATIENTS, NUTRITIONAL AND OTHER THERAPY

					OTHER TREATMENT											
						SPECIFIC DRUGS			ORAL SUPPLEMENTS			ANTI-DIARRHOEAL			ANTIBIOTICS
No	Age	Sex	Site of Disease	N T Period	Duration (W + d)	steroid	SSZ	MNZ	Fe	Folate	Other	C.P.	Lop.	Lom.	
1	16	F	SB-TI	1 IVN	5 6	NONE			✓			NONE			NONE
2	27	F	SB-TI	1 EN	3 2		✓	✓	NONE			NONE			NONE
19	25	F	SB-W	1 EN	1 6	NONE			✓	✓		NONE			NONE
				2 IVN	3 4	NONE			NONE			NONE			NONE
25	22	F	LB	1 IVN	4 4	NONE			✓	✓		NONE			7 d course
				2 EN	5 4	NONE				✓		✓	✓		NONE
26	54	M	LB	1 EN	4 1	NONE				✓		NONE			NONE
27	71	F	LB	1 EN	10 0			✓	✓	✓		NONE			NONE
28	44	F	LB	1 EN	7 3	NONE					Zn	NONE			NONE
29	27	F	LB	1 EN	4 0		✓		NONE					✓	NONE
30	22	M	LB	1 EN	1 5	✓		✓	NONE			NONE			NONE
42	33	F	SB-TI+LB	1 IVN	5 5		✓		✓				✓*		NONE
47	60	F	SB-W+LB	1 IVN	5 2	NONE			NONE			NONE			NONE
48	48	M	SB-W+LB	1 IVN	6 0	NONE			NONE			✓			NONE
				2 EN	3 5	NONE			✓	✓	Mg	✓			NONE
49	16	M	SB-W+LB	1 IVN	2 0		✓				Vit D	NONE			NONE
				2 IVN	7 3		✓		NONE			NONE			10 days
				3 IVN	7 1		✓		NONE			NONE			7 days
50	34	M	SB-W+LB	1 IVN	4 1	NONE				✓	Vit K	✓		✓	NONE
				2 IVN	3 2	NONE			NONE			✓		✓	NONE
				3 IVN	6 6	NONE			NONE			✓		✓	7 days
				4 EN 130+w at home											
				5 IVN	4 0	NONE			NONE			✓		✓	NONE
				6 IVN	3 1	NONE					Ca/Vit D	✓		✓	NONE
51	19	F	SB-W+LB	1 IVN	5 4	NONE			✓	✓		✓*			NONE
				2 IVN	2 5	NONE			NONE			NONE			2 weeks
				3 IVN	5 0	NONE			NONE			NONE			NONE
52	19	M	SB-W+LB	1 EN	4 0	NONE			NONE			NONE			NONE
				2 IVN	7 4	✓*			NONE			NONE			NONE

CONTINUED

APPENDIX 8.1 (continued)

SELECTION OF PATIENTS, NUTRITIONAL AND OTHER THERAPY

					OTHER TREATMENT					
					SPECIFIC DRUGS		SUPPLEMENTS			ANTI-DIARRHOEAL	ANTIBIOTICS
No	Age Sex	Site of Disease	N T Period	Duration (W + d)	steroid	SSZ MNZ	Fe	Folate	Other	Cod,Phos, Lop,	
53	27F	SB-W+LB	1 EN	5 0	✓*	(+ analgesics	✓	✓		NONE	NONE
			2 IVN	9 0	NONE	(+ analgesics	✓	✓		NONE	NONE
54	26F	SB-W+LB	1 EN	8 0	NONE		NONE			NONE	NONE
62	18F	SB-W+LB	1 IVN	3 6	NONE		✓	✓	Mg/K/Ca+D	NONE	NONE

TOTAL PATIENT-WEEKS OF : I V N = 102
E N = 58

Abbreviations:

N T = nutritional therapy

Site of disease: SB = small bowel LB = large bowel W = widespread small bowel involvement and/or resections TI = small bowel involvement confined to terminal ileum

IVN = intravenous nutrition EN = enteral nutrition

Duration: w = weeks d = days

Drugs: steroid = oral or intravenous corticosteroids
SSZ = sulphasalazine MNZ = metronidazole Fe = iron
C.P. = codeine phosphate Lop. = loperamide Lom. = Lomotil
Oral supplements: Zn = zinc Mg = magnesium Vit D = Vitamin D
Vit K = Vitamin K Ca = calcium

Other annotations:
* the treatment indicated was changed during a period of nutritional therapy. See text for details.

✓ named therapy given throughout

APPENDIX 8.2

NUTRITIONAL THERAPY REGIMENS

Pat, No	INTRAVENOUS NUTRITION kcal/d	kcal/kg/ day	N, Intake g/d	mg/kg/d	N, balance g/d	ORAL FOOD	ENTERAL NUTRITION kcal/d	kcal/kg/ day	N, Intake g/d	mg/kg/d	N,bal,EN g/d	PREP	ORAL FOOD
1 (1)	1550	44	10,9	311	+0,3	YES							
2 (1)							3000	63	17	354	+7,8	ENS	YES
19 (1)							3000	70	15	348	+7,9	VIV	NO
(2)	2350	55	11,5	267	+0,6	NO							
25 (1)	2248	39	10,3	178	+1,6	NO							
(2)							3000	58	15	288	+4,7	VIV	YES
26 (1)							2400	48	12	240	+3,2	VIV	NO
27 (1)							3500	88	18	450	+8,4	TRI+C	NO
28 (1)							2500	54	18	391	+3,3	TRI+C	YES
29 (1)							3000	81	17	459	+5,9	ENS	NO
30 (1)							3000	71	17	405	+1,5	ENS	YES
42 (1)	2238	64	10,7	306	-0,7	YES							
47 (1)	2115	46	9,2	200	+2,2	NO							
48 (1)	2575	48	12,8	140	+1,4	YES							
(2)							3000	57	15	283	+4,5	VIV	YES
49 (1)	2068	59	9	257	-0,6	YES							
(2)	1968	58	9,5	279	+0,6	YES							
(3)	3000	83	15,7	436	+3,7	YES							
50 (1)	2600	46	12,3	212	+3,9	NO							
(2)	2000	39	10,4	204	+3,2	YES							
(3)	2526	50	12,1	237	+2,6	YES							
(5)	3000	50	14,3	238	-1,0	YES							
(6)	3000	44	14	203	+5,2	YES							
51 (1)	2254	70	10	313	+1,0	NO							
(2)	2350	78	11,8	393	+2,8	YES							
(3)	2200	81	11	407	+7	YES							

CONTINUED

APPENDIX 8.2

NUTRITIONAL THERAPY REGIMENS

Pat. No	INTRAVENOUS NUTRITION kcal/d	kcal/kg/ day	N. Intake g/d	mg/kg/d	N. balance g/d	ORAL FOOD	ENTERAL NUTRITION kcal/d	kcal/kg/ day	N. Intake g/d	mg/kg/d	N.bal. g/d	EN PREP	ORAL FOOD
52 (1)							3000	53	15	263		C VIV	NO
(2)	3390	75	17	378	+3,9	NO							
53 (1)							3600	61	18	305	+7,4	VIV+C	NO
(2)	2800	56	14	280	+3,8	NO							
54 (1)							3000	77	15	305	+5,5	ENS	YES
62 (1)	2028	68	9,3	310	+1,6	YES							

Abbreviations:
kcal = kilocalories N. = Nitrogen kg = kilogram g = grams
d = day

EN PREP = Enteral nutrition preparations
ENS = Ensure
VIV = Vivonex
TRI = Triosorbon
C = Caloreen

APPENDIX 8.3

Patient 1 (IVN -5w 6d)

A sixteen year old girl, investigated for possible primary amenorrhoea and anorexia nervosa with gradual weight loss, had no specific abdominal symptoms. She was mildly anaemic (iron and folic acid deficiency) and a vague fullness was felt in the right iliac fossa. X-rays confirmed Crohn's disease of the terminal ileum. During a period of supervised oral feeding in hospital she continued to lose weight down to 34,5 Kg (69% of Ideal weight). Because her weight was becoming critically low she was started on IVN.

THE AIMS OF IVN WERE:

1. to increase her weight and perhaps make her more fit for possible surgery.

RESULTS:

Her weight increased 7½Kg but appetite did not improve. Later when a more definite mass emerged she developed obstructive symptoms and the diseased terminal ileum and caecum were resected resulting in a sustained and uncomplicated remission.

Patient 2 (EN -3w 2d)

A 27 year old woman with terminal ileal disease developed an ileorectal fistula associated with acute Crohn's disease. During a 3 month period she lost 4Kg in body weight to 48Kg (83% Ideal). She was given EN in addition to sulphasalazine and 'bowel rest'

THE AIMS OF EN WERE:

1. to improve her weight
2. to aid healing of her fistula

RESULTS:

During just over 3 weeks of EN her weight increased by 4Kg.Her fistula did not show any signs of healing. EN was abandoned rather prematurely because of poor tolerance.

Patient 19 (EN -1w 6d followed immediately by IVN -3w 4d)

A 27 year old woman gave a six year history of Crohn's disease presenting first with sub-acute intestinal obstruction. A year later she required resection of the terminal ileum, caecum, and a right salpingo-oopherectomy. She then developed a rectovaginal fistula. Four months before admission, she complained of colicky abdominal pain, and had lost 8Kg to 42,5Kg, (85% of Ideal).

THE AIMS OF EN WERE:

1. to restore her rapid weight loss.
2. to relieve her obstructive symptoms and hopefully avoid further surgery

RESULTS:

During a 13 day period of EN she actually lost about 0,5 Kg and her symptoms did not improve. EN was therefore abandoned and she received IVN.

THE AIMS OF IVN WERE:

1. to restore her rapid weight loss.
2. to relieve her obstructive symptoms and hopefully avoid further surgery

RESULTS:

During 3½ weeks of IVN, her weight rose only 2½Kg. Her symptoms were temporarily improved but recurred when oral food was re-introduced. She required a further bowel resection after which her obstructive symptoms resolved leaving her with a chronic discharging rectovaginal fistula.

Patient 25(IVN -4w 4d; EN 5w 4d)

This 22 year old woman with extensive colonic disease and a previous colonic resection with an ileo-rectal anastomosis was one of the 3 patients in whom nutritional deficiency was not a problem. She complained of 10-12 urgent watery motions each day and had not responded to prednisolone orally or by enema, loperamide or a short trial of EN which she tolerated poorly.

THE AIMS OF IVN WERE:

1. to improve her diarrhoea by allowing 'bowel rest'.

RESULTS;

An ill-sustained improvement with deterioration when light diet was re-introduced, She was subsequently maintained on a low residue oral diet but became ill again with severe anorectal pain on defaecation, She was able to tolerate the nasogastric tube and was given EN

THE AIMS OF EN WERE;

1, to relieve her anorectal symptoms and if possible avoid further surgery

RESULTS;

Although her bowel frequency and faecal volumes remained unchanged, there was a marked improvement in her anorectal symptoms during which started during the third of 5½ weeks of EN, Her symptoms remained settled on a low residue diet but 15 months later she required resection of an ano-rectal stricture

---

Patient 26 (EN -4w 1d)

18 months before admission, this small 52 year old man presented with an abdominal mass, Investigations showed that the mass was fixed to the posterior abdominal wall and was adherent to the left ureter, bladder, iliac vessels and abdominal wall, Surgery was not considered feasible and bowel cancer considered the most likely diagnosis, Five months later he developed an abdominal wall abscess which was excised, Eventually a sigmoidoscopic biopsy gave the diagnosis of Crohn's colitis, Following this, diseased sigmoid colon was removed but shortly afterwards he developed two abdominal wall fistulae, Barium studies revealed an enterocutaneous fistula and a separate fistula with communication between the pelvic cavity, bladder and skin, He was not badly underweight at 49,5 Kg (88% of Ideal), EN was therefore started,

THE AIMS OF EN WERE;

1, to heal his fistulae without resort to further surgery by providing partial 'bowel rest',

RESULTS;

EN was given for over 4 weeks but was unsuccessful and further colonic resection was required,

---

Patient 27 (EN -10w)

This 73 year old woman with a 6 year history of colonic Crohn's disease complicated by a rectovaginal fistula was troubled by a chronic vaginal discharge and had gradually lost weight to 40Kg (70% Ideal), EN was given

THE AIMS OF EN WERE;

1, to reverse her weight loss

2, to attempt healing of her rectovaginal fistula,

RESULTS;

Throughout she was taking antibiotics inluding metronidazole, By the 5th week of EN the discharge from the fistula had completely ceased, Despite increasing her Calorie intake from EN to 3500 kcal/day she gained only 3Kg in weight and when oral soft food was re-introduced her vaginal discharge recurred, Nine months later a diverting colostomy was performed and her vaginal symptoms then completely settled,

---

Patient 28 (EN -7w 3d)

This 45 year old woman had undergone a total colectomy for presumed ulcerative colitis, The surgical wound failed to heal and histology of the resected specimen revealed Crohn's colitis, Her weight had fallen to 46Kg and she was given EN

THE AIMS OF EN WERE;

1, to restore her weight

2, to attempt healing of her surgical wound

RESULTS;

During over 7 weeks of EN her weight rose by 16 Kg but her wound although it did become cleaner and smaller never completely healed, She would not consider further surgery,

---

Patient 29 (EN -4w)

A 27 Year old woman had a 3 year history of Crohn's colitis complicated by a peri-anal abscess had chronic rectal pain with a constant serosanguinous rectal discharge,, Her appetite had also been

poor and her weight had fallen to only 37Kg, She was given EN,

THE AIMS OF EN WERE;

1, to restore her weight loss
2, to assist healing of her fistula

During 4 weeks of EN her weight rose 8Kg but the perianal abscess remained unhealed,

---

Patient 30 (EN -1w 5d)

A 22 year old man presented with acute colitis, Rectal histology confirmed Crohn's disease, Despite a course of corticosteroids his severe bloody diarrhoea continued and his weight fell to 42 Kg (67% of Ideal), While his prednisolone was continued he received EN as well as a small amount of oral food which he would not forego,

THE AIMS OF EN WERE;

1, to restore his lost weight,
2, to improve his severe diarrhoea,

RESULTS;

His weight rose 5 Kg to 47 Kg during nearly 2 weeks of EN, There was a marked improvement in his diarrhoea,This was sustained after oral steroids and EN were withdrawn,

---

Patient 42 (IVN -5w 5d)

This 36 year old woman with a six year history of colonic and terminal ileal disease and no previous surgery, had been well for 5 years, Despite sulphasalazine she relapsed with a five month history of vague abdominal pain and anorexia, Over the period her weight fell 10 Kg to 36 Kg (73% Ideal), She also developed secondary amenorrhoea, She was unable to take food supplements and continued to lose weight, Abdominal examination revealed a tender rather ill defined mass in the right iliac fossa but surgery was not considered necessary,

THE AIMS OF IVN WERE;

1, to reverse weight loss,
2, to reverse the secondary amenorrhoea,
3, to relieve abdominal pain

RESULTS;

Her weight rose from 35 to 43 Kg and during the 4th of 5 weeks of IVN her abdominal symptoms and signs disappeared and her appetite underwent a sustained improvement, There was no other change in her therapy, During the final week of IVN her normal menstruation returned, At review 9 months later she was well and her weight was 44 Kg

