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# short bowel syndrome

## clinical, metabolic and nutritional aspects, including parenteral nutrition

l.g.j.b. engels

# SHORT BOWEL SYNDROME

*Clinical, metabolic and nutritional aspects, including parenteral nutrition*

Promotor: Dr. J.H.M. van Tongeren

The studies presented in this thesis were performed in the Division of Gastroenterology, Department of Medicine (head Prof.Dr. C.L.H. Majoor , at present Prof.Dr. A. van 't Laar), St. Radboud Hospital, University of Nijmegen, Nijmegen, The Netherlands

# SHORT BOWEL SYNDROME
## Clinical, metabolic and nutritional aspects, including parenteral nutrition

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN
DOCTOR IN DE GENEESKUNDE AAN DE
KATHOLIEKE UNIVERSITEIT TE NIJMEGEN,
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. J.H.G.I. GIESBERS,
VOLGENS HET BESLUIT VAN HET
COLLEGE VAN DEKANEN IN HET
OPENBAAR TE VERDEDIGEN OP
WOENSDAG 12 OKTOBER 1983
DES NAMIDDAGS TE 4 UUR

DOOR

LEOPOLD GEORGE JEAN BAPTIST ENGELS
GEBOREN TE MAASBRACHT

1983
DRUK: STICHTING STUDENTENPERS NIJMEGEN

Aan de man die zonder enige twijfel
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aanbieden van dit boekje:

A.L.H. Engels

In leven bijna 40 jaar huisarts te
Maasbracht

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# Chapter 1

# INTRODUCTION AND AIM OF THE STUDY

# 1 INTRODUCTION AND AIM OF THE STUDY

## 1.1 Notes on the short bowel syndrome

In defining the short bowel syndrome it is important to have information on the length of the normal small bowel in man. However, human small intestinal length has not been established exactly. Results of postmortem length measurements are extremely variable and therefore useless. Muscle relaxation during autolysis results in unpredictable intestinal lengthening[1]. Measurements during surgery also have drawbacks, such as variable influences of anaesthesia and surgical trauma on intestinal muscle tone, different sites of measurement (e.g. at the mesenteric or at the antimesenteric border, or just in between). At laparotomy, Backman found a mean small bowel length of 6.43 m (range 4.00 to 8.46 m) in 32 patients of normal body weight[2]. Duplicate measurements of the small intestinal length revealed a mean difference of 10% between each two measurements[2]. Probably the most physiological method to assess small bowel length is that using a transintestinal intubation technique. With this method, a mean length of jejunum and ileum of 2.61 m (range 2.06 to 3.29 m) was obtained in 10 subjects[3]. The main disadvantage of this technique is presumably the unevaluable degree of "telescoping" of small intestine over the tube during the procedure. Altogether, measurements of small intestinal length at autopsy or laparotomy generally produce too large values, and those with the intubation technique too small values. In practical terms the length of the human small bowel presumably varies between about 2.5 and 4 m.

After an extensive small bowel resection, reliable length measurement of the remnant can be performed by observations at surgery or by small bowel X-ray series after resection[4].

Koeberlé was the first to describe a successful extensive small bowel resection (2.05 m) in 1881[5]. In 1935, 257 cases of massive small bowel resection were collected from the literature[6]. At that time it was concluded that resection of one-third of the small bowel was generally well-tolerated. A 50% resection was thought to be the maximum compatible with life. In 1956 it was stated that a minimum of 35 to 70 cm of small intestine was necessary to maintain an acceptable nutritional state[7]. An anecdotal report on a patient with duodenotransversostomy who survived one year despite 12.5 kg weight loss and recurrent water and mineral disturbances suggests that virtually no jejunum and ileum is necessary[8].

However, in the large majority of published case histories of patients with 10 to 25 cm of remaining jejunum and/or ileum, death ultimately ensued after variable periods of severe protein-calorie malnutrition[9-17]. Considering these observations, previously proposed definitions of short bowel syndrome (SBS) implying symptoms and metabolic alterations occurring after resection of at least 2 m or 70% of the small bowel, seem valid[5,18]. This means some 1.00 m or less of remaining small intestine beyond the ligament of Treitz.

The most frequent causes of SBS in relatively young persons include multiple resections for Crohn's disease and volvulus with ensuing necrosis of the small bowel. Mesenteric infarction is the major cause of SBS in elderly patients. In figure 1* the number of persons who died from mesenteric infarction in The Netherlands is indicated from 1969 until 1980. From 1976 on, a gradual increase in death rate can be noted, averaging some 250 persons per year. Figure 2* graphically presents the mean death rate per 5-year age category over the same period. A substantial rise can be observed from age 60 on. Until age 75 there is hardly any difference between men and women, but beyond this age women die from mesenteric infarction more often than men. However, in these age categories more women are still alive than men.

Since parenteral nutrition entered clinical medicine in 1968[10], the treatment of various disorders has changed more or less. Especially patients with massive small bowel resection benefited from this treatment. From 1972, several papers have been published on the impact of long-term parenteral nutrition at home in this group of patients[20-33]. In the past decade some reports have dealt with absorption defects and nutritional needs in SBS patients on oral nutrition[34-39].

Since the advent of parenteral nutrition, SBS patients can be divided into two groups.

1 Patients with less than 40 cm of jejunum and/or ileum left and depending mainly or completely on parenteral nutrition.
2 Patients with 40 to 100 cm of remaining jejunum and ileum, exclusively maintained by oral nutrition.

*Data obtained from CBS (Centraal Bureau voor de Statistiek; Central Bureau of Statistics), Voorburg, The Netherlands

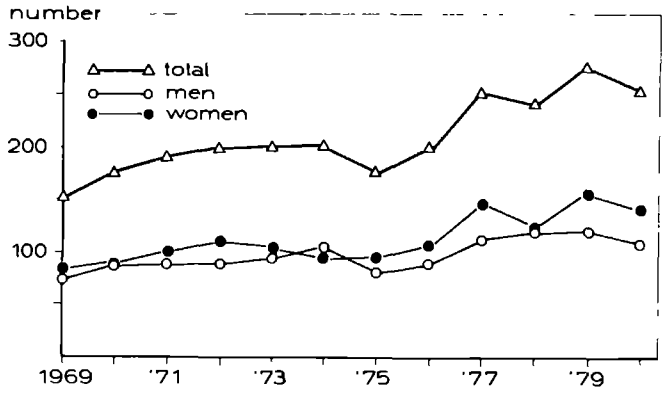


Figure 1.1
Number of persons who annually die from mesenteric infarction in The Netherlands.

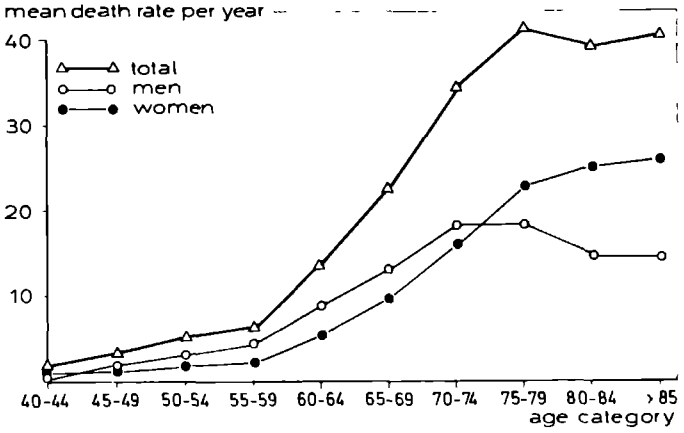


Figure 1.2
Mean death rate per year from mesenteric infarction indicated per 5-year age category in The Netherlands.

Apart from SBS, prolonged parenteral nutrition may be necessary for patients with a non-resected small bowel without function, e.g. severe radiation enteritis, scleroderma involving the small bowel and chronic intestinal pseudo-obstruction resistant to medical therapy. Other indications for long-term parenteral nutrition are of an incidental nature.

Patients of group 2 may require a period of total parenteral nutrition to maintain homoeostasis while intestinal adaptation of the small bowel remnant is developing. Intestinal adaptation, characterized by hyperplasia of the remaining epithelium enables increased absorption of oral nutrients[40].

## 1.2 Aim of the study

The aim of the study is to describe clinical and biochemical findings in patients with SBS and to present data on absorption of various nutrients, including trace elements, and on bone metabolism in these patients. When appropriate, patients are divided as described in the previous section: those depending on parenteral nutrition and other maintained by oral nutrition. Moreover, a review of intestinal adaptation is presented. Finally, some technical aspects of long-term parenteral nutrition are amplified in more detail, such as administration systems and vascular access procedures.

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Chapter 2

# SHORT BOWEL SYNDROME. EXPERIENCES IN EIGHT PATIENTS.

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Submitted for publication

# 2 SHORT BOWEL SYNDROME. EXPERIENCES IN EIGHT PATIENTS.

## 2.1 Introduction

The average length of the small bowel in vivo amounts to approximately 3 m[1]. Short bowel syndrome (SBS) has been defined as a complex of symptoms and metabolic alterations occurring after resection of at least 2 m or 70% of the small bowel[2,3], implying 1 m or less of remaining jejunum and or ileum. Causes of SBS in relatively young persons include recurrent resections due to Crohn's disease and volvulus with ensuing necrosis of the small bowel. Vascular accidents of the mesenteric circulation are the major cause of SBS in elderly persons.

After an extensive small bowel resection malabsorption of various nutrients can be expected, resulting in weight loss, diarrhoea and deficiencies. Pathophysiological mechanisms underlying malabsorption and diarrhoea in these circumstances include:

1 Reduced contact time between luminal nutrients and small bowel mucosa due to significant loss of absorptive surface and increased transit through the shortened intestine.
2 Abnormal delivery to the colon of maldigested or malabsorbed nutrients, precipitating osmotic diarrhoea.
3 Interruption of the enterohepatic circulation may result in: a) bile salt loss into the colon, causing fluid secretion and thus diarrhoea; b) increased faecal bile salt loss, which may compromise bile acid pool and impair micellar fat absorption, aggravating steatorrhoea.

After removal of the entire jejunum and ileum, sufficient absorption is no longer possible. In this situation home parenteral nutrition can be life-saving treatment[4].

This paper describes eight SBS patients on oral nutrition. Clinical and biochemical data are presented. Results of absorption and balance studies are reported. Consequences of various types of bowel resection and some specific metabolic problems are emphasized. Finally, the management of SBS patients is discussed.

## 2.2 Patients

Eight patients, six males and two females, were studied an average of 53 months (range 24-87 months) after extensive small bowel resection. Table 2.1 summarizes clinical data on these patients. In the oldest six patients

Table 2.1

EXTENT OF BOWEL RESECTION IN 8 PATIENTS WITH SHORT BOWEL SYNDROME.

| Patient | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| Sex | f | m | m | m | m | m | m | f |
| Age at time of resection | 35 | 47 | 57 | 65 | 18 | 16 | 55 | 74 |
| Cause resection | strangu-lation ileus | sup.mesen-teric art. infarction | sup.mesen-teric art. infarction | sup.mesen-teric art. infarction | sup.mesen-teric art. infarction | volvulus small bowel | sup.mesen-teric art. infarction | sup.mesen-teric art. infarction |
| Remaining jejunum (cm) | 40 | 40 | 90 | 40 | 90 | 35 | 30 | 50 |
| Remaining ileum (cm) | 20 | 20 | 20 | 0 | 2 | 15 | 15 | 0 |
| Ileocoecal valve | + | + | + | - | + | + | + | - |
| Resection colon | - | - | - | asc. | - | - | - | asc.+transv. |

* present

- absent

mesenteric infarction was the underlying disease causing SBS. The length of the small bowel remnant varied from 40 to 110 cm (mean 60 cm). In three patients (D,E and H), no or hardly any ileum was left. In two patients (D and H) the ileocoecal valve and part of the colon had to be removed as well. When discharged from hospital after resection, all patients except one had achieved an acceptable equilibrium on oral feeding. Home parenteral nutrition during one year after resection appeared to be necessary in patient F[4].

## 2.3 Methods

Data relate only to the time after discharge from hospital. At out-patient clinic visits, body weight was recorded and plasma or serum levels of albumin, haemoglobin, cholesterol, Na, K, Ca, Mg, phosphate, copper and zinc were measured. At less frequent intervals levels of fat-soluble vitamins E, carotene and 25-hydroxyvitamin $D_3$ (25 $OHD_3$) and water-soluble vitamins folic acid, vitamin $B_{12}$, pyridoxine and transketolase (equivalent of vitamin $B_1$) were determined. To test the absorptive capacity of the remaining small bowel, D-xylose tests were carried out twice or more in the course of time. The functional capacity of the ileum remnant was measured using the Schilling test. Urinary oxalate excretion was evaluated from time to time. Hyperoxaluria may be expected in SBS, predisposing to the formation of urolithiasis.

An average of 30 months (range 12-60 months) after resection, all patients were admitted to hospital for a balance study during five days. During an equilibration period of three days and during the balance period patients consumed a fixed, self-selected diet to which they had been adapted at home. The diets were prepared in advance and in multiplicate, including one for analysis. The nutrients assessed during the balance period included nitrogen, fat, calcium, magnesium and phosphate. Carmine red served as marker for stool collection. From measurements of all materials (diets, stools and urine) the balance was calculated and expressed per day.

## 2.4 Results

Figure 2.1 shows the course of the body weight in all patients at out-patient clinic visits. Body weights are expressed as mean percentage of ideal body weight[5]. After an initial small decrease, a gradual increase in body weight occurs some 18 months after discharge from hospital. At the moment, body weight is more than 85% of the ideal body weight except in patient H (72%).

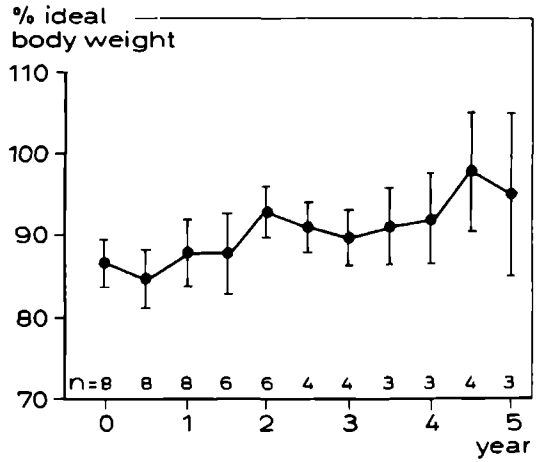


Figure 2.1
Body weight expressed as mean percentage of ideal body weight[5] (± SEM) in course of time after discharge from hospital.
n=number of patients at the time of investigation.

In figure 2.2 the course of serum albumin is presented. In two patients (D and E) moderate to severe hypoalbuminaemia was present the first two years after discharge. Serum albumin has since remained normal in all patients.

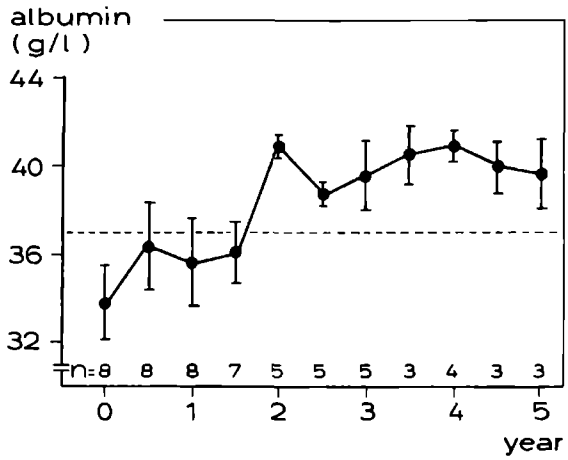


Figure 2.2
Mean serum albumin (± SEM) in course of time. The dotted line represents the lower limit of normal.
n=number of patients at the time of investigation.

Mean haemoglobin levels remained within normal limits throughout the observation period (figure 2.3). Patients D and E however, also had anaemia some 1½ to 2 years after discharge, without evidence of deficiencies of iron, folic acid, vitamin B12 and copper.

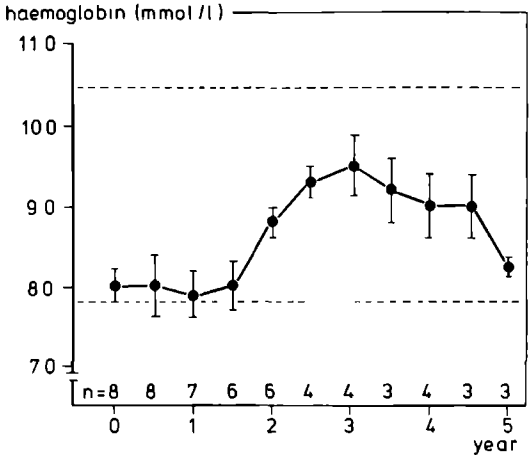


Figure 2.3

Mean haemoglobin (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

Mean plasma levels of sodium were normal (figure 2.4) while initially potassium levels were decreased (figure 2.5).

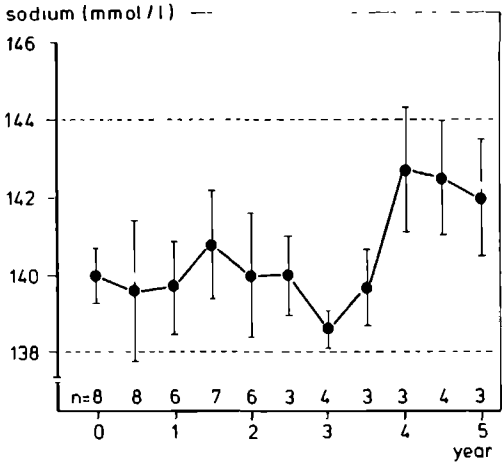


Figure 2.4

Mean plasma sodium (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

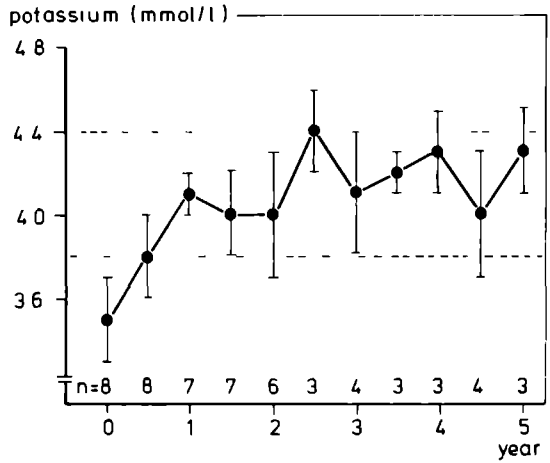


Figure 2.5
Mean plasma potassium (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

Mean plasma levels of calcium and phosphate were normal up to 5 years after discharge (figures 2.6 and 2.7), while mean levels of magnesium were slightly decreased some two years after discharge from hospital (figure 2.8).