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Patient 47 (IVN - 5w 2d)

A 60 Year old lady with small and large bowel disease and previous right hemicolectomy had suffered from dull central abdominal pain and anorexia for some months with gradual weight loss, She then developed colicky abdominal pain, associated with distension and vomiting, A barium X-ray swowed moderately distended loops of small bowel with several areas of constant narrowing suggesting active small bowel disease with sub-acute bowel obstruction, By this time her weight had fallen to 46 Kg (83% of Ideal) and although surgery was considered as possibly necessary, IVN was given,

THE AIMS OF IVN WERE;

1, to reverse her weight loss,
2, to relieve her chronic dull pain and the symptoms of subacute intestinal obstruction
3, to correct deficiencies

It was hoped that she might avoid a second operation,

RESULTS;

After 5 weeks IVN she had gained 4 Kg in weight and her chronic abdominal pain had completely settled within a week of starting IVN, When oral food was re-introduced she remained well and had no recurrence of her symptoms, Having thus gone into remission, she remained well for a year before coming to surgery for recurrent more acute obstruction

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APPENDIX 8,3 - CLINICAL DETAILS OF PATIENTS RECEIVING NUTRITIONAL THERAPY

Patient 48 (IVN - 6w ; EN - 3w 5d)

A 48 year old man with a previous colectomy, resulting ileostomy and extensive small bowel disease had developed severe watery diarrhoea associated with hypoproteinaemia, svere calcium and magnesium deficiency weight loss to 53,5 Kg (80% Ideal), Despite a previous course of corticosteroids and continuous symptomatic treatment of diarrhoea he continued to deteriorate, Ileostomy output was in excess of 2000ml per day, EN was considered but he refused to have a feeding tube so IVN was given

THE AIMS OF IVN WERE;

1, to correct nutritional deficits
2, to stop his diarrhoea by allowing 'bowel rest'

RESULTS;

His faecal output was recorded, During the first 2 weeks of IVN, he was deprived of oral food but allowed free access to fluids, There was no improvement in his diarrhoea (Table 8,4), However when oral fluid was restricted during the subsequent 4 weeks to <800 ml day, without any other changes in his treatment his diarrhoea quickly resolved first by a reduction in volume and progression to formed faeces (Table 8,4), His improvement persisted after normal diet was re-introduced and IVN stopped and he remained well for 6 months taking a normal diet, When his diarrhoea recurred, loperamide was added to codeine phosphate without success and he deteriorated with weight loss down to 53 Kg (78% Ideal), colicky abdominal pain and watery ileostomy output as before, This time he accepted the fine-bore nasogastric feeding tube and EN was given without oral food

THE AIMS OF EN WERE;

1, to improve his weight
2, to improve his diarrhoea
3, to attempt to relieve his symptoms of bowel obstruction

RESULTS;

His weight rose 3Kg during over 3 weeks of EN and there was a marked improvement in all his symptoms and a firming up of his ileostomy output, sustained after EN had ceased,

---

Patient 49 (IVN -2w; IVN -7w 3d; IVN -7w 1d)

This boy presented at age 18 for investigation of pubertal failure and folic acid deficiency, He then developed a mass in his left iliac fossa and after an episode of acute small bowel obstruction 120 cm of jejunum were removed at emergency surgery, Post operatively he developed chronic diarrhoea and over a period of 2 years remained unwell with multiple deficiencies and clinical evidence of osteomalacia, His first period of IVN was after a period of 3 weeks vomiting with rapid weight loss due to a gastric ulcer, His weight had fallen to only 35 Kg (75% Ideal),

THE AIMS OF IVN WERE;

1, to restore his rapid weight loss

RESULTS;

After 2 weeks he developed a septicaemic, After removing the iv line his pyrexia settled, His vomiting had settled and he was eating reasonably well and so was discharged home, His weight had risen 2 Kg,

6 months later he was readmitted with symptoms of subacute intestinal obstruction and his weight had fallen to 33 Kg (72% Ideal), He had tetany requiring calcium infusions,

THE AIMS OF IVN WERE;

1, to restore his weight loss
2, to relieve the obstructive symptoms by providing 'bowel rest',
3, to correct symptomatic calcium deficiency

RESULTS;

His tetany quickly settled and did not recur, During a 7 week course of IVN he gained 9Kg in weight and his abdominal symptoms settled, Recurrent pyrexia was treated with antibiotic therapy, At discharge he was feeling well,

He remained well although still pre-pubertal on multiple nutritional supplements and vitamins for more than 2 years and then presented with a rectal discharge, severe rectal pain and faecal incontinence due to new perianal and rectal disease, His weight fell rapidly by 6 Kg to 36Kg,

APPENDIX 8.3 - CLINICAL DETAILS OF PATIENTS RECEIVING NUTRITIONAL THERAPY

THE AIMS OF IVN WERE;

1. to restore weight loss
2. to relieve his rectal symptoms
3. to correct multiple nutritional deficits

RESULTS;

Again he was continually pyrexial, but his weight improved during the first 3 weeks by 3Kg. An abdominal ultrasound examination revealed a pelvic abscess which required surgical drainage. Only after a second operation to stem bleeding from a rectal wall artery did his symptoms completely settle during the 7th week of IVN. During the following month he rapidly improved and subsequently went through a normal puberty. While sustaining him before and after surgery, IVN with bowel rest did not relieve his rectal symptoms. His sustained improvement occurred after successful surgery.

Patient 50 - Five periods of IVN and prolonged EN at home,(Case Report - Scott, Med. J.), IVN -4w 1d; IVN -3w 2d; IVN -6w 6d; EN -130w and continuing; IVN -4w; IVN -3w 1d)

This 35 year old man underwent 3 operations for peptic ulcer between 1969 and 1971. At his 3rd laparotomy he was noted to have appearances of Crohn's disease of the terminal ileum. Between 1973 and 1977, he spent over seven months in hospital with recurrent weight loss, abdominal pain, diarrhoea and vomiting. Radiological examinations suggested Crohn's disease extending from the jejunum to the descending colon. He had failed to improve on long-term treatment with sulphasalazine and courses of corticosteroids. In early 1978 he developed acute intestinal obstruction. Histology of the resection specimen suggested diffuse Crohn's disease. By now he had chronic intestinal failure with severe diarrhoea, uncontrolled by drugs, steatorrhoea, multiple deficiencies. Post-operatively he lost weight and developed an enterocutaneous fistla. IVN was considered necessary

THE AIMS OF IVN (3 periods) WERE;

1. to restore his severely depleted nutritional state
2. to aid healing of the fistula by providing bowel rest

RESULTS;

Between April 1978 and May 1979, he spent more than seven months in hospital and received 3 periods of IVN totalling more than 14 weeks. During each period his weight rapidly rose, deficiencies were corrected and his fistula healed. However he rapidly lost weight with reopening of his fistula between hospital admissions Despite a carefully monitored supplemented oral diet of between 67 and 97 g of protein and 2000-3000 kcal a day at home he rapidly deteriorated. During his third admission for IVN it was decided to commence him on EN at home, supplementing his oral diet with an iso-osmolar, lactose-free liquid diet, Isocal (Mead Johnson) delivered through a fine bore nasogastric tube by a peristaltic pump (IVAC 530) overnight 6 nights a week. This gave him an average daily supplement of 55g protein and 1700 kcal while allowing him to go about his daily business. Despite this regimen his weight fell but at a much slower rate, and his fistula remained healed. After home EN was commenced he remained out of hospital for 16 months before having a 'top-up' period of IVN. He has continued on this EN regimen at home and when reviewed 3 years and 5 months after EN had started his weight was 71 Kg (97% Ideal). The success of this regimen is indicated by the continued absence of his fistula and by improved quality of life; before home EN he spent more than half of two years in hospital. After EN was started he spent only 2 months in hospital in 3½ years.

Patient 51 (IVN -5w 4d; IVN -2w 5d; IVN -5w)

An 18 year-old girl had undergone resection of all but 3 feet of her small bowel and was chronically undernourished with persistant diarrhoea despite symptomatic treatment with codeine phosphate. More recently she developed anorectal disease with pain on defaecation. Despite obvious severe anorectal disease she would not consider having an ileostomy.

THE AIMS OF IVN (3 Periods) WERE;

1. to avoid further surgery
2. to relieve the severe diarrhoea
3. to relieve the symptoms of anorectal disease
4. to restore her severe nutritional depletion

RESULTS;

IVN was commenced at a time when she was suffering from in excess of 20 motions a day, There was a rapid improvement in her diarrhoea as shown in Table 8,4, However her anorectal pain was unaltered, Her weight rose from 32 to 40Kg, She gradually lost ground and after 16 months she required further IVN (2½ weeks) during which her weight rose from 30 to 36 Kg, After a further 11 months she had a further 5 weeks of IVN followed by a colectomy after developing severe colitis, At no time did her anorectal pain alter, At regular review following surgery for the next 18 months her weight remained around 35Kg and her symptoms were much improved,

---

Patient 52 (EN 20-4w followed immediately by IVN -7w 4d)

An 18 year old boy had suffered from extensive disease for many years, characterised by episodes of a severe protein-losing enteropathy, Although responsive previously to oral steroids he had suffered severe oesophageal candidiasis from which he almost died,

THE AIMS OF EN WERE;

1, to restore his rapid weight loss,
2, to improve diarrhoea and protein losing enteropathy,

RESULTS;

A 4 week course of EN failed to halt his rapid decline, He lost 10 Kg and was severely protein depleted required intravenous albumin, EN was abandoned and IVN was commenced,

THE AIMS OF IVN WERE;

1, to restore his rapid weight loss,
2, to improve diarrhoea and protein losing enteropathy,

RESULTS;

He was given nothing by mouth, Despite total bowel rest for nearly 3 weeks his symptoms did not improve despite some improvement in his nutrition, He was eventually persuaded to accept prednisolone intravenously during weeks 3-7 of his IVN and there was a rapid and sustained resolution of his symptoms and fortunately no complications of steroid therapy, Bowel rest had therefore failed to treat his diarrhoea but IVN had sustained him during a period of severe nutritional depletion,

---

Patient 53 (EN -5w then IVN -9w)

(Case Report Brit Med J 1981;283;1221-1222)

This 27 year old woman had presented 3 years earlier for investigation of infertility, At laparoscopy her ovaries were noted to be adherent to the adnexae, Subsequent small bowel X-rays suggested active Crohn's disease of the distal ileum and proximal colon, Shortly after an episode of sub-acute intestinal obstruction, which settled spontaneously, her long awaited pregnancy occurred, During the first 11 weeks of the pregnancy her weight increased satisfactorily from 57 to 60,5 Kg, As the pregnancy proceeded symptoms of bowel obstruction recurred and became progressively worse, She started to fail to gain weight rising by only 1 Kg from the 11th to the 19th week, Surgery was considered but the risk to the foetus thought to be too great, EN was therefore commenced

THE AIMS OF EN WERE;

1, to relieve obstructive symptoms by providing partial 'bowel rest'
2, to provide sufficient nutrition to allow pregnancy to proceed

RESULTS;

After 2 weeks her obstructive symptoms were not settling and despite administration of corticosteroids, she failed to improve, During 5 weeks of EN in the mid-trimester of pregnancy when her weight should have been steadily rising, it fell from 59 to 57 Kg, EN was abandoned and IVN was started after 11 days on soft diet during which her weight fell a further 2Kg,

THE AIMS OF IVN WERE;

1, to relieve obstructive symptoms by providing 'bowel rest',
2, to provide sufficient nutrition to allow pregnancy to proceed

RESULTS;

She was fed from week 27 to week 36 (9 weeks) while taking only water by mouth, Her abdominal symptoms partially settled and the pregnancy proceeded normally, Her weight rose from 55 to 65 Kg,

At the 36th week there was a sudden fall in urinary oestriol excretion suggesting foetoplacental insufficiency. A girl weighing 2,4 Kg was delivered by Caesarian section and after a short period of endo-tracheal intubation progressed normally, with an Apgar score of 9 at five minutes. The baby subsequently reached normal motor development at 9 months. The patient subsequently required resection of her terminal ileum and proximal colon.

Patient 54 (EN -8w)

This 26 year-old woman had undergone previous small bowel resections and an entero cutaneous fistula was the sole faecal output. Her general health and weight had gradually declined and she weighed only 39 Kg (70 % Ideal).

THE AIMS OF EN WERE:

1. to restore her weight.
2. to attempt healing of her fistula.

RESULTS:

During 8 weeks of EN, her weight rose only 3Kg. The therapy had no effect on fistula output and the consistency of the faecal effluent remained watery.

Patient 62 (IVN -3w 6d)

This 17 year old girl had been ill for 10 years with diffuse and widespread disease, chronic diarrhoea, steatorrhoea, multiple deficiencies, especially of fat-soluble vitamins, growth failure and malnutrition. Previous bowel biopsy had suggested diffuse inflammatory bowel disease. She had received in the paediatric wards a number of courses of IVN resulting in increasing difficulty in gaining vascular access due to venous thrombosis. EN had been attempted but was not tolerated. Further IVN was given

THE AIMS OF IVN WERE:

1. To promote linear growth and puberty
2. To increase weight and correct deficiencies

RESULTS:

After almost 4 weeks, IVN was terminated by the development of superior vena cava obstruction which became chronic. Her next four years were characterised by recurrent episodes of non-mechanical intestinal obstruction, tetany due to Mg and Ca deficiency, night blindness due to Vitamin A deficiency a fractured femoral shaft due to osteomalacia and progressive difficulty in achieving vascular access including two unsuccessful attempts to create a permanent arterio-venous fistula. Eventually she died when the collateral venous supply to the right side of her heart (via the azygous system) failed.

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0036-9330/80/03100312$02.00 in USA

HOME ENTERAL TUBE FEEDING WITH A LIQUID DIET IN THE LONG TERM MANAGEMENT OF INFLAMMATORY BOWEL DISEASE AND INTESTINAL FAILURE

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Summary. *A 35-year-old man, who had spent 10½ out of 18 months in hospital, has required repeated courses of intravenous nutrition (IVN) because of nutritional failure due to severe inflammatory bowel disease. He has been maintained on a nocturnal pump-fed liquid diet supplementing his day-time oral diet for five months, four of which have been at home. The cost of such therapy is less than with an elemental diet and there are other advantages. This regime has been shown to be nutritionally adequate. The need to assess other cheaper liquid diets in patients with intestinal failure is recognised.*

INTRAVENOUS nutrition (IVN) has found a place in the management of Crohn's disease, particularly when there is severe malnutrition (1,2,3), fistula formation (2,3,4,5) or after multiple bowel resections (6,7). Long-term treatment at home is occasionally necessary especially in patients with a short bowel syndrome (8,9) but complications may occur (10).

Elemental, or chemically, defined diets have also been used in Crohn's disease, to treat severe malnutrition (11,12,13) to aid healing of fistulae (12,13,14), to relieve the symptoms of bowel obstruction (12,15,16), in the symptomatic management of cholerhoeic diarrhoea (17), and in the treatment of local complications (16). Goode and his colleagues (13) treated eight patients with Crohn's disease for four to six months with Vivonex (Eaton Laboratories) and showed satisfactory weight gain and increase in lean body mass. The drawbacks of such long-term treatment include unpalatability and diarrhoea, and the high cost is also considered a problem.

The need to assess other liquid diets has been recognised especially in patients with varying degrees of alimentary failure (18). Simpler liquid feeds have been used to maintain nutrition in surgical patients who are unable to eat adequately (18,19) and the advantages of a fine-bore tube delivering pump-controlled liquid diet to the upper small bowel have been emphasised (20). There may be a role for such a system in the long-term management of patients who have inflammatory bowel disease with intestinal failure, as in the case we now report.

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Case report

A 35-year-old man underwent three operations between 1969 and 1971 for recurrent peptic ulceration. At the last of these he was noted to have the appearance of Crohn's disease of the terminal ileum.

Between December 1973 and October 1977 he spent over seven months in hospital with recurrent weight loss, abdominal pain, diarrhoea and vomiting. Radiology suggested Crohn's disease extending from the jejunum to the descending colon. He also had evidence of severe malabsorption with steatorrhoea, anaemia and low levels of vitamin B_{12}, folate, albumin and trace metals. He failed to improve on long-term treatment with corticosteroids and sulphasalazine.

In March 1978 resection of the terminal ileum and a right hemicolectomy were performed because of intestinal obstruction. Histology of the resected specimen revealed a diffuse chronic inflammatory infiltrate without granulomata. Post-operatively he lost weight and developed an enterocutaneous fistula. Bowel rest was considered necessary and after an unsuccessful trial of oral Vivonex he was commenced on IVN. Over a four-week period he improved greatly with a weight increase of 10kg. His fistula healed.

Despite a carefully monitored supplemented oral diet consisting of between 67 and 97g protein and 2,000 to 3,000Kcal/day he again steadily lost weight and by October 1978 his weight had fallen to 51kg (70% of ideal weight). His skin was flaking, he had lost facial hair and had become very weak. Routine biochemical screening indicated reduced serum levels of albumin, transferrin, magnesium, zinc and copper. After a further period of IVN, he was started empirically on antituberculous chemotherapy. He again rapidly deteriorated and by March 1979, his weight had dropped to 50kg. Seven weeks of IVN,

supplemented with albumin infusion, achieved a weight gain of 18kg and deficiencies were corrected. The fistula which had recurred again healed. The IVN regime used is shown in Table I. The nitrogen source was the amino-acid preparation Synthamin 14 (Travenol Laboratories), providing 14.3g/24h. and energy (2800 Kcal/24h.) was supplied by glucose and fat emulsion (Intralipid, Kabi-Vitrum).

Table I. Daily IVN regime (March to April 1979).

Volume	— 3000mls
Nitrogen	— 14.3G (amino acid solution—Synthamin 14)
Energy	— 2800Kcal (glucose and fat emulsion)
Sodium	— 73mmol
Potassium	— 60mmol
Calcium	— 5mmol
Magnesium	— 16.5mmol
Phosphate	— 15mmol
Trace elements: Fe, Mn, Cu, F, I.	
Fat- and water-soluble vitamins	

Because of previous deterioration on an oral diet alone, it was decided to supplement his normal oral intake with an iso-osmolar, lactose-free liquid diet, Isocal (Mead Johnson), administered overnight by a peristaltic pump (IVAC 530) through a fine-bore tube (Vygon Code: 393/06) into the upper small bowel.

He has remained well on this overnight regime for over five months, of which four have been spent at home. He administers eight cans of Isocal made up in a Viomedex enteric nutrition bag, four nights per week, giving an average daily supplement of 55g protein and 1700 Kcal of energy. Because of previous severe deficiency, magnesium (magnesium chloride 20mmol/feed—average 11mmol/day) is added to the feed. He also takes oral zinc (zinc sulphate, 660mg/day), antidiarrhoeal agents, and antituberculous drugs. Biochemical and haematological screening have indicated satisfactory progress and his weight is maintained at 68kg (92% ideal), with satisfactory skinfold thickness and triceps muscle circumference (Table II). His fistula has remained healed.

Discussion

The aims of nutritional treatment in this patient have been to correct severe nutritional deficiency, to maintain a good nutritional state at home, and to allow a return to a reasonably normal life style after spending 10½ out of the last 18 months in hospital. Success in the first aim has been achieved by repeated courses of IVN. The second and third aims have been fulfilled by nocturnal enteral tube feeding at home.

Isocal contains balanced amounts of protein (sodium caseinate and soy protein isolate), fat (soy oil and medium chain triglycerides) and carbohydrate (corn syrup oligosaccharides) as well as added vitamins and trace metals. It has been chosen in this patient for several reasons. It may be used straight from the can with obvious practical advantages for home management. It is also iso-osmolar. High osmolality is a cause of diarrhoea in tube feeding (21) particularly with elemental diets (13,22,23). Our patient already has chronic diarrhoea requiring large doses of antidiarrhoeal agents. His diarrhoea has been no worse since starting the tube feeding. Isocal is also free of lactose, a potential advantage since lactose deficiency is common in patients with a damaged small intestine.

Large-bore nasogastric tubes are poorly tolerated for long periods in the conscious patient (19), whereas fine-bore tubes are well

Table II. Progress on nocturnal liquid diet.

	Ref range					
Hb (g/dl)	13—18	10.9	12.3	13.5	13.5	12.1
Albumin (g/l)	33—55	37	39	39	37	34
Ca (mm/l)	2.2—2.6	2.15	2.05	2.3	2.25	2.1
Mg (mmol/l)	0.7—1.0	0.74	0.68	0.80	0.88	0.83
Zn (μmol/l)	14—18	9.2	8	13.3	12.1	19.9
Weight (Kg)	(% Ideal)	69.9 (95)	70.3 (96)	70 (95)	70 (95)	68 (92)
Skin-fold thickness mm	(% Standard)	14.5 (116)	12.6 (101)	12.8 (102)	15.2 (122)	12.1 (97)
Triceps muscle circumference cm	(% Standard)	22.1 (87)	23 (91)	24 (95)	22 (87)	23.3 (92)
		Start	6	9	11	21 weeks

21 Weeks on liquid diet (Isocal) — 40 cans/week average daily supplement: 1700 kcal, 55 G Protein, Mg + Zn supplements

tolerated (20). Various types of fine-bore tubes have therefore been preferred for this type of feeding. The patient passes the tube himself each evening, and for safety injects 3 to 5ml of water to ensure correct positioning before connecting up to the feeding bag.

Pump-controlled feeding has several advantages over gravity feeding. It prevents blockage of the tube which is narrow, due to kinking or to the high viscosity of the feed, and also allows reliable administration while the patient is asleep. It prevents bolus ingestion with resultant abdominal discomfort or diarrhoea.

Cost is important in a patient on long-term treatment and should be cut to a minimum. Isocal costs £5.60 per 3,000 Kcal compared with £11.13 for the equivalent amount of an elemental diet, Vivonex Standard. Other less expensive feeds also require to be tried.

Although controlled trials have always been difficult to conduct in assessing any treatment in inflammatory bowel disease, there is a need for such studies comparing different liquid diets in patients with chronic but stable intestinal failure, while carefully monitoring clinical, biochemical and haematological status.

ACKNOWLEDGEMENTS. The Gastroenterology Unit would like to thank Travenol Laboratories for their support.

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148-6071/81/0501-0015$02.00/0
OURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 5, No. 1

Printed in U.S.A.

Mg Deficiency in Chronic Inflammatory Bowel Disease and Requirements During Intravenous Nutrition

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ABSTRACT. Assessment of magnesium (Mg) status by serum and 24-hr urine estimations has been used to study a group of 17 patients with severe Crohn's disease, 10 of whom have required intravenous (IV) nutrition. Mg depletion was present in 15 (88%) and severe enough to cause symptoms in two. Urine levels were low in most patients and would appear to be a more sensitive indication of Mg depletion than serum levels alone. Serum Mg levels were significantly lower in the Crohn's group than in a group of hospital controls; 5–10 mmol of IV Mg were required daily to prevent Mg depletion during IV nutrition and some patients required higher intakes. Three patients with particularly severe malabsorption required oral Mg supplements in the long-term. The rationale for using our method of assessing Mg status, and the importance of recognizing and treating chronic Mg deficiency are presented.

Magnesium (Mg) is an essential mineral, the fourth most plentiful cation in the body, with many biological functions,[1] and particularly important as a cofactor in enzyme reactions involving adenosine triphosphate (ATP). The utilization of high energy phosphate groups is crucial during protein synthesis and emphasizes the importance of Mg during periods of anabolism expected with intravenous nutrition (IVN).

Assessment of Mg status can be made by measuring serum and urine levels. Low urine Mg levels give an early indication of its depletion and have been used by Heaton[2] as an index of deficiency. Serum levels may remain normal at first, but are likely to fall when depletion is more prolonged.

In normal adults, about one-third of ingested Mg is absorbed almost entirely from the small bowel; less may be absorbed in malabsorption states or after extensive bowel resection. Booth and his colleagues[3] noted subnormal serum Mg levels in 15/42 patients with various types of small bowel malabsorption, and hypomagnesemia in 9/63 patients with Crohn's disease.[4] Further information is required on Mg status in patients with inflammatory bowel disease and other malabsorptive states, as serum Mg level alone may not be an accurate indicator of body Mg status. Patients with inflammatory bowel disease are often nutritionally deficient and may require IVN. Mg deficiency, which may already be present in this group, might be exacerbated when an anabolic response is achieved during IVN. Recommendations for IV provision of Mg during IVN have varied considerably (Table I), and their rationale is not always clear.

Received for publication, June 19, 1980.
Accepted for publication, October 29, 1980.
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The aims of this study were therefore: 1) to assess Mg status in patients with severe Crohn's disease; 2) to determine the daily IV Mg requirements in those undergoing IVN; and 3) to assess long-term Mg requirements in these patients after a period of IVN.

PATIENTS AND METHODS

Seventeen patients requiring admission to the hospital were studied (Table II). Mg status in all patients was determined by measuring serum Mg and 24-hr urine Mg on several occasions by atomic absorption spectrometry (Perkin-Elmer Model 403). The mean serum and urine Mg level was calculated for each patient. Biochemical Mg deficiency was defined as a serum Mg of <0.7 mmol/liter and/or urine Mg <2 mmol/24 hr (Glasgow Royal Infirmary Biochemistry Department Reference range). A control group, in whom serum Mg levels alone were measured, consisted of preoperative patients about to undergo nonurgent orthopedic operations. Because of the skewed distribution in the Crohn's group, a Mann-Whitney test was used to compare the Crohn's group with controls.

Ten of the 17 patients (#1–10) required 14 periods of IVN; 7 of them had one period, 2 had two periods, and 1 had three periods of IVN (Table III). Nitrogen (N) was provided as amino acid (AA) solution (Synthamin: Travenol Laboratories Limited), energy from hypertonic glucose and fat emulsion (Intralipid: KabiVitrum), fat-soluble (Vitlipid: KabiVitrum) and water-soluble vitamins (Solivito: KabiVitrum), as well as a mixture of trace metals (Addamel: KabiVitrum) and zinc sulphate. Details of Mg intake will be described. These 10 patients underwent a total of 64 complete patient-weeks of IVN, of which complete data are available in 60 patient-weeks.

Mg status (Table IV) was also calculated for each complete patient-week of IVN, from the mean serum and urine estimations. IV Mg was provided from three sources: AA solution (Synthamin): 5 mmol/liter, Addamel: 1.5 mmol/vial, and 50% Mg sulphate solution: 2

TABLE I
Recommendations for IV Mg during IVN

Reference	IV Mg (mmol/day)
5	2–4
6	5.6–7.8
7	5–6
8	15–20
9	10–21
10	12

TABLE II
Patient details and reasons for hospital admission

Patient	Sex	Age	Diagnosis	Present problems
		yr		
1	F	60	Crohn's	Weight loss; subacute intestinal obstruction
2	M	48	Crohn's	Weight loss, diarrhea, hypoalbuminaemic edema, muscle stiffness, paresthesiae
3	M	16	Crohn's	Steatorrhea, vitamin deficiencies, delayed puberty
4	M	34	Diffuse inflammatory bowel disease	Enterocutaneous fistula, recurrent weight loss, chronic diarrhea
5	F	22	Crohn's	Diarrhea and urgency
6	F	33	Crohn's	Abdominal pain, anorexia, anemia and secondary amenorrhea
7	F	19	Crohn's	Diarrhea, weight loss, pubertal failure, severe anorectal disease
8	F	18	Intestinal pseudo-obstruction ? Crohn's	Pubertal failure, severe steatorrhea, tetany
9	F	16	Crohn's	Anorexia, weight loss
10	M	19	Crohn's	Severe diarrhea, protein-losing enteropathy
11	M	27	Crohn's	Right iliac fossa mass, weight loss
12	F	29	Crohn's	Problems with ileostomy
13	F	64	Crohn's + diverticular disease	Ileocolonic fistula, severe diarrhea
14	M	28	Crohn's	Weight loss, diarrhea, abdominal pain
15	F	23	Crohn's	Rectovaginal fistula
16	F	25	Crohn's	Acute intestinal obstruction
17	F	60	Crohn's	Weight loss, rectovaginal fistula

mmol/ml). The total intake was calculated as a daily average for each patient-week of feeding. It was thus possible to relate IV Mg intake to Mg status during IV feeding and to assess the minimum amount of Mg required to maintain normal Mg status during IVN. The intake groups were compared using Fisher's modification of Yates's chi-squared test.

Following IVN, serial serum Mg measurements were performed on an outpatient basis, 2–20 months after IVN, and were used to assess the requirements of oral Mg supplements.

RESULTS

Magnesium Status in Patients with Severe Crohn's Disease

Mg status in the 17 patients is shown in Table V. Using the criteria for Mg deficiency described, only 2 patients had a normal Mg status. Serum Mg in the Crohn's group (0.70 ± 0.035 mmol/liter) were lower than in the controls (0.82 ± 0.014 mmol/liter, $p < 0.01$) (Fig. 1). Low serum Mg levels occurred in 6 of 17 Crohn's patients. In patient #2 a 48-year-old man with diffuse small bowel Crohn's disease, a very low serum Mg level was found (0.4 mmol/liter). Skeletal pain and muscle cramps had been prominent symptoms. Extensive investigation of his calcium status revealed no evidence of calcium deficiency. Patient #8, a young girl with growth failure associated with diffuse inflammatory bowel disease and severe steatorrhea, had suffered several attacks of tetany corrected on occasions by calcium infusion and at other times with Mg infusion. Despite oral Mg supplementation she was still Mg deficient.

Magnesium Status and IV Requirements During IVN

Table IV is the combined serum and urine data during IV feeding. Combined low serum and urine levels indicating definite Mg deficiency occurred in 3 of 60 patient-weeks, all associated with a Mg intake of <5 mmol/day. The difference in incidence of Mg depletion between this low intake group and each of the other two groups was significant. These results indicate that 5–10 mmol of Mg are required daily IV if Mg depletion is to be prevented.

Individual low serum or urine levels occurred in 16 of 60 patient-weeks. Five low results occurred sporadically in different patients, but 11 low levels occurred in 2 patients: #2, who had a very low pre-IVN Mg status, suffered from severe diarrhea throughout the early part of IVN. When the IVN line became temporarily blocked, he developed frank tetany which resolved quickly when the IVN was restarted with a solution containing Mg. The serum Mg level remained low until the fourth week of IVN despite an intake of more than 10 mmol/day. Patient #3 had multiple nutritional deficits, but was not initially Mg depleted. Difficulty was encountered in establishing IVN, and during a period of inadequate intake associated with rapid weight loss he developed biochemical Mg deficiency and clinical tetany. None of the other patients developed symptoms to suggest Mg deficiency during IVN.