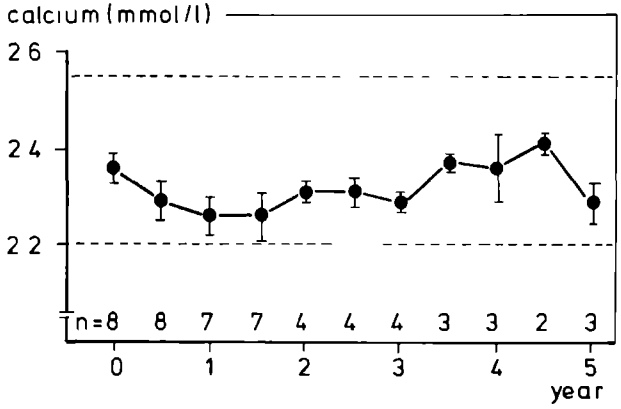


Figure 2.6
Mean plasma calcium (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

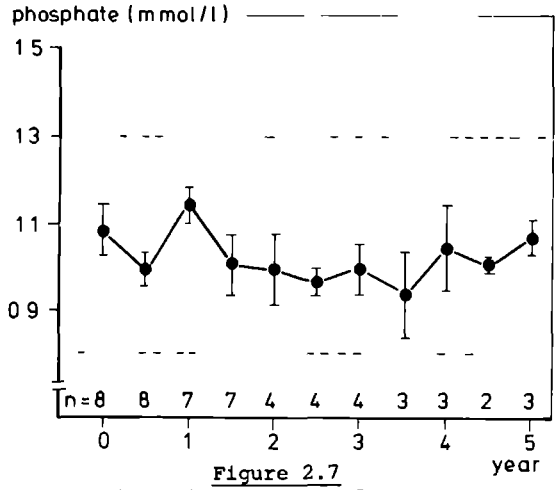


Figure 2.7

Mean plasma phosphate (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

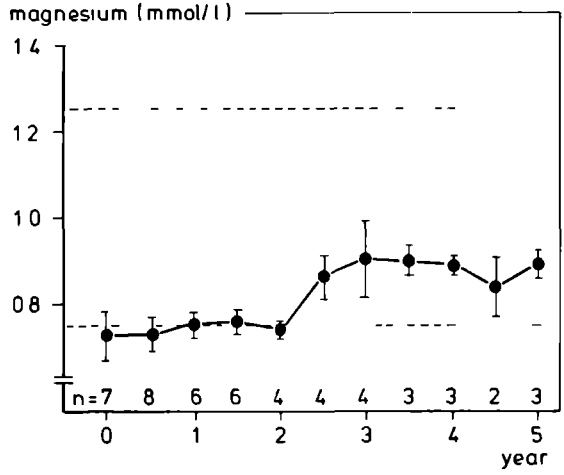


Figure 2.8

Mean plasma magnesium (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

Mean serum copper and zinc remained within normal limits (figures 2.9 and 2.10).

Serum cholesterol was permanently decreased after resection (figure 2.11). Plasma vitamin E levels fluctuated considerably (figure 2.12), while serum carotene levels were decreased some two years after discharge and became

normal after that period (figure 2.13).

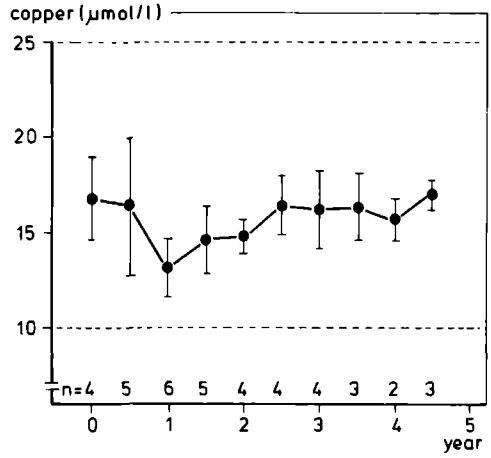


Figure 2.9

Mean serum copper (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

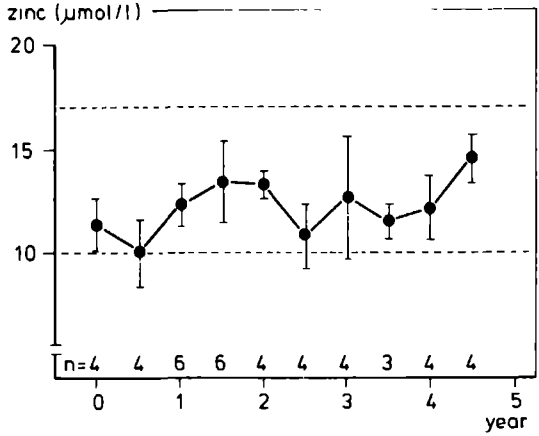


Figure 2.10

Mean serum zinc (± SEM) in course of time.
n=number of patients at the time of investigation. The area between the dotted lines represents normal values.

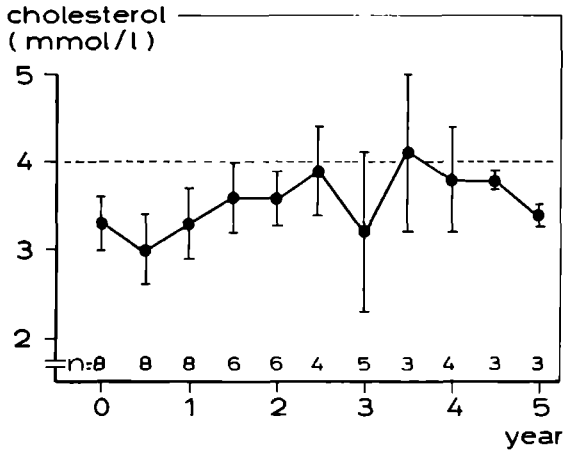


Figure 2.11

Mean serum cholesterol (± SEM) in course of time.
n=number of patients at the time of investigation. The dotted line represents the lower limit of normal.

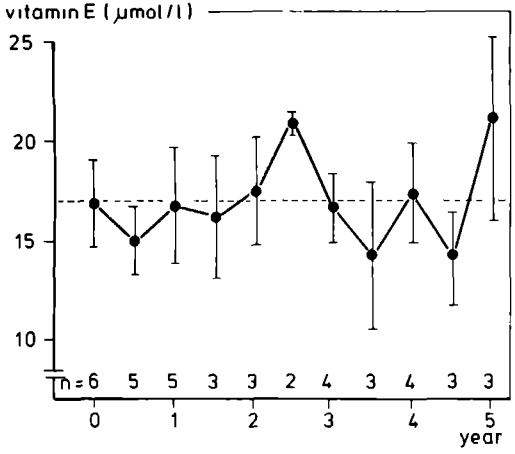


Figure 2.12

Mean plasma vitamin E (± SEM) in course of time.
n= number of patients at the time of investigation. The dotted line represents the lower limit of normal.

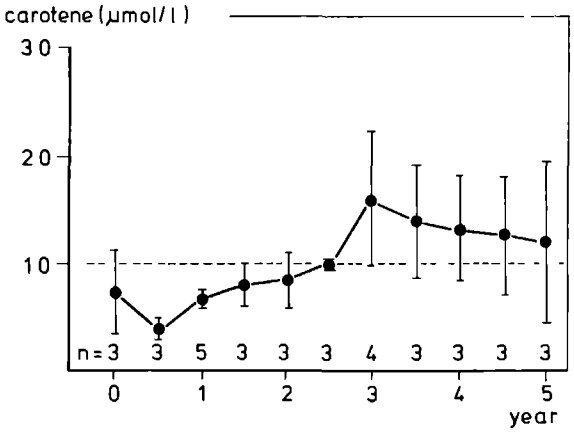


Figure 2.13
Mean serum carotene (± SEM) in course of time.
n=number of patients at the time of investigation. The dotted line represents the lower limit of normal.

Mean 25 $OHD_3$ levels were clearly depressed (10,6 ng/ml ± 8.9 SD, n 14.5-37.0). Results of serum cholesterol and levels of fat-soluble vitamins reflect fat malabsorption which was present in nearly all patients (table 2.2).

Serum levels of water-soluble vitamins, measured during the first three months of 1983, were normal in all patients.

The D-xylose test appeared to be a valuable, simple method for assessment of the small bowel remnant capacity to absorb monosaccharides. In patients with preserved ileum (A, B, C and G), xylose absorption improved considerably in the course of time (figure 2.14). In patients without ileum hardly any increase in xylose absorption was noted.

Results of Schilling tests (figure 2.15) indicate that 15 to 20 cm of remaining ileum is sufficient to absorb vitamin $B_{12}$ adequately.

Table 2.2 summarizes results of balance studies and provides information on bowel movements and stool weight during the balance period. The N-balance was positive or in equilibrium in all patients except patient F. In this patient, the transition from combined parenteral and enteral nutrition to completely oral feeding had just been completed.

Table 2.2

RESULTS OF BALANCE STUDIES AN AVERAGE OF 30 MONTHS (RANGE 12-60 MONTHS) AFTER EXTENSIVE SMALL BOWEL RESECTION IN 8 PATIENTS.

| | All patients | Patients with ileum | Patients without ileum |
|---|---|---|---|
| N (g/day) | 0.1±0.6 (SD) | 0.1±0.7 (SD) | 0.3±0.6 |
| Fat (absorption %) | 74 ±18 | 82 ±17 | 59 ±7 |
| Ca (mmol/day) | 1.7±2.6 | 1.8±2.4 | 1.6±3.6 |
| Mg (mmol/day) | -0.2±1.5 | 0.3±0.9 | -0.9±2.1 |
| P (mmol/day) | -2.2±3.4 | -4.0±3.4 | 0.7±4.5 |
| Bowel movements per day | 2.4±1.0 | 1.9±0.8 | 3.2±1.6 |
| Faeces weight per day(g) | 800±450 | 640±490 | 1070±250 |

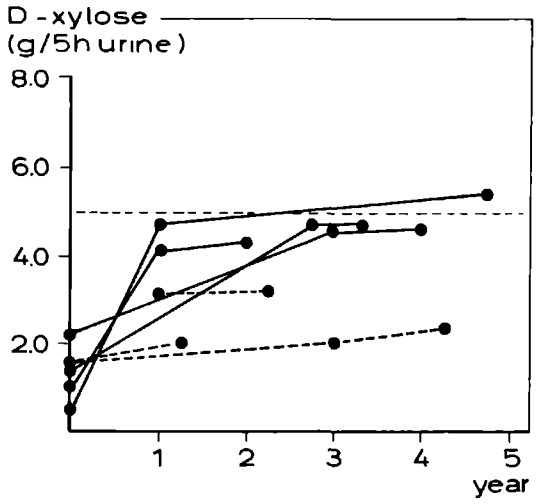


Figure 2.14
D-xylose absorption in course of time. Patients with 15 to 20 cm retained ileum are indicated with a solid line; those without any ileum with a dotted line. The horizontal dotted line represents the lower limit of normal.

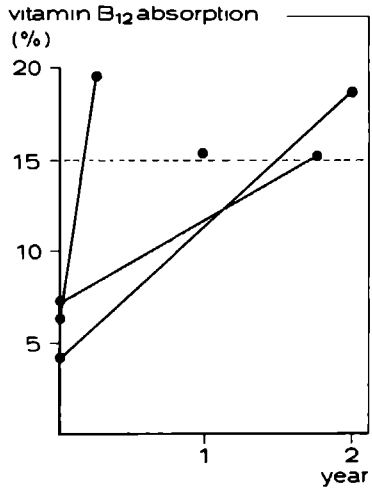


Figure 2.15
Vitamin B12-absorption in 4 patients with 15 to 20 cm retained ileum (A, B, C and G). The dotted line represents the lower limit of normal.

Probably this condition temporarily influenced N-metabolism. Fat absorption varied from 52 to 95% (mean 74%). Results in patients with retained ileum were obviously better than those in patients without ileum. The latter also showed more frequent bowel movements per day, and stool weight was higher. Balances of calcium, phosphate and magnesium were about equilibrium.

Hyperoxaluria (0.9-1.3 mmol/24 h; n<0.6) was present in 5 out of 8 patients. Apart from dietary oxalate restriction, 4 patients received 2 g calcium carbonate orally per day in order to complexate excess soluble oxalate intraluminally. In 2 of these 4 patients urinary oxalate excretion became normal. In one patient (E) hyperoxaluria persisted to the same extent and in another (F) urinary oxalate excretion could not be evaluated. It is to be noted that none of the patients had shown clinical signs of urinary calculi since the resection.

Except for slight osteoporosis in 3 patients, no signs of osteomalacia were found in a concurrently performed osteological study[6].

### 2.4.1 Psychosocial aspects

Of the initial 8 patients, 7 are still alive. One patient (B) died untimely due to ruptured aortic aneurysm in August 1982. None of the

patients is socially restricted due to frequent diarrhoea (table 2.2). Three patients have retired because of age (D and H) or for non-SBS-related medical reasons (C). Only one (E) of the remaining four patients is physically no longer able to do his former job. A tendency to depression, probably related to slight dementia, has recently been observed in one patient (H).

## 2.5 Discussion

### 2.5.1 Length and composition of the remaining small bowel

Survival is unusual if, in addition to the duodenum, less than 25 cm jejunum or ileum is left[7-13]. Not only the length but also the composition of the small bowel remnant is important. After an extensive resection hyperplasia of the remaining small bowel occurs, a phenomenon called intestinal adaptation[14]. As a result of this adaptation, absorptive function increases in the bowel remnant. The adaptive response in an ileal remnant is considerably greater than in its jejunal counterpart. When the ileocoecal valve is retained, diarrhoea seems to be less of a problem than when this valve is lacking[15,16]. Diarrhoea after extensive small bowel resection is significantly aggravated when an additional colectomy is performed[7,15-18]. The colon is normally able to absorb some six litres of fluid a day[19]. In SBS, a preserved colon is therefore of extraordinary importance. In end-jejunostomies, very large losses of fluid and minerals with recurrent episodes of dehydration and renal insufficiency have been observed[4,20-23]. In this condition, frequent parenteral supply of water and minerals or even indefinite parenteral nutrition may be needed[4,21]. Regular oral administration of solutions containing glucose or glucose polymers together with Na en K salts may also be of value in these circumstances[22]. In the case of an extensive bowel resection complications increase in the following sequence:

1 Predominantly proximal small bowel resection with duodeno- or jejunoileostomy
2 Predominantly distal small bowel resection with jejunoileostomy
3 Jejunocolostomy
4 End-jejunostomy

The prognosis in children with SBS is more favourable than that in adults. Like the child itself, the remaining small bowel has the potential of linear growth, which does not take place in adults. Normal growth and development

in children on oral nutrition appears to be possible when only 15 to 20 cm of small bowel is present[24-31].

2.5.2 Absorptive capacity of the remaining small bowel

Comparing literature data on the absorptive capacity of the remaining small bowel is difficult due to interindividual differences in the extent and site of resection and the interval since resection. Absorption of glucose(using GTT) appeared to be normal in patients with 40 to 100 cm of retained small intestine 2 to 10 months after resection[25,27,32-35].We used the D-xylose test to measure absorption of monosaccharides in the small bowel remnant. When a relatively small part of ileum was preserved, a gradual increase of D-xylose absorption was observed in the course of time (figure 2.14).This was not the case when no ileum at all was left. This finding again confirms the superiority of ileal versus jejunal remnants in terms of functional adaptation.

Ileal resection limited to 1 m or less does not give rise to clinically relevant steatorrhoea[36]. The more ileum is removed, the more faecal fat excretion increases[36-39]. This applies only partly to jejunal resections[37-38]. In extensive distal small bowel resection a strong correlation exists between oral fat intake and degree of steatorrhoea[38,40].In extensive proximal small bowel resection, however, increased fat consumption is often followed by increased fat absorption[38]. Some investigators found increasing fat absorption after months to years in their SBS patients[35,41,42]. However, other groups could not confirm this finding[27,34,43].Our data are in agreement with those from literature: patients with a retained part of the ileum and the ileocoecal valve have better fat absorption than those who have no ileum left at all.

The body does not store protein as it stores fat. Certain quantities of protein have to be ingested daily in order to maintain various metabolic functions. Absorption of oligopeptides and amino acids primarily takes place in the jejunum[44]. A positive N balance has seldom been obtained in patients with less than 20 cm of small bowel[8,9,11,13,45]. These patients almost invariably died with signs of severe protein and calorie malnutrition [8,9,11,13]. When more than 20 cm of small bowel is retained, a positive N balance can be achieved after some time[25,33,35,41,43].Except for patient F, our data on N balance agree with those from literature.

In view of its importance in bone metabolism, Ca balances are relatively

frequently determined in SBS. Pietz[41] generally obtained negative results, which was subsequently confirmed[13,45,46] and denied[25,35]. In our patients, the mean Ca balance proved to be slightly positive, probably resulting from the rather high calcium intake (mean 29.1 mmol/day). Regarding the Mg balance in SBS, again conflicting results have been reported[13,34,46]. As with Ca, a relatively low dietary fat intake has a positive effect on the Mg balance[34]. In our SBS patients acceptable Mg and P balances were obtained.

Absorption of vitamin B12 gradually decreases when increasing parts of the ileum are removed[39]. However, vitamin B12 absorption doubled in patients after proximal small bowel resection[47]. Additionally, vitamin B12 absorption increased in the course of time in rats after partial distal small bowel resection[48]. Data on our patients indicate that normal vitamin B12 absorption is finally possible when only 15 to 20 cm of ileum is retained (figure 2.15).

### 2.5.3 Specific metabolic problems in short bowel syndrome

#### 2.5.3.1 Gallstones

In the case of ileal disease or resection, bile may become lithogenic due to the reduced bile acid pool resulting from bile acid loss into the colon. Gallstones can frequently be found in patients with ileal disease or resection[18,23,49-51]. In three of our patients (A, B and D) gallstones were detected, without causing symptoms. Especially in these patients, a reserved attitude concerning surgical treatment of silent gallstones is warranted[52].