Outpatient Followup and Long-term Mg Status

On follow up, 3 patients had low serum Mg levels after periods of IVN (Table VI); all 3 had particularly severe malabsorption in association with diffuse inflammatory bowel disease. Patient #2 had intermittent trouble with bone pain and muscle cramps. Patient #4, who has required three periods of IVN, has constant diarrhea and is now maintained at home on a nocturnal enteral feeding regime with Mg supplements. Patient #8, who had suffered tetany before IVN, subsequently developed tetany despite oral supplements, but since intake has been increased to 60 mmol/day she has had no further symptoms.

DISCUSSION

Our results indicate a high incidence of Mg deficiency in patients with Crohn's disease requiring admission to hospital. Furthermore, in the IVN group, Mg deficiency, sometimes severe, was present before all but two periods

TABLE III
Patients receiving IVN: details of regimes and weight gain

ient #	IVN period	Reasons for IVN	Starting weight		Length of IVN	IVN Regimes						Weight gain kg/wk
			Kg	% Standard		Energy kcal (MJ)/kg/day	Kcal:N ratio	Electrolytes mmol/kg/day				
								Na	K	Ca	PO_4	
					wk							
1	1	Relief of obstructive symptoms Nutritional improvement before surgery	46.2	83	5⅔	45.7 (0.19)	257:1	1.6	1.3	0.11	0.81	0.76
2	1	Bowel rest to improve diarrhea Nutritional improvement	53.8	80	6	47.8 (0.20)	200:1	1.4	1.1	0.09	0.70	1.08
3	1	Promote puberty Improve nutrition	34.7	74	2	59.6 (0.25)	227:1	2.1	1.7	0.14	1.08	1.1
	2	Relief of bowel obstruction	33.5	72	7⅔	58.7 (0.25)	203:1	2.2	1.8	0.15	1.15	1.14
4	1	Improve nutrition Healing of enterocutaneous fistula	57.6	78	4½	45 (0.19)	205:1	1.3	1.0	0.08	0.65	2.48
	2	Improve nutrition Healing recurrent sinus	51.3	70	3⅔	38.9 (0.16)	191:1	1.4	1.2	0.10	0.73	1.63
	3	Improve nutrition Healing recurrent sinus	50.5	69	6⅔	50 (0.21)	236:1	1.4	1.2	0.10	0.74	2.61
5	1	Bowel rest for relief of chronic diarrhea	57.6	103	4½	39 (0.16)	196:1	1.3	1.0	0.09	0.65	0.88
6	1	Improve nutrition Relief of abdominal pain	35.2	72	5⅔	63.6 (0.27)	209:1	2.1	1.7	0.14	1.06	1.35
7	1	Improve nutrition Relief of diarrhea	32.1	64	5½	70.2 (0.29)	247:1	2.3	1.9	0.16	1.16	1.49
	2	Relief of anorectal symptoms	29.5	59	2⅔	79.6 (0.33)	199:1	2.5	2.0	0.17	1.27	2.3
8	1	Promote linear growth and puberty Correct deficiencies	30.3	54	3⅔	66.9 (0.28)	218:1	2.4	2.0	0.17	1.23	1.23
9	1	Reverse weight loss	24.5	69	5⅔	44.9 (0.19)	167:1	2.1	1.7	0.14	1.09	1.59
10	1	Improve nutrition Relief of diarrhea with bowel rest	45	63	7½	76.5 (0.32)	199:1	1.6	1.3	0.11	0.83	2.1

TABLE IV
g status during 60 patient-weeks of IVN related to IV Mg intake

Mg intake mmol/day)	Low serum Mg[a]	Low urine Mg[a]	Combined low serum + urine Mg
	5/8	3/8	→ 3/8 ← $p < 0.05^b$
0	2/16	0/16	$p < 0.01^b$ → 0/16 ←
	4/36	2/36	→ 0/36
tals	11/60	5/60	3/60

[a] The number on the left of each pair is the number of patient-weeks which low levels occurred. The number on the right is the total nber of patient-weeks.
[b] Each of the higher intake groups [(5-10 mmol/day) and (> 10 nol/day)] is compared with the low intake group (<5 mmol/day).

IVN. It may be symptomatic and require urgent treatnt. The incidence in our group of Mg depletion is her than in Beeken's series,[4] in which he used serum levels alone as an index of deficiency. Although 5–10 nol/day of IV Mg would seem to be sufficient in most ients with Crohn's disease undergoing IVN, a higher ount may be required in some cases, particularly when rrhea or steatorrhea is severe. In patients with severe malabsorption, Mg deficiency is likely to be a long-term problem and supplements should be given.

Mg is present in most foodstuffs[11] and Mg depletion due to poor dietary intake alone is therefore unusual. In the normal adult, the proportion of Mg absorbed may vary according to the dietary Mg content[12] and factors such as phytate may inhibit Mg absorption.[13]

The clinical importance of Mg deficiency relates not only to skeletal muscle function but also to heart muscle function. Attention has been drawn to the possible role of Mg deficiency in the causation of cardiac arrhythmias.[14] A predisposition to digitalis toxicity may exist in patients rendered Mg-deficient by long-term diuretic therapy.[15] Low Mg content of soft water has been suggested as a possible explanation for increased mortality following myocardial infarction.[16]

Mg deficiency has been demonstrated to occur commonly in severe Crohn's disease where increased loss and failure of absorption of Mg may coexist. Although most patients were asymptomatic, despite biochemical evidence of Mg deficiency, patients with Crohn's disease would appear to be a population at risk. Symptoms occurred in 3 patients and required urgent treatment.

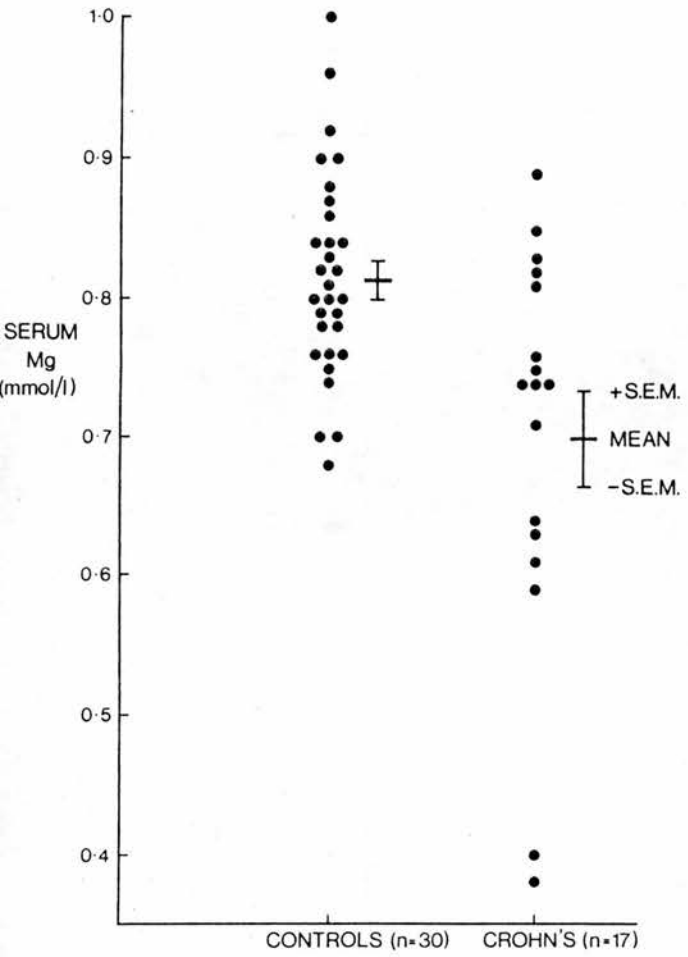

FIG. 1. Serum Mg levels in Crohn's patients and control group.

TABLE V
Mg status in 17 Crohn's patients admitted to the hospital

Mg status	Number	%	
Low serum + low urine Mg	5	29	88% Mg-deficient
Low serum + normal urine Mg	1	59	
Normal serum + low urine Mg	9		
Normal serum + normal urine Mg	2	12	12% normal

	Mean	Range	SEM[a]
Serum Mg (mmol/liter)	0.70	0.38–0.89	0.035
Urine Mg (mmol/day)	0.85	0.05–2.85	0.22

[a] Standard error of mean.

Calcium deficiency may also cause paresthesia and tetany, but did not appear to be an important problem in our patients. Serum calcium levels, when adjusted for low albumin, were normal.

The assessment of Mg status, as with other predominantly intracellular substances, poses problems. Studies of Mg kinetics have been hampered by the relatively short half-life of radioactive ^{28}Mg,[17] but ^{26}Mg, a stable isotope is being investigated.[18] Measurement of tissue biopsy levels may not reflect total body reserves.[19] Early observations of serum Mg levels[20-22] showed that levels were maintained within a narrow range. The mechanism

TABLE VI
Outpatient Mg status (serum Mg) following IVN

Patient #	IVN period	Months after IVN	Serum Mg (mmol/liter)[a]	Oral Mg supplement (mmol/day)
2	1	1	0.42	Nil
		2½	0.52	20
		12	0.62	60
		20	0.78	60
4	1	2	0.58	Nil
		4	0.48	Nil
	2	2	0.54	Nil
	3	3	0.83	11–20
		10	0.70	25
8	1	2 weeks	0.96	30
		1½	0.38	30
		6½	0.57	60

[a] Normal range: 0.7–1.0 mmol/liter.

is complex and incompletely understood but would appear to be regulated at the cellular level,[23] in the kidney and in the intestine. Parathyroid hormone is an important regulator of serum Mg levels, although other factors may play a part. The net effect is Mg conservation by the kidney in response to lowered serum Mg levels, so that in conditions of Mg depletion, Mg almost disappears from the urine. Thus, low urine Mg levels are the earliest indicator of Mg depletion. Serum Mg levels fall later and symptoms are likely to occur when the serum levels drop <0.5 mmol/liter.[24] Measurements of serum and urine Mg levels provide a fairly sensitive and practical way of measuring Mg status.

The rationale for IV Mg recommendations during IVN is seldom clear from the literature and recommendations have varied from 2–21 mmol/day (Table I). In the earliest days of IVN, Dudrick and his colleagues[5] based their recommendations on work in infants with severe congenital anomalies. In later patients, Dudrick[7] as well as Meng and Sandstead,[8] aimed with their IV Mg to maintain serum levels in the normal range. Jeejeebhoy[9] based his Mg requirements on measurements of urine, stoma, and fecal losses before IVN and adjusted the intake according to serum Mg levels during IVN. Driscoll and Rosenberg's recommendations[10] were for a group of patients similar to our own. More recently, Shenkin and Wretlind[25] have offered guidelines for different types of patients—0.04 mmol/kg/day as a basal recommendation to cover minimal requirements, a moderate amount (0.15–0.2 mmol/kg/day) for depleted patients or those with increased losses, and a high supply (0.3–0.4 mmol/kg/day) for patients during or subsequent to a period of severe catabolism. Our patients probably fall into the middle category, but Mg needs may be higher in individual cases. IVN solutions available in Britain contain variable amounts of Mg (Table VII) and Mg requires to be added in some cases. Addamel (KabiVitrum) contains only 1.5 mmol/vial and is insufficient by itself to provide Mg needs; 50% Mg sulphate solution (2 mmol/ml) is a suitable IV preparation for addition to AA and glucose solutions.

Long-term follow-up has indicated chronic Mg deficiency in several patients. Oral Mg supplements are available as liquid suspensions. Mg chloride mixture is

TABLE VII
Mg content of substances used in IVN

Product name	Main Constituents	Manufacturer	Magnesium content (mmol/liter)
Synthamin 9[a] Synthamin 14[a] Synthamin 17[a]	L-amino acids Electrolytes	Travenol Laboratories Ltd.	5
Vamin with fructose Vamin with glucose Vamin N	L-amino acids Electrolytes	KabiVitrum Ltd.	1.5
Aminofusin L 600 Aminofusin L1000 Aminofusin L Forte	L-amino acids Sorbitol, ethanol Vitamins, electrolytes	Pfrimmer and Co. (BDH Pharmaceuticals)	5
Aminoplex 12	L-amino acids Electrolytes	Geistlich Sons Ltd.	2.5
Glucoplex 1000 Glucoplex 1600	Hypertonic glucose Electrolytes	Geistlich Sons Ltd.	2.5
Electrolyte solution 'A' in dextrose	Electrolytes Glucose	Travenol Laboratories Ltd.	14
Addamel	Electrolytes Trace metals	KabiVitrum Ltd.	1.5 (in 10 ml)

[a] Also available without electrolytes.

vailable in three strengths (8, 10, and 25 mmol Mg/10 ml). It is probably the preparation of choice but in larger loses may have a purgative action. In patients who annot tolerate it, Mg hydroxide (BPC) containing 13.6 mmol Mg/10 ml may be used. A combination of alumium hydroxide and Mg hydroxide (Maalox-Pharmax) nay reduce the purgative effects. Mg sulphate BPC ontaining 21 mmol Mg/10 ml is normally used as a owel evacuant and is poorly absorbed. It is reserved for atients who cannot tolerate the other preparations.

ACKNOWLEDGMENT

The Gastroenterology Unit wish to thank Travenol Laboratories Limited for their support.

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Reprinted from the **BRITISH MEDICAL JOURNAL,**

7 November 1981, 283, 1221 - 1222

Intravenous feeding to sustain pregnancy in patient with Crohn's disease

Total intravenous nutrition has been used in pregnancy for short periods for the management of hyperemesis gravidarum and severe eclampsia[1] and to maintain fetoplacental function just before delivery.[2] It has rarely been required for longer periods to sustain pregnancy.[3 4]

Case report

A 27-year-old woman with Crohn's disease causing narrowing of the terminal ileum and ulceration of the proximal colon was admitted to hospital with vomiting and severe colic due to partial obstruction of the terminal ileum. Her symptoms settled with conservative treatment. One month later she became pregnant and her weight increased satisfactorily from 57·0 to 60·5 kg during the first 11 weeks. As the pregnancy proceeded colic, abdominal distension, and vomiting recurred and became progressively worse. From the 11th to 19th weeks of gestation she gained only 1 kg. Surgical resection was considered when she started to lose weight but was rejected because of the risk to the fetus and she was again managed conservatively.

The figure shows the patient's subsequent progress. A low-residue elemental diet (Vivonex) with additional energy (Caloreen) administered through a fine-bore nasogastric tube achieved a daily intake of 15·1 MJ (3600 kcal) and 18 g nitrogen with some success. After two weeks vomiting and abdominal pain recurred and did not improve despite corticosteroid treatment. Tube feeding was abandoned after five weeks. She was therefore fed intravenously from week 27 by means of a central venous cannula. She received 11·8 MJ (2800 kcal) non-protein energy daily, 4·2 MJ (1000 kcal) from 20% fat emulsion (Intralipid) and the remainder from glucose; 14 g nitrogen from amino-acid solution with electrolytes (Synthamin); and 7·5 mmol (300 mg) calcium, 100 μmol (6·5 mg) zinc, trace metal, and vitamin supplements (Addamel, Solivito, and Vitlipid). Additional iron and folic acid were administered by mouth. With this regimen her weight, mid-arm skinfold thickness, and muscle circumference increased. Blood pressure was normal. Glucose and protein were not detected in urine. Serum concentrations of routine electrolytes, magnesium, zinc, and bilirubin were normal, as were alanine and aspartate transaminase activities. Serum calcium concentration adjusted for low albumin value was normal, and alkaline phosphatase activity rose slightly towards term.

Caesarean section was performed at 36 weeks when a fall in urinary oestriol excretion suggested fetoplacental insufficiency. A girl of 2400 g

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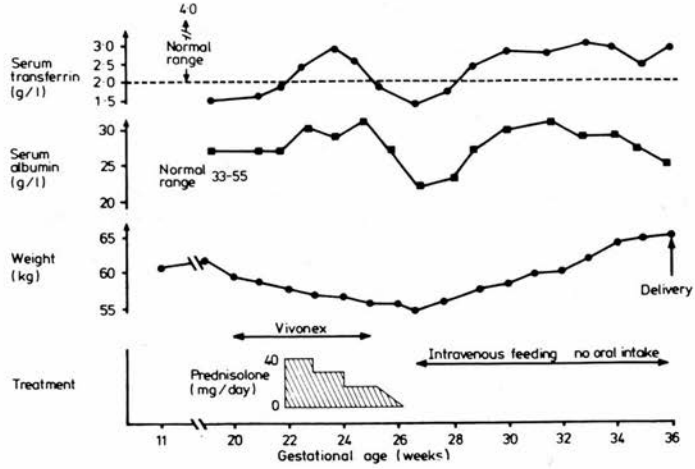

Progress and treatment during pregnancy.

(expected 2800 g) was delivered and after a short period of endotracheal intubation progressed normally (Apgar score 9 at five minutes). She had reached normal motor development by nine months. The patient subsequently required resection of her terminal ileum and proximal colon.

Comment

Intravenous nutrition for seven weeks with successful outcome for both mother and child has only recently been reported in a patient with benign oesophageal stricture.[4] Moreover, Webb[3] used intravenous nutrition for four and a half weeks in a patient with widespread malignancy and bowel obstruction, with survival of the fetus but death of the mother. Our patient received intravenous nutrition for nine weeks, during which recommendations for the provision of nutrients in pregnancy[5] were largely met. Successful protein synthesis was indicated by a positive nitrogen balance and rise in serum transferrin concentration.

Major complications of intravenous nutrition did not occur. Heller[1] recommended avoidance of fat emulsion in pregnancy because of the theoretical dangers of maternal ketonaemia, premature labour, and placental infarction due to fat emboli. Maternal ketonuria occurred only once during intravenous nutrition after a period of vomiting. Premature labour did not occur. There was biochemical evidence of fetoplacental insufficiency at 36 weeks and, though the fetus came to no harm as judged by subsequent development, the placenta was small (20th percentile) with some ischaemic necrosis of the villi. Fat emulsion did, however, provide essential fatty acids and its contribution to the energy supply permitted an infusion concentration of glucose low enough to prevent urinary loss. Total intravenous

nutrition allowed pregnancy to proceed when otherwise unavoidable major abdominal surgery might have resulted in fetal death.

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(*Accepted 22 July 1981*)

Printed in Great Britain by Bourne Offset (Iver) Ltd., Iver, Bucks.

Scott Med J (1981) 26: 89

URINARY 3-METHYL-HISTIDINE EXCRETION FOLLOWING AORTO-ILIAC RECONSTRUCTIVE SURGERY. **J D Robertson***. J D B Miller and J Broom, *Department of Surgery, University of Aberdeen.*

The effect of lower limb ischaemia on skeletal muscle protein catabolism during aorto-iliac reconstruction was studied using the urinary 3-methyl-histidine-creatinine molar ratio as a measure of the fractional protein catabolic rate. Nitrogen balance demonstrated a substantial loss of body protein in the first five days post-operation (males 0.37 kg, females 0.16kg). The fractional catabolic rate of skeletal muscle protein increased post-operation, reaching a peak three times the pre-operation value in males and 2.7 in females. This increase in catabolism of muscle protein is sufficient to account for the protein losses observed.

cAMP LEVELS MODULATE COMPLEMENT PRODUCTION BY MONOCYTES. **D. Lappin** and K. Whaley, *University Department of Pathology, Western Infirmary, Glasgow G11 6NT.*

Monocytes give rise to macrophages, major effector cells in chronic inflammatory responses. The production of complement components by these cells is probably important in inflammation.

Monocytes cultured *in vitro* synthesise a number of complement components. When intracellular levels of cAMP are increased by dibutyryl cAMP, phospho-diesterase inhibitors or cholera toxin production is decreased. Pulse label studies using ^{3}H-aminoacids have shown that, initially, protein secretion is impaired but later the degradation of intracellular protein is increased and protein synthesis is decreased.

These results indicate a way by which the local production of complement components may be pharmacologically modulated.

The Scottish Society of Physicians

The annual scientific meeting of the Society was held on 19/20 September 1980 at Aberdeen under the presidency of Dr C. MacLeod.

The Fitzgerald-Peel Lecture was given by *Professor Raymond Hoffenberg*. The title of the lecture was **Clinical implications of thyroid hormone metabolism.**

The Fitzgerald-Peel prize for the best communication delivered by a junior (*i.e.* non-consultant) physician was awarded to Dr A. MacKay of the MRC Blood Pressure Unit, Glasgow Western Infirmary.

The following papers were presented:

A CLINICAL EVALUATION OF INTRAVENOUS NUTRITION (IVN) IN INFLAMMATORY BOWEL DISEASE. A. N. H. Main, R. J. Morgan, H. J. Hall, J. F. MacKenzie, A. Shenkin, G. Fell and R. I. Russell. *Gastroenterology Unit and Department of Biochemistry, Royal Infirmary Glasgow.*

Inflammatory bowel disease, especially Crohn's disease, may be accompanied by severe nutritional insufficiency.

Twelve patients (11 Crohn's disease; 1 ulcerative colitis) underwent 16 IVN periods, mean duration five weeks (2-9): total 83 patient-weeks. Clinical, biochemical, haematological and anthropometric data were used to assess the indications and efficacy of IVN.

The mean weight before IVN was 76 per cent Ideal. This increased during IVN; mean 1.48 (0.15-2.61) Kg per week. It was sustained 4 to 25 months after IVN in four of eight patients.

Low albumin levels were present in six and improved on IVN alone in two patients. Anaemia was not improved by IVN alone. Daily IV magnesium and zinc requirements were >5 mmol and 50 to 100 µmol respectively.

Bowel rest, with IVN as the sole source of nutrition six patients, improved symptoms of bowel obstruction in two, improved diarrhoea in two and allowed pregnancy to proceed in one; additional corticosteroids were necessary in one.

Fifteen episodes of pyrexia occurred, nine attributable to IV cannula sepsis. Pneumothorax (2) and superior vena cava obstruction (1) also occurred. Liver function abnormalities in 9 patients, were severe in three; liver biopsies revealed possible Dubin-Johnson syndrome, acute hepatitis and pericholangitis respectively.

Introduction of three litre nutrition bags and continuous pump delivery increased mean cannula life from 15 to 27 days. IV insulin is not required and occurrence of rebound hypoglycaemia has been prevented.

Conclusions

1 IVN can predictably improve weight and correct some deficiencies. Its long term effects are less certain.

2 Bowel rest may relieve symptoms of bowel obstruction and reduce diarrhoea.

3 Pump-delivery of IV nutrients and three litre nutrition bags are significant advances in technique.

HLA-DR MATCHING AND B LYMPHOCYTE ANTIBODIES IN RENAL TRANSPLANTATION. A. M. MacLeod, R. J. Mason, H. B. M. Lewis, W. G. Shewan, J. Engeset, N. Edward, and G. R. D. Catto.
Department of Medicine and Surgery, University of Aberdeen and Blood Transfusion Service, Aberdeen Royal Infirmary.

The HLA gene system, a single chromosomal complex in man, codes for the known major histocompatibility antigens. These antigens are designated HLA—A, B, C, D and DR; both D and DR antigens are expressed on B but not T lymphocytes. For more than ten years clinical transplantation has relied upon matching of donors and recipients for HLA-A and B antigens but still more than 35 per cent of transplanted cadaver donor kidneys are rejected in the first year.

Animal studies indicate (a) that allograft survival is improved when donor and recipient share certain B lymphocyte antigens and (b) that the presence of pre-transplant antibodies directed against donor B lymphocytes may also increase graft survival. To determine whether these data apply to clinical transplantation 10 ml samples of venous blood were obtained from six patients before transplantation and twice per week thereafter. The following investigations were performed (1) the cytotoxicity of recipient serum was assessed against donor B and T lymphocytes, against normal panel B and T lymphocytes and against leukaemic B lymphocytes at 5°C, 23°C and 37°C (2) B lymphocyte antibodies (DR) in the recipient serum were monitored using the EA rosette inhibition technique against donor, normal and leukaemic B lymphocytes. Eleven donor-recipient pairs were tissued typed for HLA-DR antigens.

Despite the fact that all patients had received blood transfusions prior to transplantation no B or T lymphocyte antibodies were detected prior to transplantation. Moreover no consistent pattern of antibody production was noted after transplantation.

Clinical experience of zinc supplementation during intravenous nutrition in Crohn's disease: value of serum and urine zinc measurements

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Reprinted from Gut
Volume 23, No. 11. pages 984-991, November 1982

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, WC1H 9JR

Gut, 1982, **23**, 984–991

Clinical experience of zinc supplementation during intravenous nutrition in Crohn's disease: value of serum and urine zinc measurements

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SUMMARY Serum zinc concentrations and urine zinc excretion have been studied in 10 patients with severe Crohn's disease before and during 59 patient-weeks of intravenous nutrition. Before serum zinc concentrations (9·9±1·0 μmol/l: mean ± SEM) and urine zinc excretion (3·3±0·6 μmol/24h) were less than controls ($p<0·01$). No patients had clinical signs of zinc deficiency before intravenous nutrition and none developed signs during it. There was no overall change in serum zinc concentrations, despite improvements in body weight, skinfold thickness, and mid-arm circumference in all patients, and increased serum albumin and serum transferrin concentrations during all but two periods of intravenous nutrition. Nor was there any relationship between serum zinc concentrations and zinc intake (up to 220 μmol/day), serum zinc concentrations remaining significantly lower than control levels. Urine zinc excretion during the first week of intravenous nutrition showed a 1·2 to 53-fold increase (mean 11-fold) over pre-intravenous nutrition levels, and a positive relationship was demonstrated between zinc intake and urine zinc excretion. It is suggested that zinc supplied by the intravenous route is inefficiently transported to the tissues, and that some is excreted in the form of small molecular weight chelates into urine. Recommendations are made for the supply of intravenous zinc, based on monitoring urine zinc excretion in individual patients.

Zinc is an essential element in man and is required for the function of over 70 metallo-enzymes.[1] Clinical manifestations of zinc deficiency include acrodermatitis, hair loss, hypogonadism, growth retardation, delayed wound healing, and impaired immune competence.[2–5]

Zinc deficiency has been described in Crohn's disease,[6 7] the causes including low intake, poor absorption,[8] and excess faecal losses.[9] Intravenous nutrition can be complicated by the development of zinc deficiency.[10–13] Some patients with extensive Crohn's disease may need intravenous nutrition[14] and zinc deficiency may occur, especially when patients become anabolic.[10 15] Zinc is thus an important component of the intravenous diet but daily requirements are not certain, as they will vary according to zinc losses principally in faeces and urine, and also in fistula fluid, wound exudates, shed skin and hair.

Determination of zinc in serum and urine is, however, readily available as part of the biochemical monitoring of patients receiving intravenous nutrition. As we have used a wide range of intravenous zinc supplements in our patients, we have sought to relate the results of such zinc measurements to the quantity of zinc given, to clinical progress, and nutritional indices. Serum and urine zinc values are considered in relation to serum protein changes, body weight, skinfold thickness and muscle circumference, and an estimate of nitrogen balance.

Methods

PATIENTS

Ten patients with Crohn's disease requiring intravenous nutrition were studied, comprising six women and four men of mean age 28·5 years. Clinical details including the extent of disease,

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Received for publication 6 March 1982

previous surgery, drug therapy, and reasons for intravenous nutrition, as well as baseline anthropometric and biochemical data, are shown in Table 1. Body weight standard, and reference values for triceps skinfold thickness and mid-arm circumference were based on WHO Tables.[16] These 10 patients underwent 14 periods of intravenous nutrition of mean duration five weeks for a total of 64 complete weeks (Table 2). Because of occasional breakages and urine contamination, serum values are available for only 57 weeks and urine values for 59 weeks.

Intravenous nutrition was administered by a cannula inserted into a central vein. All patients received sufficient nitrogen in the form of an amino acid solution (Synthamin: Travenol Laboratories) to maintain a positive nitrogen balance as judged from 24-hour urine nitrogen excretion, which was measured twice weekly with a faecal allowance as indicated in Table 2. The nitrogen input ranged from 9–17 g per day. Energy was supplied in the form of glucose (10–50%) and fat emulsion (10 and 20% Intralipid: KabiVitrum) to maintain the calorie to nitrogen ratio between 150 and 250 to 1: (0·16–0·33 MJ/kg/day (39–80 kcal/kg/day)). Other additions were electrolytes (Na, K, Ca, Mg, PO_4), fat-soluble and water-soluble vitamins including folic acid (Vitlipid, Solivito: KabiVitrum), and a trace metal solution (Addamel: KabiVitrum) which contains 5 mmol Ca^{++}, 1·5 mmol Mg^{++}, 50 μmol Fe^{+++}, 20 μmol Zn^{++}, 40 μmol Mn^{++}, and 5 μmol Cu^{++} per vial. Additional zinc was supplied as zinc sulphate solution containing 100 μmol (6·5 mg) zinc/vial. No patients received oral zinc supplements.

Patients were examined throughout for clinical signs of zinc deficiency such as hair loss and acrodermatitis.

Estimations of zinc in serum and urine by flame atomic spectrophotometry were performed throughout by the method of Peaston.[17] Patients taking oral food were fasted overnight and all serum samples were taken early in the morning. Urine was collected in stainless steel urinals and transferred to cleaned plastic bottles for estimations of 24-hour zinc excretion, as *papier-mâché* disposable bottles seriously contaminate urine with zinc and other metals. Assessment of serum and urine zinc status was made in the Crohn's patients before intravenous nutrition and twice a week during it. The average weekly value was calculated. Daily intravenous zinc intake was determined for each patient-week of feeding.

Control groups consisted of 36 healthy patients fasting before minor orthopaedic surgery (serum values) and 12 healthy volunteers (urine values).

Serum albumin and serum zinc levels were also compared in the following groups: (1) 50 fasting hospitalised patients about to undergo minor orthopaedic surgery (controls); (2) 21 hospitalised patients with active inflammatory bowel disease (inflammatory bowel disease group); (3) in all 10 Crohn's patients throughout their periods of intravenous nutrition (intravenous nutrition group).

Statistical comparisons between groups were by a Mann Whitney test, but, in addition, mean values and standard errors of the mean are quoted. Relationships between serum albumin and serum zinc were examined by linear regression.

Results

PRE-INTRAVENOUS NUTRITION STATUS (Table 1)
All but two patients were 80% or less of standard weight for height. Patient number 5, whose nutritional state was normal, was fed intravenously to allow bowel rest for the relief of severe rectal symptoms. The skinfold thickness and mid-arm muscle circumference were low in most patients.