#### 2.5.3.2 Urolithiasis

In chronic inflammatory bowel disease, especially when ileal resection has taken place, the incidence of urolithiasis is increased[53-55]. Hyperoxaluria is positively related to ileal resection[56-60], and is caused by increased oxalate absorption[57]. Oxalate absorption from luminal contents mainly occurs via diffusion, especially in the colon[61]. Normally, calcium binds oxalate intraluminally, forming insoluble calcium oxalate. Two theories are available to explain small bowel resection-related hyperoxaluria:

1 Solubility theory

When fat malabsorption is present, calcium in the intestinal lumen may bind with excess fatty acids, forming soaps. Oxalate solubility, absorption

and urinary excretion are subsequently increased. A correlation has been established between the degree of fat malabsorption and hyperoxaluria[57,59]. After dietary fat restriction, a decreasedoxalate excretion has been observed[62,63].

2 Permeability theory

Colonic permeability to oxalate increases in the presence of excess fatty acids and bile salts[64] . Both mechanisms are probably involved in SBS-related hyperoxaluria. It has to be emphasized that other factors such as urinary volume, pH, Na and K content are of additional importance for the actual development of urinary calculi[65] . Hyperoxaluria may be managed by dietary reduction of fat and high-oxalate foods[56,62,63], and oral calcium suppletion[66]. In at least two of four hyperoxaluric SBS-patients, urinary oxalate excretion normalized with such treatment.

## 2.6 Management of short bowel syndrome

As a result of gradual intestinal adaptation, the clinical course of the SBS shows three stages.

I Postoperative period.

In this stage, characterized by massive diarrhoea, parenteral nutrition is often necessary in order to maintain nutritional status and to prevent mineral and trace element losses. With restored continuity of the bowel and in the absence of intra-abdominal sepsis, oral feeding can be resumed very cautiously while parenteral nutrition still continues.

II Transition from parenteral nutrition to oral feeding.

The presence of luminal nutrients and thus enteral nutrition is a prerequisite for the development of intestinal adaptation. There are conflicting opinions regarding the ideal composition of oral nutrition in this stage. Elementary diets, containing very small amounts of fat or fat replaced almost entirely by medium-chain triglycerides (MCT), have acquired considerable support[13,67-69]. These diets are thought to be ideal since little digestion is required, facilitating absorption. However, absorption of various nutrients from a blenderized regular diet in SBS occurred to the same extent as absorption of the same nutrients from various elementary diets[20]. Furthermore, prolonged administration of elementary diets to animals caused mucosal hypoplasia in the the ileum[70]. Finally, ordinary fat (long-chain trigylcerides) exerts a greater influence on intestinal adaptation than MCT, carbohydrates or protein[71]. Altogether, there is hardly any place for MCT or elementary diets in the

management of SBS. When tube feeding is indicated, a liquid formula containing as few predigested nutrients as possible has to be given.

In this stage, frequent small meals (6 to 8/day) will help to utilize optimally the absorptive capacity of the small bowel remnant. Dietary fat reduction (40 to 50 g/day) is indicated in order to reduce stool volume and minimize faecal calcium and magnesium losses[34,72]. Dietary lactose restriction[73], or lactase suppletion of milk products[74], makes sense since the amount of lactase in the normal small bowel is only marginal. In SBS, therefore, lactose deficiency very easily occurs, resulting in osmotic diarrhoea. The size of the meals must be very gradually increased while titrating against stool production. In this situation loperamide or codeine phosphate may be of help. When the amount of tolerated orally administered food reaches some 2000 Kcal, patients can be gradually weaned of parenteral nutrition.

Stage II may last weeks to months.

III Oral feeding

A relatively stable situation has been achieved regarding the capacity to consume relatively large quantities of calories and stool production. Outpatient clinic follow-ups have to be made very frequently. Attention has to be given to body weight, serum albumin, haemoglobin, minerals, vitamins zinc and copper. Rarely suppletion of one of these substances may be indicated. Urinary oxalate excretion should be evaluated from time to time. Monthly parenteral vitamin B12 suppletion has to be given when less than 15 to 20 cm of ileum is retained. Dietary fat restriction is no longer necessary[40,75], unlike lactose restriction or lactase suppletion of milk products. Relatively large quantities of these milk products are advised, supplying considerable amounts of calcium. When hyperoxaluria is established, high-oxalate foods have to be avoided and oral calcium carbonate (up to 3 g/day) may additionally be prescribed.

To maintain equilibrium the average caloric intake remains relatively high (2540 Kcal/day in our patients).

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Chapter 3

# INTESTINAL ADAPTATION.

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## 3.1 Introduction

In normal circumstances the absorption of carbohydrates and many minerals, water-soluble vitamins and trace elements is completed before chyme reaches the ileum. Absorption of protein, fat and fat-soluble vitamins also predominantly occurs in the jejunum, although some absorption of these nutrients also takes place in the ileum[1-3]. Vitamin $B_{12}$ and conjugated bile salts are almost exclusively absorbed in the ileum. In quantitative terms, the jejunum is the most important site of nutrient absorption. This functional distribution is reflected in mucosal morphology in that an aboral villus height gradient is present in the small bowel[4]. Consequently, the number of cells per villus is larger in the jejunum than in the ileum.

The small bowel has a large functional reserve. The ileum is very important in this respect. After extensive small bowel resection the absorptive capacity of the remaining bowel increases, a phenomenon called intestinal adaptation. Most scientific data pertaining to intestinal adaptation have been obtained in animal studies, especially in the rat.

## 3.2 Morphological aspects of intestinal adaptation

Intestinal adaptation is morphologically characterized by hyperplasia of the remaining small bowel mucosa. Due to the larger number of cells populating each villus, its height and consequently its absorptive surface increases[5-8]. These events have also been established in man[9-11]. In the adaptation of small bowel segments, crypt depth also increases[12]. However, the number of villi remains constant[13]. Compensatory growth of the small bowel after partial resection involves all layers of the bowel wall, but lengthening of the intestinal remnant generally does not occur[12,14,15]. Besides, the luminal diameter may increase[14,15]. The size of isolated epithelial cells populating hyperplastic villi is equal to or even smaller than that of normal enterocytes as a result of increased migration from crypts along the villi[5,6] due to increased cellular proliferation in the crypts[16]. The intensity of the hyperplastic response is directly proportional to the length of intestine resected[17]. A resection of at least 30% of the small intestine is required to provoke hyperplasia in the bowel remnant[12,17,18]. A schematic impression of intestinal adaptation is presented in figure 3.1. The hyperplastic response in the ileum is much greater than

that in the jejunum, which is favourable for the functional reserve of the ileum[5,6,8,12,14,15]. Adaptive changes are always maximal near the anastomosis, and taper off distally[12,14,15]. After jejuno-ileal bypass, hyperplasia of the remaining ileum is considerably more marked than that of its jejunal counterpart, in animals as well as in man[19-22]. Apart from jejunectomy, partial or total colectomy causes hyperplasia in the ileum[23-26]. On the other hand, ileal resection provokes colonic hyperplasia[27].

### 3.3 Functional aspects of intestinal adaptation

As often seen, changes in morphology are related to functional changes. Increased absorption has been established in small bowel remnants of animals[15,28-31] and man[10,11,32,33]. The absorptive capacity of each individual epithelial cell does not increase[5,6], leaving villus surface enlargement as explanation for increased absorption. The activity of various mucosal enzymes, expressed per weight unit of DNA (in other words, per cell) generally does not increase and occasionally even decreases[5,15,19,34-36].

#### 3.3.1 Time required for intestinal adaptation to develop

In the rat, hyperplasia of the small bowel remnant has been noted within 48 hours of resection and is complete after 7 to 12 days[8,37]. In the dog this process probably takes about 1-2 months[38]. In man it generally takes even longer. Our own experiences generally indicate a period of several months to about 2 years[39].

#### 3.3.2 Mechanisms of intestinal adaptation

The principal factors promoting intestinal adaptation include:

-luminal nutrition

-hormones

-pancreatico-biliary secretions

##### 3.3.2.1 Luminal nutrition

A regular supply of nutrients is indispensable for maintenance of the normal villus structure. Hypoplasia of the small bowel mucosa develops when food is restricted, e.g. in total starvation, in hypophysectomy-induced anorexia and during total parenteral nutrition[40-44]. Hypoplasia disappears after resumption of oral feeding[40,45]. Hyperplasia of the small bowel mucosa can be induced by hyperphagia. This phenomenon has been

established during exposure to low environmental temperatures, in hyperthyroidism, in artificial hypothalamic damage and during lactation[46-49]. After transposition of ileum and jejunum, hyperplasia is found in the proximally situated ileum and hypoplasia in the distally situated jejunum[15,50,51]. Transposition of a segment of the colon between jejunum and ileum induced hyperplasia in the transposed colonic segment[52]. Hypoplasia can be found in excluded loops of small intestine, e.g. in jejuno-ileal bypass and in Thiry-Vella fistulae[20-22,53,54]. Perfusion with an elementary diet in such an isolated bowel loop prevented mucosal hypoplasia[53]. Hyperplasia in the ileum does not follow jejunectomy when nutrition is exclusively provided parenterally[44]. Altogether, there is overwhelming evidence that luminal nutrition is important in maintaining small bowel structure and stimulating adaptive changes after intestinal resection. Various nutrients in the luminal contents are known to have a trophic effect on small bowel mucosa. Such an effect has been established for some mono- and oligosaccharides[55-57], complete amino acid solutions[56] and some isolated amino acids[58]. Long-chain triglycerides are by far superior in this respect[59].

The mechanism by which luminal nutrition exerts its trophic effect on small bowel epithelium is not completely understood. Transport processes of nutrients into the cell are probably more important than metabolism of the nutrients by the mucosal cell itself[55]. Direct contact between nutrients and mucosal surface has also been implicated as stimulating release of gastro-intestinal hormones and/or inducing other biochemical mechanisms. In this respect, the enzyme ornithine decarboxylase (ODC) probably plays an important role. ODC is the first and rate-limiting enzyme in polyamine synthesis. The polyamines contained in all karyotic cells, play a role in DNA, RNA en protein synthesis[60]. Short-term increased tissue ODC activity and polyamine synthesis are associated with the onset of hyperplasia, as has been established in ileal remnants after jejunectomy and in the ileum of intact lactating rats[61].

Apart from luminal nutrition, other mechanisms have to be involved in the development of intestinal adaptation, as demonstrated by the following observations. The occurrence of hyperplasia in the proximal jejunum after intraileal instillation of dextrose and amino acid solutions in rats[56,58]. The absence of hypoplasia in excluded loops of small intestine during lactation[49] and when an additional small bowel resection was carried

out[62-64]. Furthermore, the increased proliferative activity observed in extraintestinally transplanted ileal mucosa after partial small bowel resection is at odds with the luminal nutrition theory[65].

3.3.2.2 Hormones

It has been firmly established that gastrin and prolactin do not play a significant role in the adaptive processes[66-69]. Other, as yet unidentified anterior pituitary and/or hypothalamic hormones may exert some influence in this respect[41,48,49].Cholecystokinin and secretin have been regarded as important factors promoting hyperplasia. Combined intravenous administration to dogs given exclusively parenteral nutrition, prevented mucosal hypoplasia[70]. Infusion of cholecystokinin octapeptide and secretin alone in parenterally fed rats did not prevent hypoplasia[71]. It is not likely that these hormones have a significant trophic effect on gut structure. The effects observed in the dogs can be explained also by pancreatico-biliary secretions induced by these hormones.

The most serious hormonal candidate promoting intestinal adaptation is enteroglucagon. An extraordinary clinical observation initiated research on enteroglucagon in this field. In 1971, a patient with an enteroglucagon-producing tumour was described as showing marked intestinal hyperplasia and small bowel dilatation. After removal of the tumour, the gut structure and the increased plasma enteroglucagon level became normal[72,73]. Enteroglucagon is predominantly found in the ileum and colon. It is synthesized in specific mucosal endocrine cells, called EG cells[74]. Its release is stimulated particularly by fat and carbohydrate[75]. Increased plasma levels and tissue concentrations were found in the jejunum and especially in the ileum of rats made hyperplastic by hypothermia-induced hyperphagia[76]. Increased ileal enteroglucagon contents were found also in intact lactating rats[76]. Plasma enteroglucagon levels were significantly increased after jejunectomy[76]. In similar experiments a higher crypt cell proliferation rate was associated with increased plasma enteroglucagon levels[77]. The latter were found also after ileal-duodenal transposition, in correlation with striking adaptive changes in the transposed segment which contained more EG cells assessed on a weight basis[78]. Increased baseline and postprandial plasma enteroglucagon levels were found also in patients with untreated coeliac disease, after jejuno-ileal bypass and distal small bowel resection[79-81]. In adequately treated coeliac patients the plasma

enteroglucagon response was normal[79]. In ileostomy patients the baseline plasma enteroglucagon level was low, but the postprandial rise was similar to that in control subjects[82]. This phenomenon has been explained as a sign of relative adaptive response by the small intestine after the loss of colonic cells containing enteroglucagon[82]. In normally fed neonates a striking increase in plasma enteroglucagon was found within one week[83]. However, newborns maintained by intravenous dextrose without any oral nutrition showed no increase in plasma enteroglucagon[83]. During long-term exclusively parenteral nutrition in adults, the baseline plasma enteroglucagon level remained normal. Shortly after resumption of oral feeding a significantly increased postprandial plasma enteroglucagon level was found[84]. A correlation between enteroglucagon level and intestinal adaptation seems evident. However, increased plasma and/or tissue levels of this hormone occurred only in the presence of luminal nutrients.

3.3.2.3 Pancreatico-biliary secretions

Local hyperplasia can be induced by diverting the main biliary and pancreatic duct to the ileum or to self-emptying loops of ileum[85-87]. Ileal hyperplasia induced by jejunectomy can be further increased by pancreatico-biliary diversion to the mid-point of the intestinal remnant[88]. Whether bile or pancreatic juice is the most potent hyperplasia-promoting factor cannot be definitively stated[85,89]. Recent studies cast some doubt on the pancreatico-biliary secretions theory. After transposition of the jejunum between stomach and duodenum, not only ileal hyperplasia was found but also hyperplasia in the jejunum (deprived of pancreatico-biliary secretions)[90]. Similar observations were made after identical surgery in parenterally fed rats, where hypoplasia was in fact expected[90]. The latter observation can only be explained as a result of humoral influences.

Neurovascular and other mechanisms probably exert no significant influences on intestinal adaptation[91].

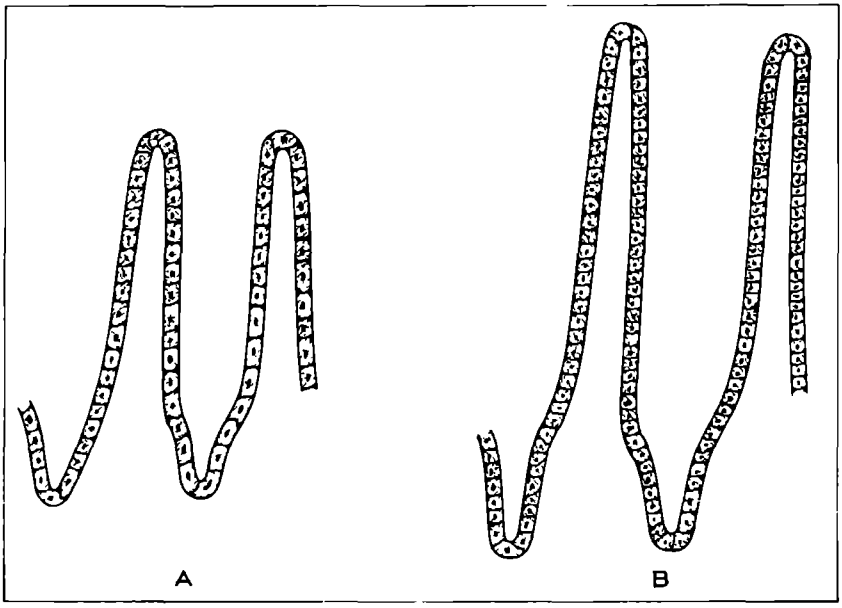


Figure 3.1
A schematic impression of normal (A) and hyperplastic (B) villi and crypts of the small bowel.

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Chapter 4

# METABOLIC BONE DISEASE AND SHORT BOWEL SYNDROME.

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# 4 METABOLIC BONE DISEASE AND SHORT BOWEL SYNDROME

## 4.1 Introduction

Short bowel syndrome (SBS) can be defined as a complex of symptoms and metabolic disturbances occurring when at least 70% of the small intestine is removed[1]. Malabsorption of various nutrients is common in patients with SBS[2-4]. After some time, absorption in the small bowel remnant generally increases due to intestinal adaptation[5]. Nevertheless, prolonged calcium and/or vitamin D malabsorption may cause osteoporosis and/or osteomalacia in this condition. Diminished enterohepatic circulation of 25-hydroxyvitamin D (25 OHD), the most abundant form of vitamin D in the circulation, may further compromise the vitamin D status[6]. Chronic acidosis may cause hypercalciuria and subsequently osteoporosis[7,8]. Not only calcium absorption, but also phosphate and probably magnesium absorption is influenced by vitamin D[9,10].

The occurrence of metabolic bone disease in small bowel disorders has been frequently reported. Especially in celiac and Crohn's disease, bone abnormalities and signs of vitamin D deficiency have been noted[11-15]. In most reports dealing with bone metabolism and SBS, Crohn's disease was the principal cause of extensive small bowel resection[16-22]. Calcium malabsorption[21,22], reduced 25 OHD levels[18,20], vitamin D malabsorption[18,20] and osteomalacia in some 25 to 36% of these patients have been documented[17,19]. Recently, increased fecal loss of 25 OHD probably due to interrupted 25 OHD enterohepatic circulation has been established in these patients[23,24].

Ill-defined, sometimes disabling bone diseases have been reported in patients on long-term parenteral nutrition for chronic intestinal disease, including SBS[25-28].

We studied 9 short bowel patients with a mean small intestinal remnant beyond the ligament of Treitz of 52 cm (range 0 to 110 cm). Two patients were dependent on parenteral nutrition, while the others took their food orally. No residual disease was present in the bowel remnants of these patients. We tried to find answers to the following questions: 1) Is metabolic bone disease present in short bowel patients on oral nutrition without residual bowel disease?, 2) Are parameters on bone metabolism abnormal in these patients? Assessed parameters include serum levels of calcium, phosphate, magnesium and 25 OHD, absorption of $^{47}Ca$ and balance

studies of calcium, phosphate, magnesium and fat. 3) is there any relation between these parameters and bone structure? 4) Is metabolic bone disease present in patients on long-term parenteral nutrition?