Serum zinc values (mean±SEM μmol/l) in the 10 Crohn's patients (9·9±1·0) were less than in the 36 controls (13·2±0·3; $p<0·01$). Urine values (mean±SEM μmol/24h) for eight of the Crohn's group (3·3±0·6) were less than in 12 controls (7·0±0·8; $p<0·01$). No patients had clinical signs of zinc deficiency.

PROGRESS ON INTRAVENOUS NUTRITION (Table 2)
The nutritional state of all patients improved with increases in body weight, skinfold thickness, and mid-arm circumference. This was accompanied by positive nitrogen balance and increases in serum transferrin concentrations in most patients. Increases in serum albumin concentrations occurred during 12 of the 14 periods of intravenous nutrition. Patients 2 and 4 received intravenous protein or blood during intravenous nutrition.

Severe diarrhoea, likely to increase zinc loss, occurred in patients 2, 4, 8, and 10. Systemic sepsis occurred only in patient 3. Minor local sepsis related to the intravenous cannula occurred in several patients and was readily corrected by its replacement. The only major complication of intravenous nutrition was in patient 8 who developed superior vena cava obstruction which necessitated stopping this form of nutrition.

SERUM ZINC LEVELS
The improvement in nutritional state in all patients was not accompanied by a predictable overall change in serum zinc levels, which increased during nine periods of intravenous nutrition and decreased

Table 1 *Clinical, anthropometric, and biochemical details of Crohn's patients before intravenous nutrition*

Patient	*Sex*	*Age (yr)*	*Previous surgery and reasons for IVN*	*Drug therapy*	*Period of IVN*	*Body wt kg*	*(% standard)*	*Triceps skinfold (mm)*	*Mid arm muscle circumference (cm)*	*Serum albumin (g/l)*	*Serum transferrin (g/l)*	*Serum zinc (μmol/l)*
1	F	60	Right hemicolectomy. Extensive small bowel disease with obstruction. IVN before surgery	Analgesics		46	(83)	9·8	17·3	24	1·1	7·2
2	M	48	Panproctocolectomy. Chronic diarrhoea due to small bowel disease. IVN for bowel rest and correction of deficiencies	Sulphasalazine, calcium, magnesium, Vit D, Vit K		54	(80)	7·2	18·9	17	n/a	7·7
3	M	16	Extensive small bowel resection. Recurrent subacute obstruction. IVN for bowel rest and correction of deficiencies	Sulphasalazine, Vit D, Vit K	1	35	(74)	7·2	15·2	39	n/a	13·1
					2	34	(72)	n/a	n/a	40	2·4	11·5
4	M	34	Recent right hemicolectomy. Diffuse small bowel disease. IVN to aid healing of post-operative fistula and to correct deficiencies	Folic acid, Vit K, antidiarrhoeal drugs	1	58	(78)	7·6	19·6	27	1·3	15·3
					2	51	(70)	5·8	17·5	16	0·1	5·4
					3	51	(70)	4·8	18·2	18	0·9	9·8
5	F	22	Previous colectomy and ileorectal anastomosis with subsequent inflammatory stricture at anastomosis. IVN for bowel rest to relieve pain and faecal urgency. (No nutritional deficit)	Iron, folic acid		58	(103)	14·8	21·6	44	3·2	13·5
6	F	33	No surgery. Abdominal pain and weight loss IVN to reverse weight loss	Sulphasalazine, iron		35	(72)	12·5	15·7	33	2·5	6·4
7	F	19	Extensive small bowel resection. Active colonic and anorectal disease. IVN to aid healing of rectum and improve nutrition	Folic acid, iron, codeine	1	32	(64)	7·0	13·8	24	1·0	10·1
					2	30	(60)	7·4	13·1	37	2·0	10·1
8	F	18	No resection. Severe malabsorption with diffuse ileocolonic disease. IVN to promote linear growth and correct deficiencies	Magnesium, calcium, low fat oral diet		30	(54)	13·8	14·8	33	2·3	10·8
9	F	16	No surgery. Primary amenorrhoea. Colonic Crohn's. IVN to reverse rapid weight loss.	Iron		35	(69)	10·5	13·3	29	2·0	7·9
10	M	19	No surgery. Diffuse Crohn's disease. IVN for bowel rest to relieve diarrhoea and reverse rapid weight loss	Folic acid, sulphasalazine, corticosteroids, antidiarrhoeal agents		45	(63)	5·4	17·9	27	1·0	11·0
								12·5 ♂	25·3	35	2·0	12·0
								16·5 ♀	23·2	55	4·0	16·0
								Reference values[16]		Normal range		

n/a = not available

Table 2 *Progress on IVN*

	IVN		Increase in anthropometric parameters (mean gain per week)			Total change in biochemical parameters during IVN + = increase − = decrease			N balance† + = retention − = loss	Mean daily zinc supply
Patient	Period	Duration (weeks)	Body wt (kg)	Skinfold (mm)	Muscle circum. (cm)	Serum albumin (g/l)	Serum transferrin (g/l)	Serum Zn (μmol/l)	(g/day)	(μmol/day)
1		5⅔	0·76	0·6	0·13	+1	+0·8	+3·7	+2·2	126
2		6	1·08	0·7	0·33	+8*	n/a	+2·2	+1·4	120
3	1	2	1·10	2·1	0·05	+6	n/a	−0·6	−0·6	57
	2	7⅓	1·14	n/a	n/a	+0	+1·5	−2·0	+0·6	39
4	1	4⅓	2·48	0·8	0·46	+5*	+0·5	−3·0	+3·9	100
	2	3⅔	1·63	1·4	0·73	+9*	+1·2	+5·9	+3·2‡	109
	3	6⅔	2·61	1·3	0·55	+18*	+1·2	−0·6	+2·6‡	108
5		4⅓	0·88	0·4	0·11	+0	+0·3	+0·1	+1·6	42
6		5⅓	1·35	0·6	0·05	+6	+0·6	+5·9	−0·7‡	111
7	1	5⅓	1·49	0·7	0·32	+16	+1·7	+4·6	+1·0	89
	2	2⅓	2·30	1·1	0·33	−2	−0·2	+0·2	+1·6‡	120
8		3⅔	1·23	1·4	0·47	+13	+2·6	+0·7	+2·8‡	120
9		5⅔	1·59	0·8	0·50	+2	+0·4	+3·5	+0·3‡	120
10		7⅓	2·10	0·9	0·55	+10	+2·2	−3·2	+3·9	70
Mean (SEM) increase			1·6(0·2)	1·0(0·1)	0·35(0·06)					

† An estimate from known iv intake, urine output, and an arbitrary faecal excretion allowance of 2 g/day.
‡ Small additional quantities of oral food given.
* IV blood or protein administered during IVN.
n/a: not available.

during the remaining five periods (Table 2). Serum zinc levels in patients with diarrhoea (nos 2, 4, 8, 10) were not different from those without diarrhoea. There was no relationship between the mean daily zinc supply and the overall changes in serum zinc concentration. Nor had the level of zinc supply an influence on serum zinc concentrations (Fig. 1). The serum zinc concentrations (mean±SEM μmol/l) in the low intake group (9·4±1·0) and the two higher zinc intake groups (11·0±0·8; 10·5±0·4) were not significantly different from baseline values, and were less than controls ($p<0·01$ for each group). No patient received more than 220 μmol of zinc per day.

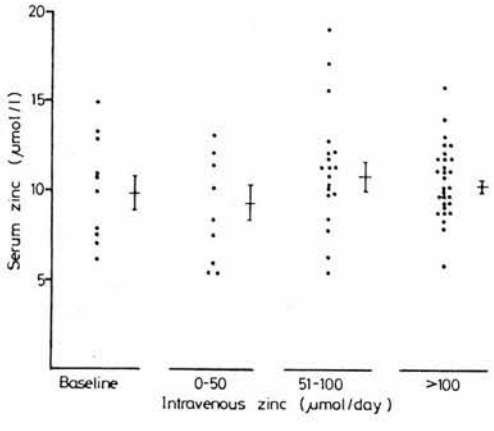

Fig. 1 *Serum zinc concentrations before intravenous nutrition (baseline) and during each of 59 patient-weeks of intravenous nutrition, separated according to the quantity of zinc supplied. Bars indicate the mean and standard error for each group.*

Patient 10, whose period of intravenous nutrition is illustrated in Fig. 2, was the only patient to exhibit a fall in serum zinc concentration (13·0 to 7·8 μmol/l) after his serum proteins had risen and his body weight increased 8 kg in only two weeks. His zinc intake was 70 μmol/day.

The relationship between serum albumin and serum zinc is shown in Table 3. Serum albumin was lower in the inflammatory bowel disease group ($p<0·001$) and intravenous nutrition ($p<0·001$) group than in controls. Serum zinc, similarly, was lower in the inflammatory bowel disease ($p<0·001$) and intravenous nutrion ($p<0·001$) groups than in controls. There was a significant correlation between serum albumin and serum zinc only in the combined group and in the inflammatory bowel disease group.

URINE ZINC EXCRETION

As illustrated in Fig. 3, all levels of intravenous zinc supply were associated with a rise in urine zinc excretion above baseline values. The differences between each of the intake groups and the baseline

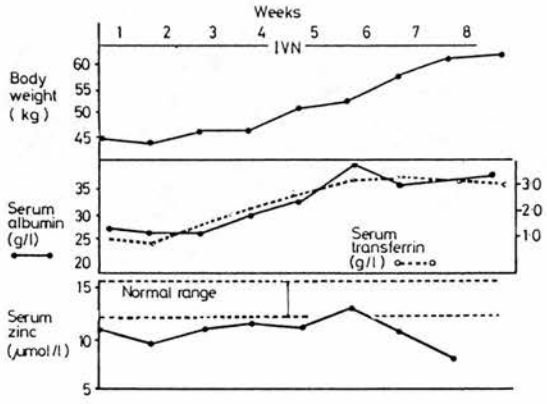

Fig. 2 *Intravenous nutrition in patient 10.*

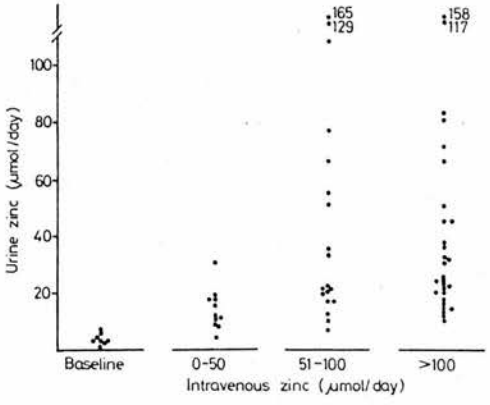

Fig. 3 *Daily urine zinc excretion before intravenous nutrition (baseline) and during each of 59 patient-weeks of intravenous nutrition separated according to zinc supply.*

values were significant. Urine zinc excretion in the two highest groups was greater than when the zinc supply was less than 50 μmol/day ($p<0·005$; $p<0·01$). When urine zinc excretion was expressed as a percentage of intake for each intake group (Table 4), however, there was no difference in the mean percentage of intake excreted between the intake groups, a wide range being present in each group. Low urine zinc excretion (mean±SEM) (3·3±0·06 μmol/24h) was observed before intravenous nutrition. During the first week of feeding a rise in urine output was observed in all patients varying from a 1·3 to a 53-fold increase, the mean increase being 11 times the value before intravenous nutrition. In one patient, urine zinc losses diminished markedly after albumin (93 g) was given intravenously during the second week of intravenous nutrition (Fig. 4), while serum zinc levels remained low (<10 μmol/l) throughout. Patient 2 showed a similar drop in urine zinc output (158 to 18 μmol/24h) after a transfusion of blood was given. No other patients received protein during intravenous feeding.

Discussion

SERUM ZINC VALUES

This study has demonstrated low serum zinc levels in severe Crohn's disease and confirms the findings of other workers.[6–8] Despite nutritional improvement in all patients, low serum zinc levels were not changed during intravenous nutrition despite zinc supply up to 220 μmol/day. Fleming and colleagues[18] suggested that persistently low serum zinc concentrations during intravenous nutrition in the absence of disease associated with hypozincaemia might indicate zinc deficiency. The three patients they described, however, did have conditions which might be associated with depression of serum zinc concentration (abscess, alcoholism with pancreatitis, short bowel syndrome). We believe, however, that the only

Table 3 *Relationship between serum albumin and serum zinc*

	Number of values	*Serum albumin (g/l)*		*Serum zinc (μmol/l)*		*Correlation between serum albumin and serum zinc*	
		Mean	*SEM*	*Mean*	*SEM*	*r*	*p*
Controls	50	43·1	0·5	13·8	0·3	+0·22	NS
IBD*	21	27·4	1·6	9·6	0·7	+0·48	<0·05
IVN†	57	31·1	0·9	10·8	0·3	+0·20	NS
Combined groups	128	35·1	0·8	11·8	0·3	+0·55	<0·001

* Inflammatory bowel disease group.
† Intravenous nutrition group.

Table 4 *Urine zinc excretion expressed as a % of intravenous intake*

Intravenous zinc intake (μmol/day)	*Urinary zinc excretion (% of intake)*		
	Mean	*SD**	*Range*
0–50	38	23	19–85
51–100	54	48	14–165
101–220	33	30	9–132

* Standard deviation.

proof of zinc deficiency is the emergence of clinical signs rapidly corrected by supplying zinc alone. Serum zinc levels do not give a direct guide to intracellular zinc content,[19] and serum zinc levels can be moderately depressed by a variety of factors unrelated to tissue depletion.

Zinc in serum bound to α-2 macroglobulin does not appear to be exchangeable[8] and albumin is the principal zinc transporting protein. Increased production of ACTH or administration of high dose corticosteroids lowers the albumin-bound zinc fraction,[20 21] as does altered pituitary activity in stress and infection.[22] These factors may be partly responsible for depressed plasma zinc levels in Crohn's disease. That hormonal influences probably play a part in regulating serum zinc levels is suggested by the diurnal rhythm in normal subjects.[23] Leucocyte endogenous mediator lowers total plasma zinc levels in infection[22] and in Crohn's disease.[24]

It has been suggested that low serum zinc in Crohn's disease simply reflects reduction in serum albumin.[8] This view is not entirely supported by our data. Although there was a good correlation between serum albumin and serum zinc in our combined group, this did not hold true for the patients receiving intravenous nutrition and serum albumin levels tended to rise during the course of this form of feeding while zinc levels did not. Wolman and colleagues were able to show a positive relationship between plasma zinc and the amount of zinc infused during intravenous nutrition.[9] They infused zinc in quantities up to almost 400 μmol/day. Their patients with diarrhoea achieved positive zinc balance with 185 μmol of zinc (12 mg) daily. Our patients with severe diarrhoea (nos 2, 4, 8, and 10) received less than this (Table 2) and it is possible that a positive relationship between zinc supply and plasma zinc would have been achieved by increasing zinc supply in these patients. In patient 10 serum zinc level fell during a period of rapid anabolism. This single observation clearly needs further documentation, but Kay and his colleagues[15] considered anabolism in the absence of adequate zinc supply to be responsible for profound falls in plasma zinc levels to less than 5 μmol zinc/l preceding clinical signs of zinc deficiency.