## 4.2 Patients and methods

### 4.2.1 Patients

Nine patients age 31 to 75 years (mean 55.8 years) were studied an average 35.3 months (range 12 to 60 months) after extensive intestinal resection. Patients were divided into an oral group (7 patients) who maintained themselves on oral nutrition and two patients depending on parenteral nutrition (PN patients). Some clinical features of the patients are listed in figure 4.1.

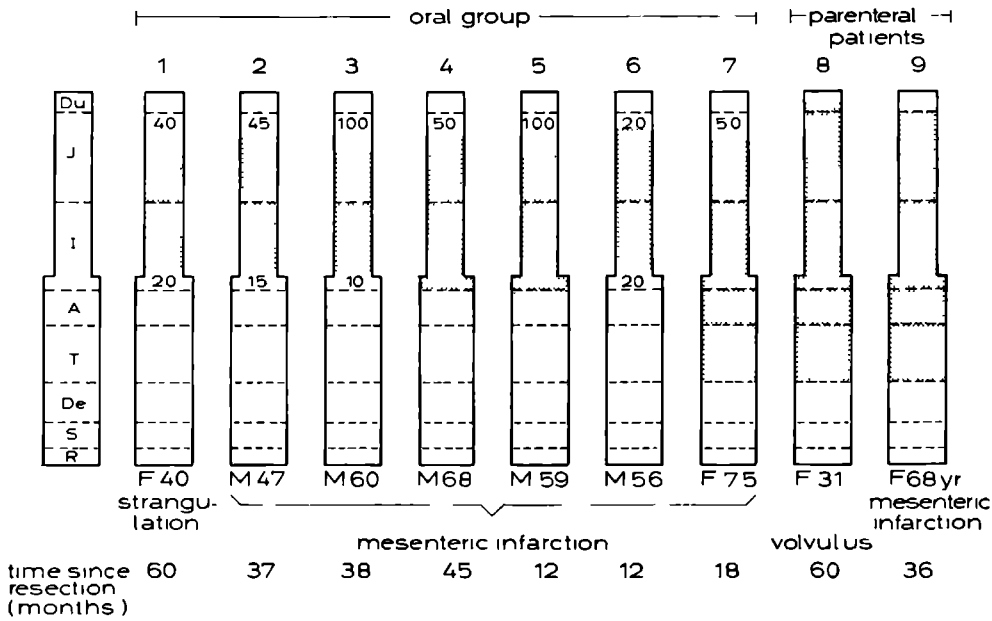


Figure 4.1

Diagrams of the bowel composition of 9 SBS patients. The upper part of each diagram represents the small bowel, the lower part indicates the large bowel. Anatomical segments are separated from each other by dotted lines and indicated by abbrevations (Du=duodenum; J=jejunum; I=ileum; A=ascending colon; T=transverse colon; De=descending colon; S=sigmoid; R=rectum). The removed parts of the bowel are hatched. The amount of remaining small bowel is indicated in cm. Some other clinical data on the patients are added.

The length of the remaining small bowel was estimated from measurements during laparotomy and by postoperative small bowel series. These methods are assumed to be reliable in the case of SBS[29]. No residual disease was detected on small bowel series and barium enemas.

The two PN patients had been on home parenteral nutrition for 5 and 3 years because of duodenotransversostomy. The parenteral nutrition scheme included 80 g amino acids, 300 g dextrose and 50 g lipid providing 2070 kCal/day. Each patient daily received 110 mmol Na, 100 mmol K, 15 mmol Ca, 15 mmol Mg, 20 mmol P, 160 mmol Cl, 25 mmol acetate and 60 mmol gluconate. In addition, one vial daily of Vitalipid$^{R}$ containing 120 IU vitamin $D_2$, 2500 IU vitamin A and 0.15 mg K and one vial of Soluvit-N$^{R}$ containing 3 mg thiamine, 5 mg ribloflavin, 40 mg niacinamide, 5 mg pyridoxine, 16.5 mg pantothenic acid,400 µg folic acid, 60 µg biotin, 5 µg vitamin B12 and 113 mg vitamin C werd administered. Trace element solutions were prepared by the hospital pharmacy. Every day, 3.0 mg Zn, 1.6 mg Cu, 2.0 mg Mn, 120 µg Se, 2 µg Cr, 20 µg Co and 120 µg I were infused.

One of the two PN patients (8) regularly consumed meals, while the other one (9) only took minor amounts of food. None of the patients of the oral group received vitamin D therapy, calcium suppletion or other drugs interfering with vitamin D or calcium metabolism during at least one year before and at the time of the study. The only dietary restrictions in the oral group concerned fat and lactose. All patients had normal creatinine clearance.

The study was approved by the Committee on Human Ethics of this hospital. Informed consent was given by all participants.

### 4.2.2 Experimental design

The investigations were carried out during a ten-day stay in the hospital. All patients consumed a self-selected, fixed diet to which they were accustomed at home. The meals of each patient were prepared in multiplicate, including one for analysis. During a three-day adjustment period urinary hydroxyproline excretion and plasma or serum levels of albumin, Ca, P, Mg, alkaline phosphatase and bicarbonate were measured. Furthermore, the renal threshold for phosphate reabsorption ($TM_{PO4}$/GFR) was determined for detection of hyperparathyroidism. 25 $OHD_3$ levels in the oral group and 25 $OHD_2$ levels in the PN patients were arbitrarily taken from winter 1980 because of its seasonal fluctuations[30].

After the adjustment period balance studies lasting 5 days were carried out. The nutrients assessed were Ca, P, Mg and fat. Carmine red served as fecal marker for stool collection in all balances. Finally, an iliac crest bone biopsy was taken and subsequently a $^{47}Ca$ absorption study was performed. The experiments took place between December 1979 and June 1982.

### 4.2.3 Biochemistry

Serum albumin was measured by the bromcresol green method[31]. Ca and Mg in plasma and in balance materials (diets, PN solutions, urine and stools) were measured by atomic absorption spectrometry. Plasma calcium was corrected in the case of hypalbuminemia[32]. Phosphate in the abovementioned substances was determined by the vanadomolybdate method[33]. Fat in diets was calculated by a dietician. Fat in stools was measured according to Van de Kamer[34]. Alkaline phosphatase activity was determined by the 2-amino-2-methyl buffer method[35] and venous bicarbonate by a continuous flow $CO_2$-procedure[36]. Hydroxyproline in urine was measured by a continuous flow modification of Prockop's method[37]. $TM_{PO4}$/GFR was calculated according to Bijvoet[38]. High performance liquid chromatography was used to determine 25 OHD[39].

### 4.2.4 $^{47}Ca$ absorption

To calculate $^{47}Ca$ absorption a modified oral $^{47}Ca$ retention study was used[40]. After a breakfast subjects orally received 10 μCi $^{47}Ca$ in 150 ml milk containing some 175 mg calcium. The retention of $^{47}Ca$ was determined by means of a shadow-shield whole-body counter, twice within 3 hours after administration of the isotope, and again after one, two and three weeks. A curve-fit was made from the latter three data, assuming mono-exponential elimination from the body of the absorbed $^{47}Ca$ in this period. Corrections were made for physical decay of the isotope and background activity. Retention at time zero (oral $^{47}Ca$ administration) was extrapolated from this curve and assumed to be equal to apparent absorption.

### 4.2.5 Bone histology and histomorphometry

Bone biopsy specimens were taken 2 cm posterior to the anterior superior iliac crest using a 4 mm internal diameter drill trephine according to Burckhardt[41]. After dehydration the specimens were embedded in a methylmetacrylate mixture (UUA). Histology was interpreted by the histologist. Undecalcified 5 μm thick sections were made using

a Yung 1140 microtome. Sections were stained with Goldner. Using a grid consisting of a succession of semicircles, the following histomorphometric parameters were measured according to Schenk[42].

os%: the percentage of the circumference line of the bone trabeculae in the section covered with osteoid.

ob%: the percentage of the circumference line of the bone trabeculae in the section covered with cubic (active) osteoblasts.

oc%: the percentage of the circumference line of the bone trabeculae in the section covered with osteoclasts.

hl%: the percentage of the circumference line of the bone trabeculae in the section covered with Howship's lacunae.

### 4.2.6 Statistical methods

For statistical analysis Wilcoxon's two-sample test was used. Correlation coefficients were calculated according to Pearson.

## 4.3 Results

### 4.3.1 Biochemistry

In two patients (nos.5 and 9) hypalbuminemia was present (29 and 25 g/l, respectively, n>37). In the other patients serum albumin was normal. None of the patients from the oral group had abnormal Ca, P or Mg levels (table 4.1). Two patients from the oral group (nos.4 and 5) had increased serum alkaline phosphatase activity (180 U/l both; n<120) and increased γ-GT (60 and 70 U/l, respectively; n<36) and serum transaminases (1.4-2.2 times the upper limit of normal), suggesting liver disease. Bicarbonate was normal in the oral group but slightly decreased in the PN patients. 25 OHD levels were clearly diminished in both groups. Normal $TM_{PO4}$/GFR results were obtained, and hydroxyproline excretion in the urine was normal.

### 4.3.2 $^{47}$Ca absorption

Figure 4.2 shows the results of $^{47}$Ca retention and the calculated $^{47}$Ca absorption. The absorption of $^{47}$Ca (normally 27.3%±6.3 SD) was significantly reduced in oral group (16.0%±7.7 SD, p<0.05). Very low values were obtained in the two PN patients (5.0 and 3.1%).

Table 4.1

BIOCHEMICAL DATA ON 9 SBS PATIENTS AN AVERAGE 35.3 MONTHS AFTER EXTENSIVE INTESTINAL RESECTION.

| Serum or plasma level | | Oral group | | PN patients | | Normal |
|---|---|---|---|---|---|---|
| | | mean | SD | 8 | 9 | |
| albumin | (g/l) | 39 | 3.2 | 37 | 25 | >37 |
| calcium | (mmol/l) | 2.37 | 0.11 | 2.20 | 2.40 | 2.20-2.55 |
| phosphate | (mmol/l) | 0.93 | 0.09 | 0.98 | 1.27 | 0.80-1.30 |
| magnesium | (mmol/l) | 0.81 | 0.11 | 0.72 | 0.79 | 0.70-1.25 |
| alkaline phosphatase | (U/l) | 104 | 53 | 120 | 67 | <120 |
| venous bicarbonate | (mmol/l) | 25.2 | 2.1 | 20.9 | 20.1 | 24.0-28.0 |
| 25 OHD | (ng/ml)* | 6.4 | 3.3 | 5.9 | 4.9 | 10.0-24.0 |
| $TM_{PO4}$/GFR | (mmol/l) | 0.85 | 0.09 | 0.82 | 0.99 | 0.80-1.30 |
| urinary hydroxyproline | (mmol/24h) | 209 | 50 | 189 | 146 | <250 |

* 25 $OHD_3$ in the oral group
  25 $OHD_2$ in the PN patients

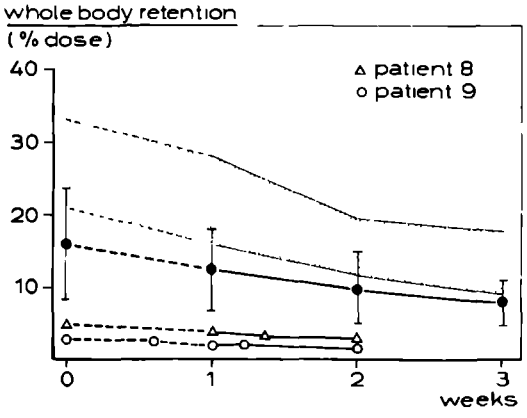


Figure 4.2
Graphic representation of mean values (±SD) of $^{47}Ca$ whole body retention in 7 SBS patients on oral nutrition.The hatched area represents values of $^{47}Ca$ retention in 7 normal controls of comparable age as the 7 SBS patients.Results in 2 SBS patients on parenteral nutrition (8 and 9) are added.Apparent absorption at time zero is calculated with a curve-fitting procedure(indicated by dotted lines).

4.3.3 Balance studies

In figure 4.3 the results of the Ca, P and Mg balances are graphically presented.

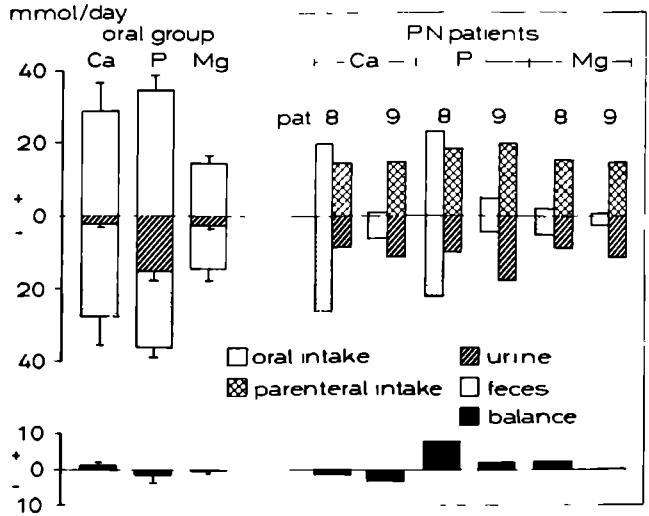


Figure 4.3

Results of balances of calcium, phosphate and magnesium, expressed as mmol/day. Mean values (±SD) are presented from the oral group; in the PN patients results are indicated individually. The lower bar represents mean balances (±SD) in the oral group while in the PN patients each balance is indicated individually.

The average calcium content of the balance diets in the oral group proved to be rather high (29.1 mmol/day). This was mainly due to abundant consumption of cheese and lactose-free milk products. Mean phosphate intake also was relatively high (34.9 mmol/day) in this group, while magnesium intake was normal (14.4 mmol/day).

Calcium balance in the oral group ranged from -2.5 to +4.2 mmol/day (mean + 1.1). The PN patients both had a slightly negative calcium balance

(-1.6 and -3.2 mmol/day). In the PN patients the daily fecal calcium output exceeded the oral intake by 6 to 7 mmols. Phosphate balance in the oral group was slightly negative (-1.5 mmol/day) while magnesium balance was almost in equilibrium in these patients (-0.2 mmol/day). The latter two balances were positive or in equilibrium in both PN patients. Not unexpectedly, a markedly decreased fat absorption (42 and 33%) was found in the PN patients despite a low oral fat intake (57 and 15 g/day). Fat consumption in the oral group ranged from 50-114 g/day (mean 79). Fat absorption averaged 77% (± 17.2 SD).

Apart from a significant correlation between phosphate content of the balance diets and phosphate balances ($R=0.7666$; $p<0.05$), no correlation was found between the other assessed balances and their related dietary constituents. No correlation was found between $^{47}Ca$ absorption on the one hand and calcium and fat balances on the other, nor between $^{47}Ca$ absorption and 25 OHD levels. Again no correlation was found between 25 OHD levels and calcium, phosphate and magnesium balances.

### 4.3.4 Histology and histomorphometry

Slight osteoporosis was histologically found in three male patients of the oral group, the other 4 were normal. The mean age of the patients with osteoporosis was 63 years, whereas the non-osteoporotics averaged 53 years. Moderate and moderate-to-severe osteoporosis was found in both PN patients. In one patient (no 3) histomorphometric analysis could not be carried out due to unsuitable sectioning of the bone specimen. Histomorphometric data on the remaining 8 patients are presented in table 4.2. Normal values of age-matched controls according to Schenk[42] are added. Generally, normal indices for bone formation (os% and ob%) and bone resorption (oc% and hl%) were obtained in the oral group as well as in the PN patients. In one patient of the oral group (4) oc% was increased, but biochemical signs of hyperparathyroidism were absent (normal plasma calcium and phosphate, normal $TM_{PO4}$/GFR and urinary hydroxyproline). When we correlated indices of bone formation and resorption on the one hand and the results of the Ca, P and Mg balances and 25 OHD levels on the other, no statistical significance could be detected.

Table 4.2

HISTOMORPHOMETRIC ANALYSIS IN PATIENTS WITH SBS

| Age (years) | Patient no. | os% | ob% | oc% | hl% |
|---|---|---|---|---|---|
| 31-40 | 8* | 7.0 | 6.0 | 1.2 | 3.3 |
| | normal (mean±SD) | 11.6±5.9 | 5.0±3.3 | 0.5±0.5 | 6.3±2.5 |
| 41-50 | 1 | 10.4 | 6.5 | 0.7 | 2.1 |
| | 2 | 4.6 | 0.9 | 0.4 | 1.9 |
| | normal | 13.1±4.8 | 3.8±0.9 | 0.6±0.7 | 7.5±4.3 |
| 51-60 | 5 | 5.8 | 1.6 | 0.6 | 1.8 |
| | 6 | 11.2 | 6.4 | 1.6 | 2.3 |
| | normal | 17.1±9.1 | 5.2±4.7 | 0.5±0.4 | 6.1±2.7 |
| 61-70 | 4 | 16.7 | 4.1 | 2.8 | 2.0 |
| | 9* | 5.9 | 3.1 | 0 | 1.9 |
| | normal | 17.5±10.4 | 5.0±5.3 | 0.5±0.5 | 8.0±3.9 |
| 71-80 | 7 | 15.3 | 2.6 | 0.7 | 2.5 |
| | normal | 20.5±14.3 | 3.5±3.6 | 0.6±0.4 | 5.8±2.9 |

* Patients on parenteral nutrition. For abbreviations see text. Normal values according to Schenk[42] (each age category comprised 16 to 32 controls).

## 4.4 Discussion

### 4.4.1 Oral group

The present study of the consequences of extensive small intestinal resection on calcium and bone metabolism differs from previous reports in that no residual bowel disease was present in our patients. This may be one of the reasons why normal data on bone formation and resorption were obtained, ruling out expected bone disease such as osteomalacia and secondary hyperparathyroidism.

Slight osteoporosis was detected in three out of four patients above the age of 59. Whether this condition was already present prior to the intestinal resection cannot be established. Calcium, phosphate and magnesium homeostasis appeared to be sufficiently maintained according to the results of the balance studies.

Although $^{47}Ca$ absorption was reduced, mean calcium balance was positive (+ 1.1 mmol/day). Calcium balance remained positive when taking integumentary calcium loss (mean + 0.4 mmol/day)[43] into account. Generally, calcium absorption decreases with age and elderly persons require larger amounts of dietary calcium in order to maintain calcium balance, probably due to insufficient conversion of 25 OHD to the active vitamin D metabolite (1,25 dihydroxy vitamin D)[44,45]. Therefore, it seems reasonable to advise a high oral calcium intake for SBS patients on oral nutrition.