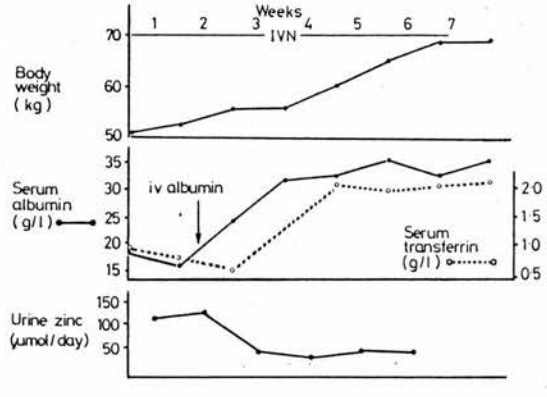

Fig. 4 *The third period of intravenous nutrition in patient 4: weight gain during the first two weeks of intravenous nutrition was attributable to the accumulation of oedema fluid which rapidly disappeared after the infusion of 93g albumin during the second week of intravenous nutrition.*

URINE ZINC EXCRETION

In this study low urine zinc levels were found in severe Crohn's disease in contrast with our previous report.[25] Low urine zinc has been considered to reflect tissue zinc depletion,[26] but may also be due to raised levels of LEM as this substance, released from white blood cells, stimulates liver uptake of amino acids[27] and might lower the ultrafilterable amino acid-bound zinc fraction and therefore the amount of zinc available for urinary excretion.

There may be inefficient retention of zinc supplied by the intravenous route. When the three intake groups were compared we found a relationship between intravenous zinc supply and urine zinc excretion but there was wide variation in the proportion of infused zinc excreted in urine within each of the intake groups and during the course of intravenous nutrition in individual patients. We also observed a rapid increase in urine zinc excretion during the first week of intravenous nutrition. These findings might be explained by a difference in chelation of zinc with other nutrients in the premixed feed and differing availability of zinc binding sites in plasma. Increasing the serum zinc ultrafilterable fraction would result in urinary losses. Van Rij and his colleagues[28] showed a six-fold increase in urine zinc excretion when amino acids and zinc were given intravenously. Freeman[29] attributed a similar rise in urine zinc excretion to the formation of amino sugar-zinc complexes.

Reduction in urine zinc excretion was seen in two patients who received plasma proteins intravenously during intravenous nutrition. This suggests that the retention of intravenous zinc may be improved by increasing zinc binding proteins, principally albumin, thereby perhaps reducing the ultrafilterable zinc fraction.

CONCLUDING REMARKS AND RECOMMENDATIONS

While serum and urine zinc measurements are poor indicators of tissue zinc status, they are, in clinical practice, the means by which judgements are made about the adequacy of zinc supplementation during intravenous nutrition. In the present study, serum zinc concentrations remained low throughout intravenous feeding despite substantial increases in serum albumin in several patients, and serum zinc levels gave no guide to zinc requirements. As a general rule we have found that the provision of 100 μmol (6 mg) of zinc/day is adequate to prevent the syndrome of zinc deficiency during intravenous nutrition. The variability of zinc excretion during intravenous nutrition makes firm recommendations about additional zinc supply difficult. Nonetheless, monitoring of urine zinc excretion may help in the management of individual patients. Low urine zinc excretion before intravenous nutrition (<2 μmol zinc/day) can be expected when the patient is zinc depleted but not catabolic. During intravenous nutrition low excretion can be expected when blood or albumin is given. We suggest that 24 hour urine zinc excretion should be measured several times during the first two weeks of intravenous nutrition. If urinary zinc excretion is persistently high (>80 μmol/day) or even exceeds input, the clinician should suspect either catabolism or poorly utilised zinc supply. In these circumstances, it might be reasonable to increase zinc supply to 200 μmol/day, especially if the patient subsequently becomes anabolic. More specific advice depends on the use of carefully controlled balance studies or better markers of whole-body zinc status.

Mechanisms of zinc absorption from the gut are complex and incompletely understood,[30] but oral supplementation of zinc has been used effectively in zinc deficiency occurring during intravenous nutrition.[10] It might be less appropriate in patients with Crohn's disease and severe diarrhoea.

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Vitamin A deficiency in Crohn's disease

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Reprinted from Gut
Volume 24, No. 12. pages 1169-1175, December 1983

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, WC1H 9JR

Gut, 1983, **24**, 1169–1175

Vitamin A deficiency in Crohn's disease

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SUMMARY Fifty two patients with Crohn's disease (31 outpatients and 21 inpatients) were investigated for evidence of vitamin A deficiency. Eleven (21%) had low plasma retinol concentrations (<1·2 μmol/l (34·3 μg%)). Five of these were outpatients and plasma retinol was only slightly reduced (>1·0 μmol/l (28·6%)). All outpatients weighed 80% or more of ideal, and were considered at low risk of developing vitamin A deficiency. In contrast, of the six inpatients with low plasma retinol concentration, five had a level of <1·0 μmol/l (28·6 μg%) and weighed <80% ideal. Three of these had impaired dark adaptation and a plasma retinol concentration of <0·8 μmol/l (<22·9 μg%). As a group, the inpatients were more protein depleted than the outpatients, with respect to serum albumin ($p<0·01$), transferrin ($p<0·001$), and prealbumin ($p<0·001$) but retinol binding protein levels were not significantly lower. It is suggested that patients with extensive small bowel Crohn's disease, who weigh <80% of ideal weight, merit measurement of plasma retinol concentration. Those with plasma retinol <0·8 μmol/l (<22·9 μg%) run a high risk of night blindness. Vitamin supplements should be given and protein depletion corrected.

Among various reports of vitamin A deficiency in gastrointestinal and liver diseases,[1–4] relatively few patients with Crohn's disease have been studied. There has been inadequate documentation of the prevalence of vitamin A deficiency in patients with Crohn's disease who are a population at risk of protein malnutrition or fat malabsorption as a result of diseased or resected small bowel. The first aim of this study was therefore to survey a large group of patients with Crohn's disease to define the prevalence of vitamin A deficiency. Two of our patients in hospital with extensive small bowel disease complained of night blindness and were found to have a severe defect of dark adaptation. Our second aim was therefore to carry out a more detailed study of patients in hospital in which we have attempted to define clinical and biochemical parameters which indicate a need for vitamin A supplementation.

Methods

PATIENTS

Fifty two patients were studied, 31 outpatients seen at routine review (group 1) and 21 inpatients, admitted with exacerbations or complications of their disease (group 2). None of the patients was receiving vitamin A supplements. Body weight was recorded, expressed as a percentage of ideal weight based on WHO tables.[5] Extent of small bowel disease and of resective small bowel surgery were recorded. Extensive disease was arbitrarily defined as disease or resections of the small bowel not confined to the terminal 60 cm of ileum. Blood samples were obtained for measurement of plasma retinol and plasma proteins, including albumin, transferrin, retinol binding protein, and prealbumin.

Analytical methods for biochemical parameters were as follows: plasma albumin and transferrin by standard laboratory techniques with reference ranges obtained from normal populations and retinol binding protein and prealbumin by a radial immunodiffusion technique using a commercial kit (LC-Partigen, Behring Company, West Germany) based on the method of Mancini.[6] This method detects prealbumin reliably down to levels of 30 mg/l and retinol binding protein down to 5 mg/l. Plasma retinol was assayed by fluorimetry based on the method of Kahan[7] with modifications by Thompson.[8] Normal ranges were established from 100 hospital orthopaedic patients without systemic

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Received for publication 18 Feburary 1983

disease. Serum zinc was measured by flame atomic absorption spectrophotometry.[9] Fat absorption was measured by means of a dual isotope fat absorption technique developed in our own laboratory.[10] The method measures percentage absorption of an ingested ^{14}C-labelled triglyceride. Mean daily faecal fat excretion[11] was based on three to five day collections of faeces.

Dark adaptation testing was performed using a Tubinger Perimeter adapted for dark adaptation testing (Oculus Optikgeräte, Wetzlar, West Germany). After bleaching retinal visual pigment by exposing the retina to white light of luminous intensity 3000 apostilbs (approximately 9500 candelas/m^2) for 15 minutes, a small area 12–14° on the nasal side of the left eye was the focus of light of increasing intensity until the light was first perceived (the visual threshold). This was retested every two minutes until no improvement could be achieved, usually after 20–30 minutes. This final visual threshold, generally accepted as a sensitive indicator of vitamin A deficiency was measured in nine of the 21 hospitalised patients (group 2), those with plasma retinol <1·4 μmol/l (40 μg%). Fourteen normal subjects were tested to establish a normal range based upon the mean and two SDs (43·4–55·4 negative $\log_{10}$ apostilbs), higher numbers indicating lower luminous intensity. Conversion factor – apostilbs × 3·142 = candela/m^2. All patients were also examined for other manifestations of xerophthalmia based on the most recent WHO classification.[12]

STATISTICAL METHODS

The relationship between retinol levels and the various plasma proteins was tested by linear regression analysis. Differences between populations were assessed by a Mann-Whitney test. Mean values and standard deviations are also quoted where appropriate.

Results

The 52 patients consisted of 17 men and 35 women of mean age 39 years. Their mean (range) body weight was 90% (54–149%) ideal. Outpatients (group 1) tended to weigh more (100% (80–149%)) than inpatients (group 2) (76% (54–103%)). Twenty patients had extensive small bowel disease, 10 in each group. Results of the biochemical analyses are shown in Table 1. Plasma proteins, apart from retinol binding protein, were lower in group 2 than in group 1. There was no association between plasma retinol levels and serum albumin or transferrin, but a significant correlation was shown between retinol and retinol binding protein (Fig. 1), between retinol and prealbumin ($r=0·71$; $p<0·001$), and between retinol binding protein and prealbumin ($r=0·81$; $p<0·001$).

Based on our normal range, 11 of the 52 patients (21%) had low plasma retinol levels. Five were in group 1 (Table 2) and these outpatients were not further studied. The remaining six patients with plasma retinol <1·2 μmol/l (34 μg%) were in group 2. These and a further three patients with plasma retinol >1·2 but <1·4 μmol/l were selected for further studies. These nine were compared with the remaining 12 patients in group 2 (Table 3). The results of further studies on these nine 'high risk' patients are shown in Table 4. Five (nos 1, 2, 4, 5, 6) had impaired fat absorption and a marked increase in faecal fat excretion. Three (nos 3, 4, 6) had impaired dark adaptation testing as indicated by a raised final visual threshold (<43·4 neg $\log_{10}$ apostilbs) but only patients 4 and 6 complained of night blindness. None of the patients had conjunctival or retinal signs of xerophthalmia.

Patient 3 had only 140 cm of small bowel remaining after previous resections for obstructive Crohn's disease. After an exacerbation with severe diarrhoea and weight loss he was noted to have a

Table 1 *Plasma proteins and retinol levels in outpatients (group 1) and inpatients (group 2)*

	Albumin (g/l)	*Transferrin (g/l)*	*Retinol binding protein (mg/l)*	*Prealbumin (mg/l)*	*Retinol (μmol/l (μg%))*
Normal ranges	35–50	2·0–4·0	M 32–91 F 28–76	M 215–400 F 165–365	1·2–2·9 (34–83)
All patients (52)	37·2±6·2*	2·8±0·8	42·0±15·1	235±87	1·7±0·9 (48·6±25·7)
Group 1 (31)	39·8±4·4	3·2±0·6	44·6±12·3	270±77	1·8±1·0 (51·5±28·6)
Group 2 (21)	33·7±6·6	2·2±0·7	37·2±18·7	172±66	1·5±0·8 (42·9±22·9)
p value†	<0·01	<0·001	NS	<0·001	NS

* Mean ± SD. † Comparisons between group 1 and group 2. NS = not significant.

Table 2 *Clinical and biochemical characteristics of group 1 patients with low plasma retinol concentrations (<1·2 μmol/l)*

Patient	*Sex*	*Age*	*Extent of small bowel disease*	*Body weight (% ideal)*	*Retinol (μmol/l (μg%))*	*Retinol binding protein (mg/l)*	*Prealbumin (mg/l)*
1	F	31	L	90	1·1 (31·5)	22	145
2	F	54	E	90	1·0 (28·6)	32	235
3	F	29	E	85	1·0 (28·6)	35	185
4	F	27	L	85	1·0 (28·6)	35	255
5	M	30	E	97	1·1 (31·5)	29	155
				Normal ranges	1·2–2·9 (34–83)	M 32–91 F 28–76	M 215–400 F 165–365

E = extensive. L = localised.

plasma retinol concentration of only 0·2 μmol/l (5·7 μg%), associated with low retinol binding protein (24 mg/l) and low prealbumin (95 mg/l). Despite abnormal dark adaptation testing he complained of no visual impairment.

Patient 4, a man with diffuse small bowel disease and steatorrhoea, had required four periods of intravenous nutrition (IVN) before 1981 because of recurrent weight loss and hypoproteinaemia. During the seven months before he noticed night blindness (Fig. 2) there was a fall in serum albumin and transferrin and very low levels of retinol, retinol binding protein, and prealbumin were noted. Dark adaptation testing at that time was impaired (Fig. 3 – upper curve). As shown in Fig. 2 there was a rapid improvement in proteins and plasma retinol over a 14 day period on intravenous nutrition including vitamin A supplements, concurrent with resolution of his visual symptoms and return of his dark adaptation testing to normal (Fig. 3 – lower curve).

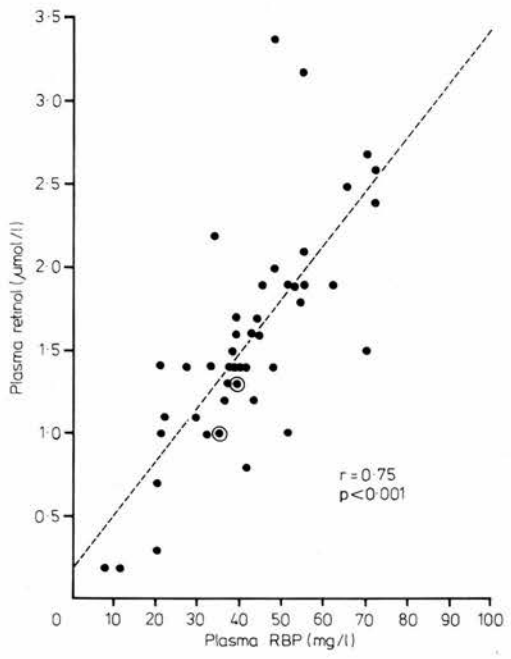

Fig. 1 *Correlation between plasma concentrations of retinol and retinol binding protein. ◉ indicates two or more identical values.*

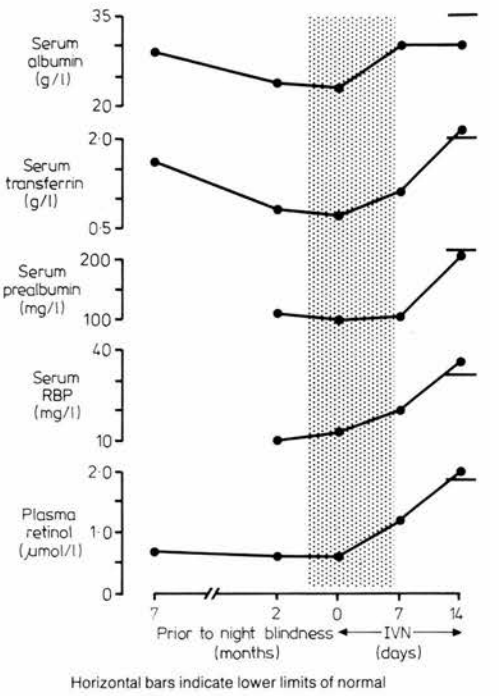

Fig. 2 *Biochemical changes before and after treatment with IVN including vitamin A (2500 IU/d) in patient 4 (Table 4). Cross hatched area indicates time during which he complained of night blindness.*

Table 3 *Clinical and biochemical comparison between high risk and low risk patients in group 2*

	Plasma retinol <1·4 μmol/l (9) (<40 μg%)		*Plasma retinol ≥1·4 μmol/l (12) (≥40 μg%)*	
Presence of extensive disease	7 out of 9		3 out of 12	
Mean body weight (% ideal)	71%	NS	82%	
Serum values (mean ± SD)				Normal range
Albumin (g/l)	31·1±6·2	NS	34·3±7·7	35–51
Transferrin (g/l)	1·7±0·8	p<0·05	2·4±0·7	2·0–4·0
Retinol binding protein (mg/l)	26·5±15·5	p<0·05	49·2±18·1	32–91
Prealbumin (mg/l)	135±66	p<0·05	213±49	215–400
Zinc (μmol/l (μg%))	9·0±1·5 (59±10)	NS	12·6±6·2 (82±40)	10·0–18·0 (65–117)

NS = not significant.