In addition, a phosphate-rich diet seems advisable in view of the positive correlation between phosphate content of the balance diets and phosphate balance. Special recommendations on magnesium are presumably not necessary since magnesium balance was in equilibrium on a normal oral magnesium intake. It has been previously shown that SBS patients generally do not comply with dietary fat restriction, as we noticed in our patients[17]. An extremely fat-restricted diet is therefore not warranted.

Serum 25 OHD levels in these patients were rather low, suggesting vitamin D malnutrition[46]. In view of the established positive calcium balance and the acceptable bone structure, routine suppletion of vitamin D is probably not necessary in SBS patients on oral nutrition up to 5 years after intestinal resection.

### 4.4.2 PN patients

Bone disorders have been reported in patients after at least two months of total parenteral nutrition by two independent groups[25-28].Symptoms included periarticular lower extremity pain up to vertebral fractures which confined some patients to a wheelchair or even made them bedridden[26,27]. There were no biochemical data to distinquish patients with symptomatic bone disease from those without such symptoms[26] . Hypercalcemia, hypercalciuria and negative calcium balances were often found. The PN composition from one center contained rather large amounts of phosphate (51 mmol/day) and vitamin $D_2$ (1000 IU/day)[26,28]. The other group administered 500 IU vitamin $D_2$ daily or on alternate days[25,27]. Normal levels of 25 $OHD_2$ were obtained from both groups, while 1,25 (OH) $D_2$ levels were invariably reduced[27,28]. Histomorphometry revealed osteomalacia with or without prior signs of increased bone turnover in addition to osteoporosis[25,26]. Surprisingly, when vitamin D was removed from the PN solutions or when parenteral nutrition was permanently stopped, symptoms abated gradually. Furthermore, calcium in

serum and urine (if increased) became normal, negative calcium balance reversed to positive and histomorphometry improved considerably[25,26]. Bone symptoms did not return in previously disabled patients after at least 14 months of PN without vitamin D, while 25 OHD levels became very low or indetectable[27]. The cause of this remarkable syndrome remains uncertain.

The main features in our two PN patients are: a slightly negative calcium balance, markedly depressed $^{47}Ca$ absorption, hypercalciuria, slight metabolic acidosis, low 25 $OHD_2$ levels and the presence of moderate or moderate-to-severe osteoporosis. The absence of bone symptoms, osteomalacia and increased bone turnover is also notable, since PN lasted 5 and 3 years in these patients. Hypercalciuria may be the result of the slight metabolic acidosis (table 4.1)[7,8]. The latter may be related to the administration of acidic aminoacid solutions[47]. Intestinal absorption of calcium is not impaired by metabolic acidosis[48]. Since fecal calcium output exceeded oral calcium intake by some 6 to 7 mmol, negative calcium balance was mainly based on net loss of calcium in stools (figure 4.3). Net loss of calcium in stools in amounts of 1 to 3 mmol/day has been reported in comparable PN patients without evidence of increased fecal calcium excretion of endogenous origin[49,50]. After calcium infusion in short bowel patients with functioning colon, fecal calcium loss generally increases[50]. The mechanism of intravenously administered calcium-induced increased fecal calcium loss has not been established. As with calcium there was a net loss of magnesium in stools in both PN patients, which also has been previously noted[49] (figure 4.3). Phosphate intake and fecal phosphate excretion were in equilibrium in the PN patients.

In conclusion, the following points can be made from our observations:

1 Having been left with 40 to 110 cm disease-free small bowel, patients appear to be able to maintain an acceptable balance of Ca, P and Mg on oral nutrition, despite low 25 OHD levels. In addition, indices of bone formation and resorption remain within normal limits. A Ca- and P-rich diet is advised in order to achieve this condition.

2 Osteoporosis due to negative calcium balance threatens parenterally fed patients with an extremely short bowel, probably partly related to PN-induced slight metabolic acidosis.

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Chapter 5

# IRON, ZINC AND COPPER BALANCE IN SHORT BOWEL PATIENTS ON ORAL NUTRITION

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# 5 IRON, ZINC AND COPPER BALANCE IN SHORT BOWEL PATIENTS ON ORAL NUTRITION

## 5.1 Introduction

Trace element research is currently receiving increased attention with the general recognition of the importance of these substances. Deficiencies of iron and iodine are well known. Since the advent of parenteral nutrition (PN), deficiencies have recently been established for an additional four to five trace elements (zinc, copper, chromium, selenium and probably molybdenum)[1-8].

In patients with short bowel syndrome (SBS) nutrition is provided orally, parenterally or orally as well as parenterally, depending on the length and the absorptive capacity of the remaining small bowel. Generally, at least some 40 cm of jejunum and/or ileum have to be left in order to maintain an acceptable nutritional state on oral feeding[9]. Nevertheless, malabsorption of various nutrients, including trace elements, and deficiencies may develop in orally fed SBS patients.

When concurrently evaluating the status of a variety of trace elements, a balance study is generally performed[10-16]. In patients with SBS, some trace element balance studies have been carried out[17-20]. However, PN was the main or only route of delivering nutrients in these studies.

This report discusses a balance study of three trace elements in seven SBS patients on oral nutrition. The assessed trace elements include iron, zinc and copper.

## 5.2 Patients and methods

### 5.2.1 Patients

Seven patients, 6 males and 1 female, aged 18-68 years (mean 50.7 years), were studied an average 2.7 years (range 1 to 5 years) after extensive small intestinal resection. The short bowel remnant averaged 64 cm (range 40 to 110 cm). Three patients had no or only 2 cm ileum left; in one of these the ascending colon was also removed. None of the patients had radiological signs of residual bowel disease after the resection. The reason for the resections was: mesenteric infarction in five patients, strangulation-induced obstruction ileus in one and small bowel necrosis due to volvulus in one patient. All patients were on oral nutrition. Ideal body weight[21] at the time of study varied from 85% to 116% (mean 93%). No medication was used other than vitamin B12 suppletion in two patients. The study was approved by the

Committee on Human Ethics of this hospital. Informed consent was given by all participants.

5.2.2 Experimental design and methods

The balance studies were performed in hospital. Patients consumed a fixed diet according to their dietary habits at home. The meals for each patient were prepared in multiplicate, including one for analysis. They were kept deep-frozen until consumption. To avoid trace element contamination during preparation of the meals, cooking was done in deionized water. In the kitchen all food was handled with knives, spoons, etc. after rinsing with deionized water. Meals were served and consumed using plastic dinnersets, first rinsed with deionized water. Tea and coffee were made with deionized water.

After an equilibration period of three days the balance study was performed, lasting five days. At the start of the balance period, serum levels of iron, zinc and copper were measured. Serum iron was determined by ferrozine colorimetry, serum zinc and copper by atomic absorption spectometry. Additional precautions were taken to avoid trace element contamination during collection and processing of balance materials. Twenty-four-urine and stools were collected in polyethylene bottles or containers washed in advance with an EDTA-detergent solution and subsequently rinsed several times with twice-distilled water.Stools collected during the balance period were marked with carmine red. Stools were homogenized with a mixer equipped with a knife of titanium (Moulinex, type MP2A, France). Homogenization of a 24-hour diet took place with a blender containing titanium knives (Waring Blender, Model 31 DL 44, USA). After weighing, aliquots were taken from collected urine, homogenized stools and 24-hour diet for analysis. During analysis of these specimens the abovementioned precautions to avoid contamination were maintained.

Samples of balance materials were ashed in a low-temperatue asher and subsequently measured by neutron activation analysis[22].

5.3 Results

Mean serum levels of iron (18.4±3.7 µmol/l SD, n 10.0-25.0), zinc (11.4±1.5 µmol/l SD, n 10.0-17.0) and copper (14.3±4.2 µmol/l SD, n 10.0-25.0) fell within normal limits.

Mean daily oral intake, mean daily fecal and urinary excretion and mean

balance of the three trace elements are summarized in table 5.1.

Table 5.1

RESULTS OF BALANCE STUDIES OF THREE TRACE ELEMENTS (EXPRESSED AS µMOL/DAY) IN SEVEN SHORT BOWEL PATIENTS ON ORAL NUTRITION.

| Trace element | Recommended or estimated appropriate daily dietary amount [26] | Mean oral intake (±SD) | Mean fecal excretion (±SD) | Mean urinary excretion (±SD) | Mean balance (±SD) |
|---|---|---|---|---|---|
| Fe | 180 (males) | 224.8 | 196.2 | 0 | +28.6 |
| | 320 (females) | (73.1) | (63.0) | | (10.6) |
| Zn | 230 | 173.9 | 154.2 | 13.3 | +5.4 |
| | | (28.7) | (24.5) | (6.2) | (6.5) |
| Cu | 32-47 | 25.4 | 22.1 | 1.7 | +1.5 |
| | | (16.8) | (14.1) | (0.7) | (2.3) |

In addition, recommended or estimated appropriate daily dietary amounts of each of the assessed trace elements are indicated. The mean balance of each trace element was positive. A negative Cu balance was only found once (-0.5 µmol/day). This patient, however, showed no signs of Cu deficiency such as anemia or leukopenia[3,4,23]. Mean oral intake of Fe, Zn and Cu in these short bowel patients did not exceed recommended dietary amounts of these substances. Net absorption of Fe (dietary intake minus fecal excretion, expressed as percentage of dietary intake) averaged 12.6% (± 1.8 SD). Mean net absorption of Zn was 9.3% (± 3.6% SD) and of Cu 12.5% (±5.1 SD).

## 5.4 Discussion

Balance studies have potential sources of error when inappropriately performed. Besides, a balance study does not provide information on true absorption, body distribution and turnover rate of the assessed nutrient. Moreover, extraintestinal and extrarenal losses are not dealt with. In the case of a trace element balance, additional precautions are required

to avoid contamination during collection and processing of balance materials. However, a carefully performed balance study is still of value to assess the nutritional response to disease or trauma, such as the short bowel syndrome[24].

When we compared the mean Fe balance in our patients with previously reported mean Fe balances in healthy controls, our results (+28.6 μmol/day) fell between those obtained from elderly men (65-74 years old) (-7.9 μmol/day)[16] and those reported in generally younger persons (19-59 years old) (+76 and +77 μmol/day)[12,15]. Regarding net Fe absorption the same conclusion can be drawn: mean net Fe absorption in our patients (+12.6%) was higher than that in elderly men (-4.0%)[16] and lower than in younger persons (+27.5 and +38.6%)[12,15]. In none of the short bowel patients was any urinary Fe excretion found. Urinary Fe excretion in healthy controls is indeed very modest (not exceeding 1.8 μmol/day)[12,15,16]. This result probably reflects maximal Fe retention in the SBS patients.

The results of mean Zn balance in our patients (+5.4 μmol/day) fitted in the range of healthy controls mentioned in literature (-9.9 to +9.2 μmol/day)[13-16]. Mean net Zn absorption in our patients (9.3%) was also comparable with data reported from normals (range -3.6 to 9.2%)[13-16].

The results of mean Cu balance (+1.5 μmol/day) also fell in the range obtained from normals (-2.5 to +7.0 μmol/day)[13-16]. Mean net Cu absorption (12.5%) was higher than that in normals (-7.6 to +1.7%)[13,14,16] with one exception (+43.0%)[15].

Certain quantities of trace elements are lost daily in sweat. These losses are not included when performing a balance study. Measurement of trace element surface losses is technically difficult and subject to methodological problems. A recent study provides reproducible data on whole body surface loss of trace elements in healthy controls[25]. Mean daily Fe surface loss was 5.9 μmol/day. Daily, an average 7.6 μmol Zn and 5.3 μmol Cu were collected in sweat. When these values are subtracted from our balance data, mean Fe balance remains positive (+22.7 μmol/day) while mean Zn and Cu balances become slightly negative (-2.2 μmol/day and -3.8 μmol/day, respectively).

In conclusion the following points can be made:

1. In short bowel patients on oral nutrition with a disease-free, mean small bowel remnant of 64 cm (range 40 to 110 cm), Fe-, Zn- and Cu-balance could be maintained in a similar way as in healthy controls.

2. Taking into account whole body surface losses of Fe, Zn and Cu, the balance of each of these trace elements remained acceptable in these patients.
3. Net absorption of Fe and Zn in the short bowel patients is comparable to that in normal controls, but net absorption of Cu tended to be somewhat higher in short bowel patients than in healthy persons.

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Chapter 6

# METABOLISM OF ORALLY ADMINISTERED $^{69m}Zn$ IN PATIENTS WITH SHORT BOWEL SYNDROME AS COMPARED TO CONTROL SUBJECTS

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# 6 METABOLISM OF ORALLY ADMINISTERED $^{69m}Zn$ IN PATIENTS WITH SHORT BOWEL SYNDROME AS COMPARED TO CONTROL SUBJECTS

## 6.1 Introduction

Zinc is an essential trace element because of its involvement in a variety of metabolic processes[1]. A role of zinc in nucleic acid and protein synthesis has been established[2-4]. Zinc deficiency is associated with retardation of growth and sexual maturation, poor wound healing, impaired immune function and skin lesions mimicking those of acrodermatitis enteropathica[5-11]. Prolonged diminished oral intake or insufficient intravenous supply during total parenteral nutrition, malabsorption due to small intestinal disease and increased losses via urine or gastrointestinal fistulae may cause zinc deficiency[3,5-7,10-14].

In short bowel syndrome (SBS), defined as resection of at least 70% of the small intestine[15], malabsorption of various nutrients can be expected[16]. However, increased absorption in the small bowel remnant of SBS patients occurs after some time when nutrition is orally provided[17]. This intestinal adaptation is histologically characterized by hyperplasia of the remaining small bowel mucosa[17].

To assess zinc metabolism in man, several methods are available. The increase in plasma zinc after a pharmacological dose of oral zinc has been used as a qualitative index of zinc absorption[14,18-20]. Another approach involves the use of radioisotope tracer techniques. In this respect, $^{65}Zn$ has most frequently been used[21-26]. The relatively long physical half-life of this radionuclide (245 days) limits its clinical usefulness. Some recent reports suggest that the short-lived istope $^{69m}Zn$ is suitable to study certain aspects of zinc metabolism[27-30].

The aim of this study was to evaluate some aspects of zinc metabolism after oral administration of $^{69m}Zn$ in patients with SBS and to compare the results obtained with those in normal controls.

## 6.2 Patients and methods

### 6.2.1 Patients

Seven patients aged 40-74 years (mean 57 years) were studied an average of 2.6 years after extensive small bowel resection. Table 6.1 summarizes clinical and biochemical data on these patients, together with the results

Table 6.1

SOME CLINICAL AND BIOCHEMICAL DATA,TOGETHER WITH THE RESULTS OF ABSORPTION STUDIES OF FAT AND D-XYLOSE IN 7 SBS PATIENTS.

| Patient (male/female) | Age at the time of study | Time since resection (months) | Small bowel remnant (cm) jejunum | ileum | % of ideal body weight | Serum albumin (g/l) | Plasma Zn (µmol/l) | Fat absorption (%) | D-xylose absorption (g/5 h portion) |
|---|---|---|---|---|---|---|---|---|---|
| 1*(m) | 47 | 37 | 45 | 15 | 96 | 45 | 12.9 | 95 | 4.8 |
| 2*(m) | 60 | 38 | 100 | 10 | 86 | 40 | 10.1 | 91 | 4.8 |
| 3 (f) | 40 | 60 | 40 | 20 | 115 | 41 | 12.9 | 91 | 5.2 |
| 4 (m) | 68 | 45 | 50 | 0 | 86 | 39 | 11.7 | 52 | 2.0 |
| 5 (m) | 59 | 12 | 90 | 2 | 86 | 29 | 9.3 | 65 | 3.1 |
| 6 (m) | 55 | 12 | 20 | 20 | 90 | 40 | 10.6 | 82 | 4.1 |
| 7 (f) | 74 | 18 | 50 | 0 | 72 | 37 | 16.2 | 61 | 2.1 |
| Range controls (mean) n=7 | | - | | | 89-130 (104.5) | 39-46 (41.6) | 12.2-17.0 (14.0) | n.d. | n.d. |
| Normal | | | | | | >37 | 10.0-17.0 | >95 | >5.0 |

*patient with normal $^{69}$Zn metabolism

n.d.= not determined

of some absorption tests. Strangulation-induced intestinal obstruction was the reason for resection in patient 3, and superior mesenteric artery infarction in the other patients. In two patients (4 and 7) a partial colectomy had to be performed as well. All patients consumed normal food products with only lactose restriction. None showed clinical signs of zinc deficiency. Decreased plasma zinc in patient 5 has to be related to the coexisting hyperalbuminaemia. Plasma zinc as well as serum albumin have permanently normalized in this patient three months after the study was performed. The healthy control group, without any previous abdominal surgery, consisted of 5 males and 2 females with a mean age of 52 years (table 6.1). The study was approved by the Committee of Human Ethics of this hospital. Informed consent was given by all participants.

### 6.2.2 Study design

After an overnight fast each subject orally received 50 Ci $^{69m}$Zn in zinc acetate (specific activity 1 Ci/mg Zn). Four hours after isotope ingestion breakfast was served. The radionuclide was measured in plasma, erythrocytes, whole body, stools, urine and over a fixed area of the liver and the lateral half of the left thigh. Red cell $^{69m}$Zn was computed as the difference between whole blood $^{69m}$Zn and plasma $^{69m}$Zn, corrected for haematocrit. Plasma sampling was done ½,1,2,3,4,5,6 and 10 hours after isotope ingestion and again after 24 and 48 hours. Whole blood measuring took place 4 hours after $^{69m}$Zn administration and subsequently at the same time intervals as plasma. Total body $^{69m}$Zn was measured several times on the day of $^{69m}$Zn ingestion and daily for another 4 days. Measurements of $^{69m}$Zn over the liver and thigh were performed hourly through 6 hours after its administration and again after one and two days. Twenty-four-hour stool and urine specimens were separately collected during 5 days.

### 6.2.3 Isotope characteristics and measurements

$^{69m}$Zn decays with a physical half-life of 13.9 hours. It emits easily detectable photons at an energy of 439 KeV. $^{69m}$Zn is produced by irradiating $^{68}$Zn (oxyde or metal) with thermal neutrons according to the reaction $^{68}$Zn (n,$\gamma$) $^{69m}$Zn (Interuniversitary Reactor Institute, Delft, The Netherlands). The product is dissolved in HCl and purified by adsorbing on a small Dowex 2x8 cm column and eluting it with decreasing concentrations of HCl. Assuming 50% absorption, the estimated whole body radiation dose from 50 $\mu$Ci$^{69m}$ is 0.67 mSv (67 mrem) .

$^{69m}$Zn in 3 ml specimens of plasma or whole blood was measured with a well-type NaI (Tl) scintillation crystal. Plasma $^{69m}$Zn was expressed as percentage of the dose per litre and red cell $^{69m}$Zn as percentage of the dose per litre red cells. Whole body $^{69m}$Zn was determined with a shadow-shield whole body counter with two 6x4 inch crystals, and expressed as percentage of administered dose.
Activity over the liver and thigh was measured at fixed sites using a collimated 2x2 inch NaI (Tl) scintillation crystal (wide hole-equipped collimator with aperture of 7 cm) with a skin-detector distance of 8 cm. Counting time over the liver at least equalled the period needed to collect 5000 counts and over the thigh at least the period to obtain 3 times background activity. As standard for liver and thigh served a bag containing 1700 ml water to which 3% of the ingested isotope activity was added. Urine and stool specimens were determined between the two scintillation crystals of the whole body counter. $^{69m}$Zn over liver and thigh and in stools and urine was expressed as percentage of dose administered. In all measurements corrections were made for physical decay and background activities.

Apparent absorption of $^{69m}$Zn was calculated from data on whole body retention during 5 days, using a curve-fitting procedure according to Heth and Hoekstra[32].

### 6.2.4 Statistical methods

For statistical analysis Wilcoxon's two-sample test was used. Data are presented as mean ± SEM.

## 6.3 Results

Analysis of the results of the SBS patients showed that $^{69m}$Zn metabolism in two SBS patients (table 6.1, nos. 1 and 2) was largely comparable to that of the normal controls. The remaining 5 SBS patients showed a completely different $^{69m}$Zn metabolism. Results will therefore be presented with regard to these observed differences. Results in controls and in the five SBS patients with abnormal $^{69m}$Zn metabolism (abnormal SBS subgroup) will be given as mean values. The data on the two SBS patients with normal $^{69m}$Zn metabolism will be presented separately.

Figure 6.1,showing curves of $^{69m}$Zn in plasma, reveals that peak plasma values were obtained 1 to 3 hours after isotope ingestion. Mean peak plasma

$^{69m}Zn$ in the controls was 2 to 2.5 times than that in the abnormal SBS subgroup.

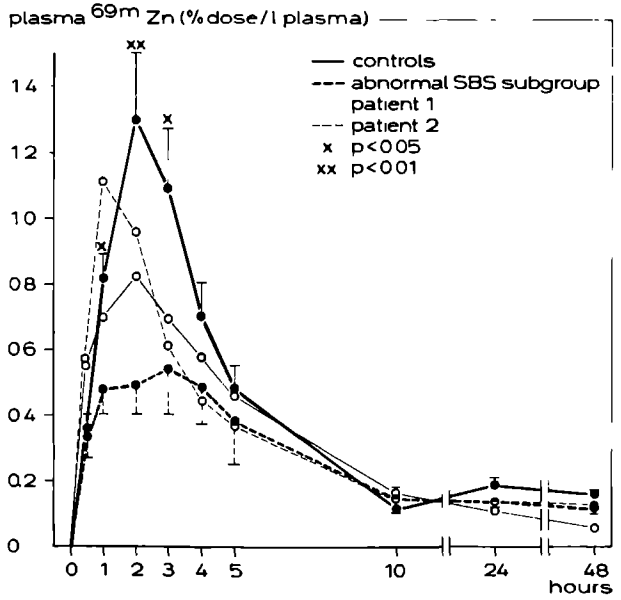


Figure 6.1

Curves of mean plasma $^{69m}Zn$ activity (± SEM) in controls and abnormal SBS subgroup. Individual curves of patients 1 and 2 are added.

Significant differences between the two groups were found one, two and three hours after isotope administration. Red cell $^{69m}Zn$ gradually increased in SBS patients and controls, without showing significant differences between controls and the abnormal SBS subgroup except four hours after $^{69m}Zn$ administration (table 6.2).

Table 6.2

RED CELL $^{69m}Zn$ (%/l red cells).

| Time (hr) | Controls | Abnormal SBS subgroup | P |
|---|---|---|---|
| 4 | 0.29±0.05 | 0.16±0.03 | 0.02 |
| 5 | 0.32±0.05 | 0.22±0.04 | n.s. |
| 10 | 0.36±0.03 | 0.31±0.09 | n.s. |
| 24 | 0.49±0.07 | 0.45±0.11 | n.s. |
| 48 | 0.73±0.09 | 0.55±0.12 | n.s. |

Cumulative urinary $^{69m}Zn$ excretion was very modest both in SBS patients and in controls, not reaching a significant difference at any time. On day 5, cumulative urinary $^{69m}Zn$ in the normal subjects was 0.57% (±0.14), in the abnormal SBS subgroup 0.20% (±0.08) and in SBS patients 1 and 2 0.09 and 0.34%, respectively.

The main excretory route of $^{69m}Zn$ was the faeces. Mean cumulative faecal $^{69m}Zn$ exceeded that in the control group (figure 6.2).

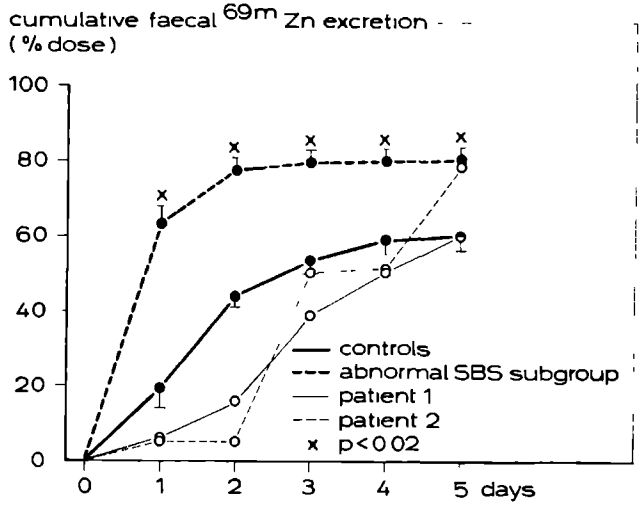


Figure 6.2
Mean cumulative faecal excretion of $^{69m}Zn$ (± SEM) in controls and abnormal SBS subgroup. Cumulative faecal $^{69m}Zn$ excretion in patient 1 and 2 are indicated separately.

Faecal isotope excretion in SBS patient 1 parallelled the mean curve in the controls. Remarkably, SBS patient 2 had no bowel movements on day 2 and 4, explaining the angular cumulative faecal $^{69m}Zn$ curve.

Data on whole body $^{69m}Zn$ proved to be the mirror of cumulative faecal istope excretion (figure 6.3). Again significant differences were noted between controls and the abnormal SBS subgroup.

Accurate calculation of apparent $^{69m}Zn$ absorption from whole body retention data appeared to be possible in 4 control subjects and in 4 patients of the abnormal SBS subgroup (figure 6.4). In the other subjects such calculation

was impossible due to insufficient data. The apparent $^{69m}Zn$ absorption in the controls was 46.5%±5.5 and that in the abnormal SBS subgroup was 23.9%±1.5 ($p<0.05$).

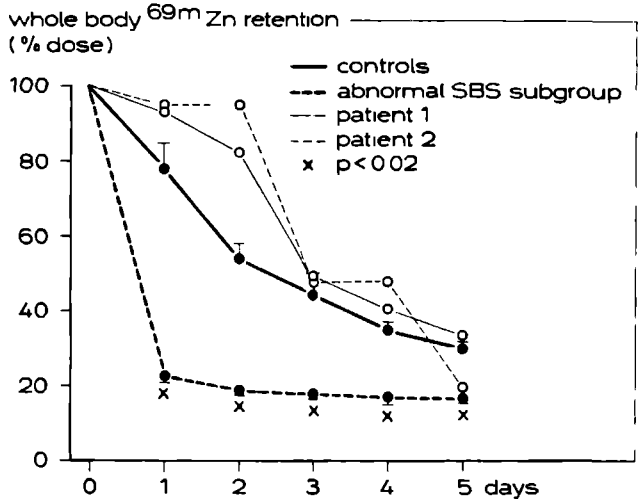


Figure 6.3

Mean whole body $^{69m}Zn$ activity (± SEM) decline in controls and abnormal SBS subgroup. Body $^{69m}Zn$ decline in patients 1 and 2 is shown in addition.

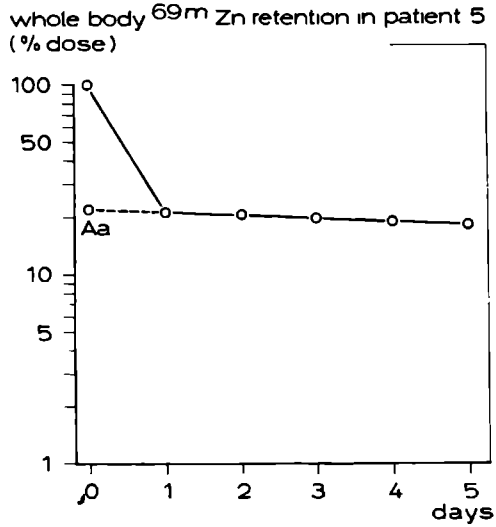


Figure 6.4

An example of curve-fitting procedure to calculate apparent $^{69m}Zn$ absorption (Aa).

Activity of $^{69m}Zn$ over the liver was clearly higher in the controls than in the abnormal SBS subgroup, reaching significant differences from 5 to 48 hours after isotope ingestion (figure 6.5). The curves of liver $^{69m}Zn$ in the SBS patients 1 and 2 were comparable to those in the controls.

$^{69m}Zn$ activity over the thigh equally increased in controls, abnormal SBS subgroup and SBS patients 1 and 2. However, the amount of accumulated $^{69m}Zn$ was small in this area of the body, not exceeding 1% of the ingested activity in any individual after 2 days.

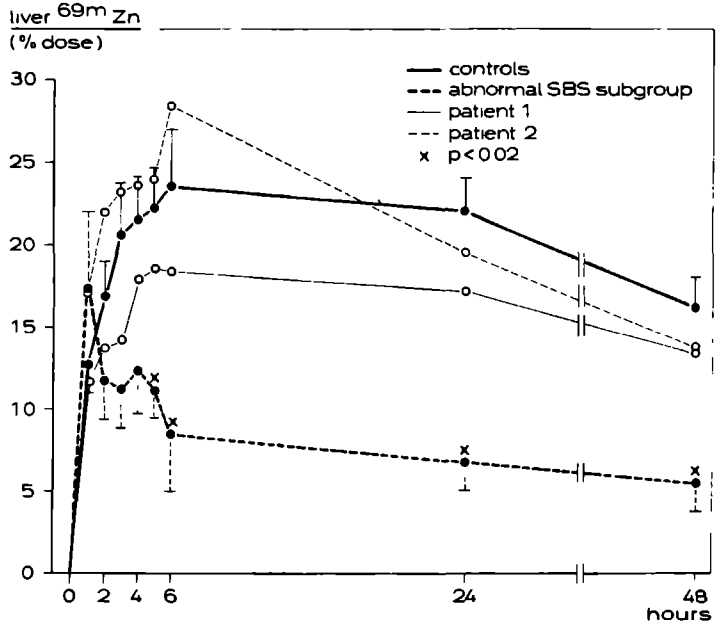


Figure 6.5
Curves of mean liver $^{69m}Zn$ activity (± SEM) in controls and abnormal SBS subgroup. Individual curves of patients 1 and 2 are added.

## 6.4 Discussion

At first sight it seems artificial to distinguish two subgroups of SBS patients after having obtained data on $^{69m}Zn$ metabolism. When comparing clinical and biochemical data as well as absorption tests (table 6.1), there are clearly two subgroups. Why patient 3 did not show normal $^{69m}Zn$ metabolism is unclear because the abovementioned parameters in this patient were comparable to those in SBS patients 1 and 2 with largely normal $^{69m}Zn$ metabolism.

This study confirms that in normal persons oral administration of $^{69m}Zn$ induces a sharp rise in plasma activity, reaching a peak value between 1 and 3 hours, followed by a rapid decline (figure 6.1)[28,29]. In the abnormal SBS subgroup mean peak plasma $^{69m}Zn$ was 2 to 2.5 times lower, suggesting impaired absorption and/or higher uptake in peripheral tissues. The latter statement is probably not valid in this subgroup since (a) apparent $^{69m}Zn$ absorption is reduced to about half (23.9%±1.5) than in the control group (46.5%±5.5), (b) whole body $^{69m}Zn$ decline and cumulative faecal $^{69m}Zn$ excretion is significantly larger in the abnormal SBS subgroup than in the controls, (c) $^{69m}Zn$ accumulation in the liver in this subgroup is clearly reduced (figure 6.5) and (d) $^{69m}Zn$ uptake in red cells and thigh is equal to that in normal controls.

These results may be understandable in view of the lower apparent absorption of $^{69m}Zn$, which reflects dietary zinc absorption, in the abnormal SBS subgroup (24%), as compared with that in the controls (46%). The amount of albumin-bound (exchangeable) Zn in the plasma is about 2 mg. The absorbed amount of zinc is much larger (46% of 50 mg = 23 mg in the controls and 24% of 50 mg = 12 mg in the abnormal SBS subgroup) than the intraplasmatic exchangeable zinc, causing the specific activity of plasma $^{69m}Zn$ to be approximately the same as that of the dose (0.92 μCi/mg in the controls). A decreased apparent absorption, as seen in the abnormal SBS subgroup, does not significantly change this situation (specific activity 0.86 μCi/mg). Thus, radioactivity can be used to compare the transport of Zn to the liver and the peripheral tissues in patients and controls. The peripheral tissues (e.g., muscle and red cells) have a constant need for Zn for incorporation in enzymes. They therefore take up a steady flow of Zn and the uptake of $^{69m}Zn$ was the same in patients as in controls. The liver not only needs some Zn for its own metabolism but apparently temporarily stores an excess of Zn when absorption is higher than the direct needs of the organism. Retention of zinc surplus has been shown in rats fed zinc-rich diets. In this situation zinc accumulated amongst others in the liver[33]. Because the absorption of Zn in the abnormal SBS subgroup is lower than that in the controls, the liver has to take up a smaller amount of excess Zn. This may explain why, although the absorption of Zn in the abnormal SBS subgroup is decreased, no clinical or biochemical signs of deficiency are observed an average of more than 2 years after extensive small bowel resection.

A drawback of oral $^{69m}Zn$ is the impossibility to calculate apparent $^{69m}Zn$ absorption from whole body retention curves in each individual. This is due to the short physical half-life of the isotope. However, in the cases in which such calculation was possible our results in controls fell in the same range as values reported by others using $^{65}Zn$ (range 43-74%)[23-25].

The main excretory route of $^{69m}Zn$ is the gastrointestinal tract. Notably, values of mean whole body $^{69m}Zn$ decline and mean cumulative $^{69m}Zn$ faecal excretion can be used interchangeably in normal subjects as well as in SBS patients (figures 6.2 and 6.3).

In conclusion the following points can be made:

1 The maximum observed in the plasma $^{69m}Zn$ curve after an oral dose of this nuclide appears to be a reliable indicator of Zn absorption (figure 6.1).

2 In over 50% of the controls and SBS patients, apparent $^{69m}Zn$ absorption can be calculated from whole body retention data. This retention can be measured either with a whole body counter or, since the urinary excretion is negligible, as difference between dose and cumulative faecal excretion.

3 Extensive small bowel resection may lead to decreased Zn absorption to about half of that in controls.

4 Because the flux of $^{69m}Zn$ to the peripheral tissues (red cells, thigh muscles) was adequate and signs of zinc deficiency were absent, the absorption of zinc in the abnormal SBS patients was presumably still sufficient. Apparently, the liver temporarily stores a smaller excess of absorbed zinc in these patients.

5 The use of $^{69m}Zn$ is limited by its short physical half-life. Still, useful information can be obtained by measuring its appearance in faeces, plasma, red cells, liver and other parts of the body and its retention in the whole body, for further elucidation of zinc metabolism in various diseases.

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Chapter 7

# HOME PARENTERAL NUTRITION. EXPERIENCE IN SEVEN PATIENTS

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# 7 HOME PARENTERAL NUTRITION. EXPERIENCE IN SEVEN PATIENTS.

## 7.1 Introduction

The length of the small bowel in vivo roughly varies between 2 and 4 m[1]. When 70% or more of the bowel is resected, a condition called short bowel syndrome (SBS) results[2]. Sufficient digestion and absorption of orally administered nutrients is generally ensured when, in addition to the duodenum, some 40 to 50 cm of jejunum and/or ileum is retained. After more extensive small bowel resection, emaciation threatens due to severe malabsorption.

In the late 1960's parenteral nutrition (PN) entered clinical medicine[3]. PN is generally indicated when oral feeding is not possible or prohibited during long periods of time. In these situations, PN may prevent malnutrition or abolish already existing malnutrition. Usually, the time required to administer PN is relatively short. Indefinite PN may be necessary to sustain life in SBS patients with less than 40 cm of remaining small bowel.To avoid prolonged hospitalization, home parenteral nutrition (HPN) is to be preferred in this situation.

In this paper we report experiences with HPN in seven patients, together with literature data on the same subject. Patient selection, vascular access procedures and administration systems to deliver PN solutions, technical and metabolic complications and some psychosocial aspects of HPN are emphasized.

## 7.2 Case histories

Patient A, a woman born in 1943,underwent extensive small bowel resection in February 1969 as a final consequence of an inadvertently performed urterine curettage for missed abortion. The result was a uterus perforation. Some two-thirds of the duodenum and 20 cm of ileum remained in situ. One year later the body weight had fallen from 60 to 26 kg despite various dietary regimens. At that time, a Scribner shunt was constructed at an upper leg for administration of hypertonic PN solutions. As a consequence, body weight had increased to 44 kg 18 months later. In July 1971, a fatal arterial haemorrhage occurred at home due to disruption of the tubing during PN infusion[4]. In this patient a number of metabolic problems resulted from 18 months of HPN, such as chronic metabolic acidosis, hypercalciuria and osteoporosis, oxalate urolithiasis, linoleic acid deficiency and marked fatty liver.