Patient 6 (Fig. 4), a girl with chronic diarrhoea and steatorrhoea of 11 years duration, complained of severe night blindness and dark adaptation testing (upper line) was grossly abnormal. Plasma retinol was very low (0·2 μmol/l) as were retinol binding protein (14 mg/l) and prealbumin (115 mg/l). After oral vitamin A therapy (6000 IU/day) her symptoms rapidly improved with improvement of dark adaptation testing (lower line).

Discussion

This study has shown that vitamin A deficiency is a significant clinical problem in severe Crohn's disease. Impaired dark adaptation, the earliest sign of vitamin A deficiency, was present in three inpatients with Crohn's disease and was associated with extensive small bowel disease, very low plasma retinol concentrations, and depletion of plasma proteins, especially retinol binding protein and prealbumin. Two patients had in addition impaired fat absorption and severe steatorrhoea.

Among the various methods of assessing vitamin A status recently reviewed by Pitt,[13] concentration of vitamin A in liver tissue is the most sensitive guide to body status, as vitamin A is stored almost entirely in the liver. There may be, however, an uneven distribution of vitamin A in liver.[14] Plasma retinol levels only fall when liver reserves are exhausted and therefore are relatively insensitive guides to vitamin A stores.[13] Retinol concentration in plasma, however, is a reasonable screening test as clinical signs of vitamin A deficiency (impaired dark adaptation) do not appear to occur when plasma retinol levels are greater than 1·4 μmol/l (40 μg%).[4] Despite differences between our method of measuring plasma retinol and that of Carney and Russell,[4] we felt it was reasonable to define our 'high risk' patients (Table 3) as those with plasma retinol <1·4 μmol/l, and to undertake dark adaptation testing only on these patients. Furthermore, very low plasma retinol levels are useful in the clinical situation, as Carney and Russell,[4] in a study of patients with a variety of diseases, reported that

Table 4 *Further studies of group 2. Patients with plasma retinol <1·4 μmol/l*

Patient	*Sex*	*Age*	*Extent of small bowel disease*	*Body wt (% ideal)*	*Final visual threshold (neg $\log_{10}$ apostilbs)*	*Plasma retinol (μmol/l) (μg%)*	*Serum zinc (μmol/l) (μg%)*	*Tri-glyceride absorption (%)*	*Faecal fat (mmol/d)*
1	F	60	E	83	44	1·2 (34·3)	7·2 (47)	15	179
2	M	48	E	80	44	1·0 (28·6)	11·0 (72)	44	168
3	M	16	E	74	38	0·2 (5·7)	10·5 (68)	98	27
4	M	34	E	78	35	0·7 (20·0)	12·5 (81)	70	121
5	F	19	E	64	46	0·6 (17·2)	6·5 (42)	82	49
6	F	18	E	54	25	0·2 (5·7)	4·5 (29)	16	153
7	F	16	L	69	57	1·3 (37·2)	10·0 (65)	96	16
8	F	71	L	70	45	1·3 (37·2)	8·5 (55)	—	22
9	F	26	E	70	46	0·8 (22·9)	10·0 (65)	—	—
E = extensive. L = localised.				Normal ranges	>43·4	1·2–2·9 (34–83)	10·0–18·0 (65–117)	≥96%	<21

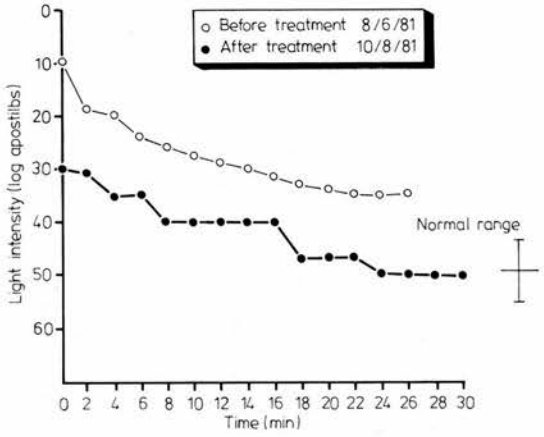

Fig. 3 *Dark adaptation testing before (upper curve) and after IVN followed by oral vitamin A therapy in patient 4.*

15 out of 21 patients with plasma retinol <1·05 μmol/l (<30 μg%) had abnormal dark adaptation testing. In this study three out of four patients with plasma retinol <0·8 μmol/l (<23 μg%) had abnormal dark adaptation testing, whereas in no patient with plasma retinol >0·8 μmol/l was dark adaptation testing abnormal.

In developed countries, vitamin A deficiency is unlikely to occur for dietary reasons alone and the search for clinical evidence of vitamin A deficiency has therefore centred on patients with liver disease[2–4] and various gastrointestinal diseases[1 3 4] among which some patients with Crohn's disease have been included.

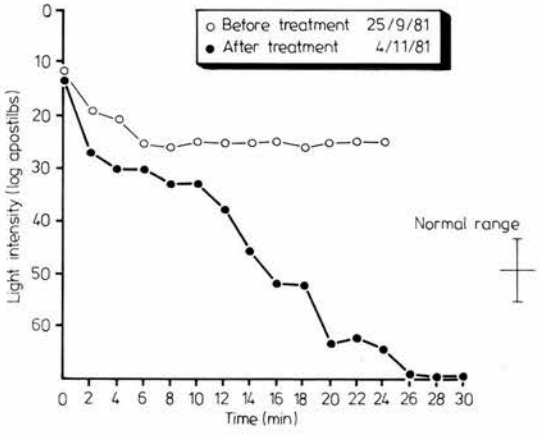

Fig. 4 *Dark adaptation testing before (upper curve) and after oral vitamin A therapy in patient 6.*

Patients with severe Crohn's disease may be protein depleted as we have shown. Indeed, retinol binding protein and prealbumin which have a relatively short half-life are more senitive to protein or energy deprivation than albumin or transferrin.[15] Plasma concentrations of retinol binding protein and prealbumin fall rapidly in protein malnutrition and rise on refeeding.[16] The expected close relationship between retinol, retinol binding protein, and prealbumin in plasma[17 18] has been confirmed in our patients with Crohn's disease and emphasises the importance of adequate protein nutrition for transport of retinol to its target tissues, principally the retina. If protein malnutrition is not corrected, plasma retinol and retinol binding protein levels may remain low despite adequate intake of vitamin A.[19] Fat malabsorption was a significant problem in some patients, and might be expected to result in vitamin A deprivation which has been shown to inhibit release of hepatic retinol binding protein into the circulation.[20] Repletion of vitamin A results in a fall in hepatic retinol binding protein and a rise in serum retinol binding protein.[21] Assessment of the relative importance of protein depletion and fat malabsorption in the pathogenesis of xerophthalmia in our patients was difficult because only three had impaired dark adaptation. All three, however, were protein depleted and two had fat malabsorption. Vahlquist and his colleagues,[3] studying patients with various gastrointestinal diseases, showed an association between steatorrhoea and low plasma retinol binding protein levels, and between very low retinol binding protein levels and impaired dark adaptation. No direct relationship between steatorrhoea and impaired dark adaptation, however, was suggested.

The possibility that zinc deficiency might contribute to the pathogenesis of vitamin A deficiency has received some attention in the literature in animals[22 23] and in humans.[24] The effect is probably because of the depression of protein synthesis and in particular impaired synthesis of prealbumin[24] and retinol binding protein.[23] Serum zinc levels were not significantly different in the two groups (Table 3). We recognise, however, as discussed in a previous report,[25] that serum zinc levels alone are not good indicators of zinc nutriture.

It was not possible to predict from the extent of small bowel disease alone which patients were at risk from vitamin A deficiency. The presence of only localised disease did not exclude low plasma retinol levels. Conversely, extensive disease was compatible with normal plasma retinol levels. None of the five patients with very low levels of retinol (<1·0 μmol/l), however, had localised disease and it

may be that patients with localised disease are unlikely to develop vitamin A deficiency.

Body weight measurement may be more useful. The outpatient group seemed at lower risk than the inpatients. All had plasma retinol levels >1·0 μmol/l (28·6 μg%) and weighed >80% of ideal body weight. In contrast the five who had plasma retinol levels <1·0 μmol/l were all inpatients admitted with exacerbations or complications. All five, including the three with impaired dark adaptation, weighed <80% of ideal weight (Table 4 – patients 3, 4, 5, 6, 9).

It could be argued that night blindness is readily reversible and tests could therefore be reserved for those patients who admit to the symptom on direct questioning. One of the three patients with impaired dark adaptation testing, however, was asymptomatic and direct questioning may not be completely reliable in the detection of retinal impairment. Furthermore, protein depletion, which has adverse effects unrelated to vitamin A deficiency, may be far advanced before night blindness develops. It seems reasonable, therefore, to improve protein status before night blindness occurs.

Conclusions and recommendations

We would suggest that patients with extensive small bowel Crohn's disease who weigh <80% of ideal weight should have biochemical tests performed including measurement of plasma retinol and plasma proteins. Our data suggest that patients with plasma retinol <0·8 μmol/l (23 μg%) run a high risk of developing night blindness which may be subclinical. If dark adaptation testing is not possible we would suggest that vitamin A supplements should be given. Protein depletion which is likely to be present should also be corrected.

The Gastroenterology Unit wish to thank Travenol Laboratories for their support.

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Vitamin E and selenium status in Crohns disease. By M. LOUGH[1], A. MAIN[2], R. I. RUSSELL[2] and A. SHENKIN[1], *Departments of [1]Pathological Biochemistry and [2]Gastroenterology, Glasgow Royal Infirmary, Glasgow G4 0SF*

Pathological conditions of the gastrointestinal tract producing steatorrhoea may produce deficiencies of the fat-soluble vitamins. It is established that vitamin E as well as selenium protect cell membranes against the effects of oxidants in vivo.

The present study included twenty-five patients with established Crohns disease. All the patients had plasma vitamin E, Se, glutathione peroxidase (*EC* 1.11.1.9) (plus red cell glutathione peroxidase), haemoglobin (Hb), reticulocyte count, haptoglobin concentration and stability of red blood cells to hydrogen peroxide measured.

Plasma Se concentration had a mean value (1 SD) of 1·21 (0·46) μmol/l with only two patients having low values (less than 0·6 μmol/l). Mean red cell glutathione peroxidase (1 SD) was 17·6 (6·8) U/g Hb (normal range 13–25 U/g Hb), five patients having abnormally low values.

Median plasma vitamin E concentration was 16 μmol/l (range 1–50 μmol/l), eight patients having low values (less than 12 μmol/l). The stability of red blood cells to hydrogen peroxide was grossly impaired, the median value being 83% haemolysis, nineteen patients having abnormal values (i.e. greater than 10% haemolysis). There was a significant correlation between vitamin E levels and hydrogen peroxide stability (r −0·68). All patients with low vitamin E concentrations had abnormal hydrogen peroxide stability.

Twenty-four hour fat excretion was measured in sixteen patients, the median value being 73 mmol/24 h (range 14–179 mmol/24 h). Twelve patients had steatorrhoea (i.e. greater than 21 mmol fat 24 h), and all patients with low plasma vitamin E concentrations were in this group.

The relevance of the above findings to in vivo haemolysis was studied. There was no relation between vitamin E concentration, Se concentration, hydrogen peroxide stability in vitro and fat excretion on the one hand, with reticulocyte count and serum haptoglobin concentration on the other. There was no evidence of significant in vivo haemolysis, since no patient had a reticulocyte count greater than 5% and only two patients had low haptoglobin concentrations.

It is concluded that while biochemical evidence of vitamin E abnormality is common in Crohns disease this does not appear to be of clinical significance.

Proc Nutr Soc. (1984) 43.

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results would support the concept that PBMC from patients with CD have an enhanced capacity to produce greater amounts of the immunomodulator PGE_2 which might be a consequence of increased availability of precursor AA.

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Changes in whole body protein synthesis and breakdown in acute malnourished Crohn's disease patients before and after nutritional restoration

T W O'CALLAGHAN, R DOCKRELL, J R LENNON, M A MORGAN, AND J P CROWE *(Mater Misericordiae Hospital Dublin and Department of Biochemistry and Soil Science, University College Dublin, Eire)* Metabolic changes were studied in seven consecutive malnourished patients with an acute exacerbation of Crohn's disease at the beginning and end of nutrional restoration with a whole protein diet. The nutritional supply provided 2·5 g. of protein and 60 kcal energy/kg/day. Rates of flux, protein synthesis and breakdown were calculated from the enrichment of urinary urea and ammonia with ^{15}N glycine.

Significant nutritional restoration was achieved with mean body weight increasing by 14% from 84% to 96% of ideal, and mean serum albumin by 23% from 35 to 43 g/l ($p<0.02$). Mean rates of whole body protein synthesis and breakdown in the malnourished state were 6·8±1·1 and 5·3±1·4 g/kg/day, respectively. After nutritional restoration these values fell significantly to 4·5±0·8 and 3·3±0·8 g. protein/kg/day ($p<0·02$). These markedly increased rates of synthesis and breakdown show that although whole body protein breakdown is increased in an acute exacerbation of Crohn's disease, this 'catabolic' state is paralled by an equal or greater increase in protein synthesis when the nitrogen and energy supply is adequate. This emphasises the importance of an adequate nutritional supply in the treatment of acute Crohn's disease which in the majority of such patients should be enteral feeding with a whole protein diet.

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Diffuse nodular lymphoid hyperplasia and western type malignant lymphoma of the small bowel, without overt immunodeficiency : a signficant association

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We thereby suggest that extensive NLH and ML of the small bowel is a significant association, which may affect caucasians born and living in western countries.

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Comparative effects of enteral liquid diets on growth; nitrogen (N) balance, whole body N, N. Wastage and faecal residue in rats.

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In conclusion, V produced least growth (N accretion) of the test diets but it and VHN had significantly lower faecal residue than the other test diets. The methods used are applicable to human subjects and the diets will be tested in patients with impaired small bowel function or bowel stricutures in whom low nitrogen wastage and low faecal residue are considered desirable.

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Physiological starch malabsorption: direct quantitation in ileostomates and effect of small bowel transit time.