In patient B, a woman born in 1952, a duodenotransversostomy was performed after intestinal resection for volvulus-induced small bowel and right colon necrosis in August 1976. At that time, she weighed 73 kg. PN was started shortly after resection via a venacaval catheter. Some four weeks later the catheter was replaced by a bovine graft located in a forearm. Before discharge from hospital the patient and her husband were given detailed instructions regarding the technique of graft puncture, administration of the PN solutions and the potential dangers related to PN. All PN requirements, including solutions, additives, graft needles and administration systems are sent monthly to the patient's address by the hospital pharmacy.

High fever accompanied with cold chills suddenly occurred during PN administration in May 1977. At admission (some 12 hours later) patients was in shock (probably septic). A stormy clinical course followed, complicated by diffuse intravascular coagulation, acute renal insufficiency and adult respiratory distress syndrome necessitating 3 weeks of artificial ventilation. Finally, ventilation tube-induced tracheomalacia had to be surgically corrected. In the meantime the bovine graft was thrombosed. A new graft was created in the other forearm. Discharge from hospital followed in July 1977. No problems have since developed. Table 7.1 summarizes clinical and biochemical data on patient B, together with those on patient C through G. Patient B visits the out-patient clinic every 8 weeks. She carries out her normal household duties. However, as compared with the situation before resection, her maximal exertional capacity has subjectively diminished to some degree.

Every evening her husband punctures the graft with a small-sized butterfly needle and subsequently attaches the needle to the PN administration system. Patient B as well as her husband have realistically adapted themselves to all PN-related inconveniences.

Patient C, a woman born in 1911, was likewise left with a duodenocolostomy because of thrombosis of the superior mesenteric artery in August 1977. PN was started immediately after resection via a venacaval catheter. Her body weight at that time was 69 kg. Two attempts to create an arteriovenous fistula unfortunately failed, and PN therefore had to be continued via a venacaval catheter. As in other patients, PN was infused during evening and night. Because the patient was living in a home for the aged, some nurses from this house were instructed in all aspects of PN.

Table 7.1

CLINICAL DATA OF PATIENTS B THROUGH G. BIOCHEMICAL DATA OF PATIENTS B, D, E AND G ARE FROM JUNE 1981, OF PATIENT B FROM AUGUST 1980 (TWO MONTHS BEFORE DEATH) AND OF PATIENT F FROM JANUARY 1981.

| Patients | B | C | D | E | F | G |
|---|---|---|---|---|---|---|
| Sex | f | f | m | f | f | m |
| Year of birth | 1950 | 1911 | 1963 | 1940 | 1957 | 1916 |
| Length (m) | 1.65 | 1.60 | 1.80 | 1.57 | 1.71 | 1.74 |
| Weight (kg) | 64 | 66 | 64 | 49 | 48 | 70 |
| Indication HPN | SBS | SBS | SBS | high output jejunostomy | intraabdominal malignancy | scleroderma small bowel |
| Vascular access | bovine graft | vena cava catheter | bovine graft | Cimino fistula | vena cava catheter | bovine graft |
| PN since | aug. 1976 | aug. 1976 | nov. 1979 | okt. 1980 | june 1980 | okt. 1980 |
| HPN since | nov. 1976 | see text | juli 1980 | okt. 1980 | sept. 1980 | dec. 1980 |
| Plasma or serum levels (normal) | | | | | | |
| -haemoglobin (7.8-10.0 mmol/l) | 7.8 | 6.2 | 8.5 | 8.0 | 9.7 | 7.2 |
| -albumin (>37 g/l) | 36 | 25 | 43 | 38 | 31 | 36 |
| -transferrin (2.0-4.0 g/l) | 2.8 | 1.6 | 2.4 | n.d. | n.d. | n.d. |
| -bilirubin ( 15 µmol/l) | 12 | 15 | n.d. | n.d. | 310 | n.d. |
| -alkaline phosphatase ( 120 U/l) | 116 | 97 | 118 | 115 | 244 | 99 |
| -ASAT ( 25 U/l) | 21 | 21 | 15 | 28 | 174 | 19 |
| -ALAT ( 25 U/l) | 23 | 17 | 19 | 13 | 138 | 11 |
| -Ca (2.20-2.55 mmol/l) | 2.19 | 2.47 | 2.29 | 2.52 | 2.21 | 2.41 |
| -P (0.80-1.30 mmol/l) | 0.82 | 1.15 | 1.31 | 0.74 | 1.48 | 1.10 |
| -Mg (0.75-1.25 mmol/l) | 0.71 | 1.10 | 0.77 | 0.73 | 0.92 | 0.81 |
| -Cu (10.0-25.0 mmol/l) | 15.0 | 16.7 | 12.6 | 18.5 | 35.0 | 20.5 |
| -Zn (10.0-17.0 mmol/l) | 10.1 | 14.5 | 11.4 | 10.0 | 14.4 | 10.6 |
| -vitamin B12 (225-600 pmol/l) | 320 | 265 | 345 | 510 | n.d. | 335 |
| -folic acid (10.0-35.0 nmol/l) | 10.0 | 9.4 | 13.9 | 17.5 | n.d. | 20.5 |
| -vitamin E (17.0-34.0 µmol/l) | 15.8 | 32.5 | 14.3 | 11.4 | n.d. | 23.9 |

n.d. = not determined

In this patient a devastating number of technical and metabolic problems accumulated in the course of time. Catheter migration necessitating its removal occurred three times, and catheter sepsis even five times. Consequently, a congested face finally resulted from catheter-induced, obliterated veins in the infraclavicular,, supraclavicular and neck area. The longest catheter life-span was 9½ months. Catheter complications frequently necessitated hospitalization. Altogether, during 38 months of PN, this patient spent only 10 months in her nursing home. In the course of 1980 the situation deteriorated significantly. A trauma-induced vertebral fracture, further limiting the patient's mobility, periods of fever of unknown origin, mental depression, increasing dementia and finally unexplained prolonged episodes of disturbed consciousness led to a practically vegetative existence. Patient died in October 1980.

The postmortem revealed adhesive pericarditis, myocardial hypertrophy and sclerosis of the coronary vessels. In addition, marked atherosclerosis was present elsewhere. The liver showed moderate fatty changes and haemosiderosis. Hypertrophic Kupffer cells containing many intracytoplasmic granulae were noted. These granulae are probably related to prolonged Intralipid administration[5]. Moderate-to-severe osteoporosis was also observed.

The major metabolic problems in this PN patient included unexplained anaemia and hypalbuminaemia, and zinc deficiency.

Volvulus-induced necrosis of the small bowel in November 1979 was the cause of SBS in patient D, a man born in 1963. PN was started immediately after resection via a venacaval catheter. The clinical course was characterized by recurrent intra-abdominal sepsis, necessitating repetitive abscess drainage, etc. Patient was transferred to this hospital in January 1980. Massive diarrhoea was present in addition to abdominal colics and vomiting after ingestion of small amounts of food. Zinc deficiency developed with characteristic skin lesions. Small bowel series revealed stenosis in the small bowel remnant and some adjacent fistulae between various bowel segments. The stenotic and fistula containing bowel segments were successfully removed. Finally, some 50 cm of small bowel was retained, a part of which showed a peculiar X-ray pattern. Virtually no folds were left, probably due to disturbed venous outlet but intact arterial supply. A bovine graft was constructed in a forearm

and has been used for PN since June 1980. Two months after its construction thrombectomy has to be performed. No graft problems have since occurred. Patients was discharged from hospital in June 1980. At home, he proved able to manage himself completely in PN.

From 1981 patient was taking large amounts of food in addition to the PN. The amount of nutrients taken intravenously was being gradually reduced. In July 1981 PN could be finished because at that time the functional capacity of the remnant bowel has increased sufficiently.

Patient E, a woman born in 1940, had suffered from Crohn's disease since 1958. Many bowel resections including proctocolectomy had to be performed due to prolonged increased disease activity. By the end of 1979 only 1 m of jejunum was retained. The jejunostomy output proved to be invariably high (2-5 l/day), causing recurrent dehydration and renal insufficiency. In addition, hypocalcaemic and hypomagnesaemic tetany was frequently observed. Attempts at adequate compensation by oral suppletion failed. Daily parenteral suppletion of large amounts of fluid and minerals became necessary. Recurrent disease in the bowel remnant was excluded. In view of relatively poor oral food intake, amino acids and concentrated dextrose were also infused. For this reasons a venacaval catheter was introduced. After 2 months of HPN without trace element suppletion, zinc deficiency developed (serum zinc 1.6 µmol/l, n 10.0-17.0) which could easily be managed by parenteral administration of zinc. Some months later catheter sepsis occurred. HPN has since taken place via a Cimino fistula previously created in a forearm.

In January 1980 gastrectomy was perfomed for carcinoma of the stomach in a woman born in 1957 (patient F). Since the tumour was not radically removed, additional abdominal radiotherapy was given (6000 Rad). Mechanical ileus in June 1980 prohibited oral feeding. PN was started at that time. Laparotomy in August 1980 revealed unresectable intra-abdominal tumour growth, causing intestinal obstruction. Although she realized that the prognosis was poor, the patient positively indicated her desire to remain alive as long as possible while staying at home. To organize and learn all aspects of HPN, patient was admitted to this hospital in September 1980. In view of a modest life expectancy a venacaval catheter was used to administer PN.
The first 4 months at home were uneventful. She almost completely

succeeded in carrying out household activities. After these 4 months her physical condition gradually deteriorated. She became jaundiced and liver function progressively deteriorated, probably due to hepatic metastasis. She died in April 1981. Abdominal pain did not occur until the day of her death.

Patient G, a man born in 1916, had had scleroderma since 1971. In subsequent years, the lungs and gastrointestinal tract became involved in the disease process. Persistent reflux oesophagitis was caused by a dilatated, rigid oesophagus. To relief heartburn patient excessively consumed milk and antacids, which occasionally caused hypercalcaemia. The small bowel became considerably dilatated, with signs of bacterial overgrowth. In 1980, anorexia and significant weight loss developed due to recurrent paralytic ileus. PN was started in October 1980 via a venacaval catheter, which had to be replaced twice because of catheter migration and sepsis. From May 1981, HPN has been administered through a boven graft.

### 7.3 Some aspects of prolonged parenteral nutrition at home.

Scribner et al were the first to point out the feasibility of HPN[6]. At present, the longest reported period of HPN is 90 months[7]. In 1980, some 600 patients were depending on HPN in the USA, and some 30 in England[8,9]. A summary of literature data on HPN till 1981, together with our experiences, is presented in table 7.2. Obviously, this way of delivering nutrients relatively often entails technical, metabolic or psychosocial problems.

#### 7.3.1 Patient selection.

A. The main indication for HPN is SBS. Causes of SBS include recurrent intestinal resection for Crohn's disease, volvulus-induced necrosis of the small bowel and thrombosis or embolism in the superior mesenteric artery. The incidence of mesenteric infarction gradually increases after age 40. This rise shows significant progressiveness after age 60.

Exact information on the length, composition and quality of the small bowel remnant is required to evaluate the indication for prolonged PN. When in addition to the duodenum 40 to 50 cm of small bowel is retained, equilibrium is generally achievable by oral feeding alone, due to intestinal adaption. After extensive small bowel resection, oral nutrition provokes hyperplasia and subsequently increased absorptive function of the remaining mucosa[10]. For patients B and C (both were left with a duodeno-transversostomy

Table 7.2

DATA FROM LITERATURE AND OWN EXPERIENCES ON TECHNICAL, METABOLIC AND

| Patients | Ivey e.a.[62] (1975) | Shils[63] (1975) | Jeejeebhoy e.a.[64] (1976) |
|---|---|---|---|
| Number of patients | 40 | 11 | 12 |
| Age | 4-71 yr | n.m. | 19-64 yr |
| Time on HPN (months) | n.m. | n.m. | 4-62 |
| average | 11 | 8 | 24-3 |
| Indication HPN | n.m. | | |
| -SBS | | 9 | 10 |
| -Crohn's disease | | | |
| -radiation enteritis | | 1 | |
| -intestinal pseudo-obstruction | | | 1 |
| -coeliac disease | | | |
| -scleroderma small bowel | | | 1 |
| -gastrointestinal fistulae | | | |
| -intraabdominal malignancy | | | |
| -other | | 1 | |
| Average catheter survival (months) | n.m. | n.m. | 10.5 |
| Catheter complications | | n.m. | |
| -sepsis | 6 | | 3 |
| -skin entry site infection | | | |
| -blockage | | | |
| -leakage | | | |
| -unacceptable migration | | | 3 |
| -thrombosis vena subclavia or vena cava superior | 3 | | |
| Metabolic complications | n.m. | | |
| -linoleic acid deficiency | | | 3 |
| -Zn deficiency | | | |
| -Cu deficiency | | | |
| -Cr deficiency | | | 1 |
| -liver function disturbances | | 1 | 1 |
| -metabolic bone disease | | | 1 |
| Psychosocial aspects | n.m. | n.m. | |
| -recurrent mental depression | | | 2 |
| -socially partly active | | | 3 |
| -socially fully active | | | 7 |

n.m.= not mentioned
n.a.= not applicable, since majority of patients ultimately received PN via

PSYCHOSOCIAL ASPECTS OF HOME PARENTERAL NUTRITION (HPN).

| Rault e.a.[65] (1977) | Byrne e.a.[66] (1979) | Dudrick e.a.[67] (1979) | Fleming e.a.[7] (1980) | This study |
|---|---|---|---|---|
| 51 | 106 | 25 | 19 | 7 |
| 5-69 yr | 2wk-77 yr | 2-66 yr | 27-67 yr | 18-69 yr |
| 1-56 | 1½-60 | 36 | 3-90 | 5-53 |
| 12.9 | n.m. | n.m. | 25.5 | 25 |
| | | | | |
| 20 | 16 | 9 | 13 | 5 |
| 13 | 43 | 4 | 4 | |
| 5 | 9 | | | |
| 3 | | | 1 | |
| | | | | |
| 1 | 2 | | 1 | |
| 3 | 2 | | | 1 |
| 1 | 4 | 5 | | |
| | 10 | 2 | | 1 |
| 5 | 22 | 5 | | |
| | | | | |
| 8.8 | n.m. | 9 | n.m. | n.a. |
| | | | | |
| | | | | |
| 10 | 18 | | 2 | 7 |
| 4 | 14 | | 2 | |
| 17 | 6 | 2 | | |
| 13 | 26 | 1 | | |
| | | | | 4 |
| | | 1 | | |
| | | | | |
| | | n.m. | n.m. | |
| 3 | 1 | | | 1 |
| 1 | 3 | | | 3 |
| 1 | 1 | | | |
| | | | | |
| 5 | | | | |
| | 5 | | | |
| | | | | |
| n.m. | n.m. | n.m. | | |
| | | | | 1 |
| | | | 7 | 3 |
| | | | 12 | 3 |

arteriovenous fistulae (see text).

or -colostomy) life-long PN is indicated without any doubt. In borderline cases (patient D) a high caloric oral diet, only lactose-restricted, is recommended to promote intestinal adaptation. Additional PN may be needed during several months to maintain equilibrium. When optimal adaptation is not achieved, a decision to start life-long PN can still be made.

In SBS a retained colon is enviable. It is capable to absorb daily some 6 litres of fluid and electrolytes[11]. In SBS, calcium absorption is positively correlated with the presence of the colon[12]. Furthermore, colonic hyperplasia has been observed in animals after distal small bowel resection[13]. Consequently, problems due to excessive losses of fluid, minerals and trace elements may be expected after end-jejunostomy. Permanent PN at home may alleviate this situation[14], as demonstrated in patient E.

The largest group of SBS patients for whom HPN may be of vital importance is probably that with mesenteric infarction. The question arises whether all these persons should be considered for HPN, because most of these patients are aged or very aged. Various factors determine the answer to this question, such as mental condition before and after resection, family structure, living circumstances, etc. No absolute rules can be given in such a situation.

B. When the absorptive function of a non-resected small bowel is markedly compromised or practically nil, HPN may offer alternative help. Examples of this condition are severe radiation enteritis, intestinal pseudo-obstruction, scleroderma or amyloidosis of the small bowel and refractory coeliac disease (see patient G).

C. HPN for Crohn's disease has received special support in the USA. Reported indications for Crohn's disease are therapy-resistant prolonged increased disease activity, recurrent gastrointestinal fistulae despite frequent surgical therapy and growth retardation in children or adolescents[15-18]. Providing "bowel rest" and subsequently reducing disease activity is the principle of treating Crohn's disease with PN. Once it is decided to administer PN in such patients, various factors determine whether this treatment is to be given in hospital or at home. One of these factors is the expected period of PN administration. No prospective studies are available indicating any superiority of prolonged PN (at least 2 months) over conventional medical management in comparable groups of

patients. Furthermore, it is not clear whether PN effectively reduces the operation rate.

D. Whether HPN is an acceptable treatment in patients with incurable intra-abdominal malignancies, depends on several factors. A discussion on this subject is beyond the purpose of this article. Nevertheless, even more cautious selection is required in these patients.

### 7.3.2 Vascular access in home parenteral nutrition

Infusion of hypertonic PN solutions into peripheral veins invariably causes thrombophlebitis. Dudrick et al abolished this problem[3] by introducing a catheter into the superior vena cava via the sublcavian vein. The large diameter of the superior caval vein allows rapid dilution of the hypertonic PN solutions, avoiding damage to vein walls. By tunelling the catheter across the anterior chest before reaching the subclavian vein, the incidence of ascending infections is reduced[19]. Obviously, continuous meticulous catheter care is necessary to minimize the risk of catheter sepsis[20]. Initially a Scribner shunt was used for prolonged PN administration[4,6]. In view of recurrent shunt clotting this method has been abandoned[21]. Another route of vascular access for HPN is via a subcutaneous arteriovenous fistula or a bovine graft. Preferably it should be placed in a forearm. The arterial blood flow widens the venous part of the arteriovenous fistulae, enabling easy puncture. The high blood flow in the fistula of graft ensures sufficient dilution of the PN solutions. In our opinion this method is to be preferred in HPN. This vascular access was successfully used in patients B, D, E and G. In patient B, for example, a bovine graft has been functioning for 4 years without any complication. This way of HPN administration has so far received little attention[22-24].

### 7.3.3 Administration system

One of the main principles of PN is to maintain constant flow rates during infusion in order to avoid dangerous variations in blood sugar and other side effects such as nausea and vomiting during rapid amino acid infusion[25]. Electrical pumps or a pneumatic pressure system ensure constant flow rates during PN administration. A new development is the ingenious flow regulator which forms part of the Isoflux administration set[26]. It

enables concomitant gravity drip infusion of several different sterilized PN solutions at a constant flow rate, making energy-requiring pump systems superfluous.

### 7.3.4 Technical complications

Technical complications are encountered in every HPN vascular access procedure. Important reasons for catheter replacement include catheter sepsis, blockage, etc. (table 7.2). Thrombosis is the main arteriovenous fistula complication.

Before discharge from hospital, the patient and the nearest relative(s) have to be thoroughly instructed in all practical aspects of PN administration, e.g. catheter exit care, attachment and detachment of bags with PN solutions to the venacaval catheter or the needle in a subcutaneous fistula, etc. Furthermore, they have to acquire some theoretical knowledge about PN in order to realize better the potential risks of this treatment. A printed manual describing all these aspects is therefore indispensable. Generally, most patients satisfactorily adhere to the protocol after longer periods of time[27].

### 7.3.5 Composition of the parenteral nutrition

The department of clinical pharmacy of this hospital prepares concentrated dextrose solutions to which various minerals are added. Trace element solutions are prepared as well. Commercially available amino acid solutions, fat emulsions and water- and fat-soluble vitamins are used.

Each patient adds trace elements and vitamins to dextrose-mineral solutions just before administration. At home, PN infusion takes place during the evening and night. Table 7.3 shows the PN composition for patients B, C, F and G, who are completely dependent on PN.

### 7.3.6 Metabolic complications of prolonged parenteral nutrition

In the earlier days of PN, various deficiencies developed rather frequently, mainly due to insufficient intravenous supply of the nutrients in question. Sometimes deficiencies were observed due to excessive losses, such as minerals and trace elements in upper gastrointestinal fistulae and high output end-jejunostomy.

A. Clinical signs of linoleic acid deficiency (patient A) include dryness, thickening and desquamation of the skin[28]. Linoleic acid deficiency states

Table 7.3

DAILY COMPOSITION OF PN OF PATIENTS B, C, F and G

| | | | |
|---|---|---|---|
| Glucose 15% | | 300 | g |
| Fat (Intralipid 10%) | | 50 | g |
| Amino acids (Aminoflex 8%) | | 80 | g |
| Minerals | | | |
| Na | | 80-110 | mmol |
| K | | 70-110 | mmol |
| Ca | | 15 | mmol |
| Mg | | 15 | mmol |
| P | | 20 | mmol |
| Cl | | 110-150 | mmol |
| Trace elements | | | |
| Cu | | 1.6 | mg |
| Zn | | 3.0 | mg |
| Mn | | 2.0 | mg |
| Se | | 120 | µg |
| Cr | | 2 | µg |
| Co | | 20 | µg |
| J | | 120 | µg |
| Vitamins | | | |
| -Fat soluble vitamins | | | |
| A (retinol) | present in | 0,75 | mg |
| D (calciferol) | one vial | 3 | µg |
| $K_1$ | Vitalipid | 0,15 | mg |
| E(tocoferol) present in 500 ml | Intralipid 10% | 50 | mg |
| -Water soluble vitamins | | | |
| $B_1$ (thiamin) | | 3.09 | mg |
| $B_2$ (riboflavin) | present in | 4.93 | mg |
| niacinamid | one vial | 40 | mg |
| $B_6$ (pyridoxin) | Soluvit-N | 4.86 | mg |
| folic acid | | 0.4 | mg |
| $B_{12}$ (cyanocobalamin) | | 5 | µg |
| pantothenic acid | | 16.5 | mg |
| biotin | | 60 | µg |
| C (ascorbinic acid) | | 113 | mg |

were primarily seen in the USA[29-32], because the use of fat emulsions was only recently approved by the Food and Drug Administration. Biochemical signs of linoleic acid deficiency may arise within a few weeks of fat-free PN[32]. Skin abnormalities generally appear afterwards. Prevention of linoleic acid deficiency requires intravenous administration of at least 1000 ml 10% Intralipid per week[33]. Topical application of linoleic acid may enable healing of skin lesions and correction of serum fatty acid levels[34].

B. Trace element deficiencies during prolonged PN are being increasingly reported. Acute zinc deficiency was observed in patients C, D and E. It is characterized by indolent, scaly, pustular eruptions surrounded by a brownish erythema[35,36]. These are typically located in the corners of the mouth, along the nose, in the axillary and the inguinal region and the perineum. Serum zinc is depressed markedly, often accompanied by low serum alkaline phosphatase activity (a zinc methalloenzyme). Skin lesions very rapidly disappear after sufficient intravenous suppletion.

Other reported trace element deficiencies include copper, chromium and selenium. In copper deficiency, neutrocytopenia and anaemia are the predominant features[37,38]. Chromium deficiency has been related to insulin-resistant diabetes mellitus[39,40]. Pain and weakness in muscles are signs of selenium deficiency[41]. All these deficiency states are completely reversible after adequate suppletion.

C. Deficiencies of various vitamins during prolonged PN have been reported[42-48]. The vitamin in question was generally not contained in the PN solutions, or in insufficient amounts.

D. Patient C developed some metabolic problems which further increased the hospitalization time for repeated analysis. There was permanent anaemia, necessitating blood transfusion every three or four months. Bone marrow aspirates repeatedly revealed no abnormal findings. Blood loss and haemolysis were ruled out, as were deficiencies of iron, folic acid, vitamin $B_{12}$ and copper.

Chronic hypalbuminaemia (albumin 25 g/l, n≥37) was the second unexplained phenomenon in patient C. There was no proteinuria and increased enteric protein loss was excluded. Liver biopsy after 2½ years of PN revealed slight

fatty changes. At autopsy 9 months later, hepatic steatosis had become somewhat more prominent. Repeatedly performed amino acid analysis of the amino acid solution administered confirmed the content of each individual amino acid, including tryptophan, as indicated by the manufacturer. However, before and after infusion of all PN solutions, no tryptophan could be detected in patient's serum. Tryptophan plays an important role in hepatic albumin synthesis[49]. Albumin synthesis, measured with the aid of $^{131}$I-albumin, was evidently reduced to 8.0 g/day (normal 21.9±6.6 SD)[50]. Intravenous supply of 2 g tryptophan/day during 2 weeks in addition to the usual PN solutions did not change the hypalbuminaemia but normalized the serum tryptophan level. Finally, metabolic end-products of tryptophan such as 5-hydroxyindoleacetic and kynurenic acid, could not be detected in urine.

It is remarkable that anaemia and hypalbuminaemia were not present in patient B, who for 5 years received the same PN solutions as patient C.

E. Liver function disturbances and liver disease may be seen in prolonged PN. Extreme fatty liver was found in patient A after 18 months of PN[28]. A relation has been established between fatty changes of the liver and PN calories exclusively consisting of concentrated dextrose[28,29,33,51]. Excessive dextrose delivery to the liver increases hepatic fatty acid and triglyceride synthesis. One may speculate that the increased triglyceride synthesis may compromise VLDL assimilation or release, causing triglyceride accumulation in the liver. On the other hand, VLDL assimilation may be reduced in the case of linoleic acid deficiency. Since linoleic acid is an essential constituent of phospholipids, deficiency of this fatty acid may impair phospholipid and subsequently VLDL synthesis. In histologically proven, concentrated dextrose-induced hepatic steatosis, addition of Intralipid to the PN scheme considerably reduced fatty changes of the liver[33,51]. To prevent fatty liver, a well-balanced PN composition including fat emulsions can be recommended.

PN-related liver function disturbances are rather frequently noted[52-54], but poorly understood. Liver function disturbances are usually modest and transient, even when PN is continued. There is no characteristic biochemical profile. Table 7.2 shows that liver function disturbances during HPN are not frequently encountered.

F. Metabolic bone disease in long-term PN is not a familiar phenomenon.

It is even less well understood. Osteoporosis in patient A was probably related to infusion of acidic amino acid solutions, causing metabolic acidosis[55]. Mobilization of bicarbonate from bone is an important mechanism to buffer chronic acidosis. In this situation excess of calcium and phosphate release from bone takes place, causing hypercalciuria[56] . Finally, osteoporosis results from this mechanism[57]. Recently, peculiar bone disease(s) such as osteomalacia, increased bone turnover and osteoporosis have been reported after long-term PN including calcium, phosphate and vitamin D[58-60]. No sound explanation of this syndrome has so far been found.

## 7.4 Psychosocial aspects of home parenteral nutrition

Table 7.2 indicates a lack of information on psychosocial consequences of HPN. A recent report has gathered some data in this regard[61] . During a mean follow-up of 7.4 months, 19 HPN patients were followed. Initially, reactive depressions were not infrequently observed. These reactions could be ascribed to the indefinite inability to eat in some patients and to permanent body changes (total small bowel loss, continuous presence of a venacaval catheter) in others. Having adapted to the new way of life, attempts were undertaken to restore previous social contacts and to resume work. Both activities frequently caused problems and disappointments. Acceptance of the new situation by the family caused the least problems. Finally, only two out of ten principal wage-earners in this group were able fully to resume their former job. Experiences of Jeejeebhoy et al[64] and Fleming et al[7] in addition to ours are somewhat better in this respect (table 7.2).

## 7.5 Conclusion

At present, long-term PN at home is feasible. Related technical problems may be solved in the future. The main obstacle in this respect is to find the ideal vascular access procedure with considerably less side-effects than those seen with the venacaval catheter and arteriovenous conduits. Metabolic consequences of prolonged PN have not all been resolved. Especially the influence of prolonged PN on bone metabolism requires further research. Difficulties may also rise in patient selection for HPN. SBS and the presence of small bowel without function remain major indications for this treatment. Less well-established criteria are available for resorting to HPN in Crohn's disease, incurable intra-abdominal malignancy and aged SBS patients. More

experience with this valuable treatment is needed to define proper patient selection.

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Chapter 8

# AN ACCURATE FLOW CONTROLLING DEVICE TO ADMINISTER SIMULTANEOUSLY DIFFERENT PARENTERAL NUTRITION SOLUTIONS

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# 8 AN ACCURATE FLOW CONTROLLING DEVICE TO ADMINISTER SIMULTANEOUSLY DIFFERENT PARENTERAL NUTRITION SOLUTIONS.

## 8.1 Introduction

Instead of administering a concentrated dextrose solution and subsequently a concentrated amino acid solution for parenteral nutrition (PN), it is attractive to administer a homogeneous mixture of both component solutions to a patient. In such a mixture of two or more different component solutions the final concentration of each nutrient will be lower than in the corresponding original solution. Consequently the incidence of unwanted side effects such as nausea, vomiting, hyper- or hypoglycemia, which are related to the high concentration of the constituents will be reduced. Simultaneous administration of all nutrients also favors an improved nitrogen balance as compared to a consecutive procedure[1]. It is possible to compound a complete mixture from component solutions before the administration. The interaction between amino acids and dextrose referred to as the Maillard reaction[2] prohibits the heat sterilization of such a mixture. As a consequence these mixtures should be compounded under aseptic precautions. This aseptic compounding is a time consuming and therefore expensive process with a potential risk of contamination. In addition such extemporaneously compounded PN mixtures have a limited shelf life.

Not only is the simultaneous administration of all nutrients favorable but a constant flow rate is another basic principle of PN[3]. Conventional control mechanisms of delivery systems using gravity drip infusion are not sufficiently reliable to guarantee a constant flow rate[4-6]. A common flow regulator in fixed position offers a constant resistance to the flowing fluid. When the fluid level in the container diminishes, a decrease of flow will be the result. Consequently, this technique necessitates repeated adjustment of the flow rate during infusion.

Ideally, a PN delivery system should be simple to handle and allow the simultaneous infusion of sterilized dextrose, amino acids, and additives at a constant flow rate obtained at gravitiy drip excluding the necessity of any mechanical support.Recently a new disposable flow controlling device (Isoflux, van Leer Medical Ltd., Mijdrecht, The Netherlands) which is an integral part of an intravenous fluid administration set, has been introduced in The Netherlands. The aim of this study was to assess the extent to which this device could maintain a constant flow rate at gravity

drip during effluence and simultaneous infusion of different sterilized PN solutions.

## 8.2 Description of the flow controlling device

The upper part of the device (figure 8.1) its size being 50x30x10 mm, contains three inlets (a,b,c) to which one to three fluid containers (A, B) can be connected. The flow controlling device either equipped with steel needles or plastic spikes is adaptable to the different types of commercially available plastic bags. The connecting tube between the device and the indwelling vena cava catheter contains a drip champer (p) and a Y-connector for administration of other solutions (q). Depending on the position of the oval shaped flow setting valve (f) at the lower part of the device a flow rate between approximately 8 and 400 ml/h can be selected.

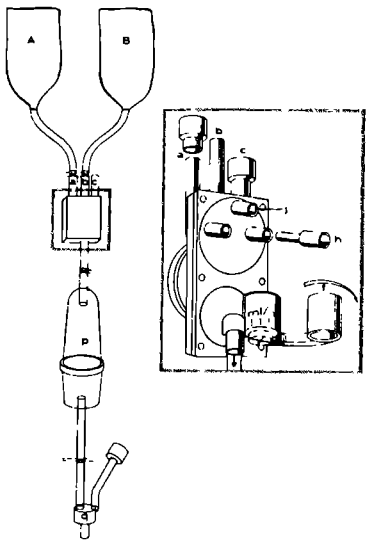


Figure 8.1
The PN delivery system is shown including connecting tubes to fluid containers and indwelling venous catheter and the flow controlling device. This is shown in greater detail in the rectangular inset (for explanation see text).

A diagram of the device is shown in figure 8.2. The device contains two silicone rubber diaphragms(d, e). In its relaxed position the upper diaphragm closes the orifice(l). Each inlet orifice a,b, or c can be closed by inserting a nonsterile plug (h into j, figures 8.1 and 8.2). By connecting a fluid container to an inlet (for instance b) the weight of the fluid column forces the upper diaphragm to a deflected position.

After passing the 15 μ filter (k), permeable for viscous solutions and Intralipid but impermeable for blood, the fluid reaches unhindered the left side and, via the flow setting valve (f), the right side of the lower diaphragm (e). The fluid force at the left side of this diaphragm is greater than at the right side, resulting in a deflection of the diaphragm to the right and in a greater or lesser closing of the outlet orifice g. By altering the radius of its deflection the lower diaphragm automatically adapts to variations in liquid level in the container. Since the infusion flow remains constant as long as a sufficient difference in pressure is maintained in the device itself, a fluid column height of at least 80 cm above the level of the injection site is necessary.

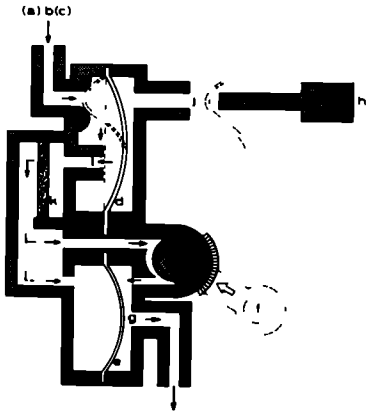


Figure 8.2
Diagram of the flow controlling device (for explanation of symbols see text).

## 8.3 Methods

Experiments on effluence of anhydrous dextrose in water solutions with concentrations varying from 10 to 40% (w/v) and Intralipid 10% (w/v) via the flow controlling device were performed in vitro. The other observations were made on routine PN via tunnelled vena cava catheters. Three different solutions in 1-L bags were administered to all patients, one bag containing anhydrous dextrose in water 20% (w/v) with vitamins, the second anhydrous dextrose in water 15% (w/v) with minerals, and the third an amino acid solution 8% (w/v). The Isoflux administration set was compared with a W-type administration set including a conventional roller clamp for flow control. In a W-type administration set the three tubes attached to the PN containing bags are joined by two Y-connectors prior to the drip chamber.

After initially having set the fluid flow by the lever stuck to the flow setting valve (f) accurate counting of the drip rate (drops/min) at fixed intervals was performed. Assessment of drop volume was not carried out, because in most instances drop volume slightly increases with rising drip rate[7]. During the infusions the flow rate was not readjusted and in some infusions the weight drop of the three bags was measured using spring balances.

## 8.4 Results

The drip rate during the in vitro effluence experiments of the tested solutions did not exceed 8% of the set rate. The variation in drip rate in six experiments using the Isoflux system during an PN infusion period of 10 h and in eight similar experiments during an administration period of 24 h is presented in figure 8.3. These results show that the set drip rate is accurately kept constant within narrow limits during both infusion periods. An example of the satisfactory simultaneous emptying of the three PN containing bags is presented in figure 8.4. On the other hand, an unstable flow necessitating repeated flow adjustments was the result when the same PN solutions were administered to the same patients using the W-type administration set.

Since its introduction this new flow controlling device has been used at more than 3000 occasions for the administration of three different PN solutions. The outcome of all these PN infusions was always the same: a very constant flow rate during all infusions without unwanted side effects.

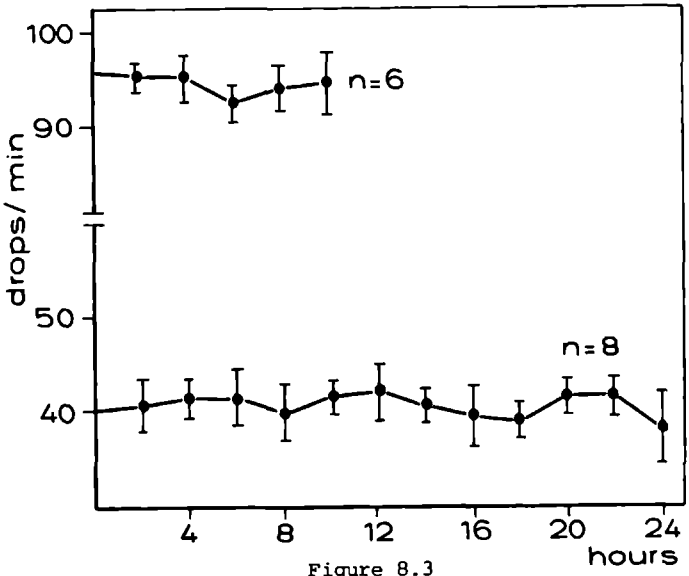


Figure 8.3

Variation of drip rate in time (mean ± SD) of six infusions during 10 h and eight infusions during 24 h. Simultaneously administered were 1 L anhydrous dextrose in water 20% (w/v), 1 L anhydrous dextrose in water 15% (w/v), and 1 L amino acids 8% (w/v).

weight drop three bags

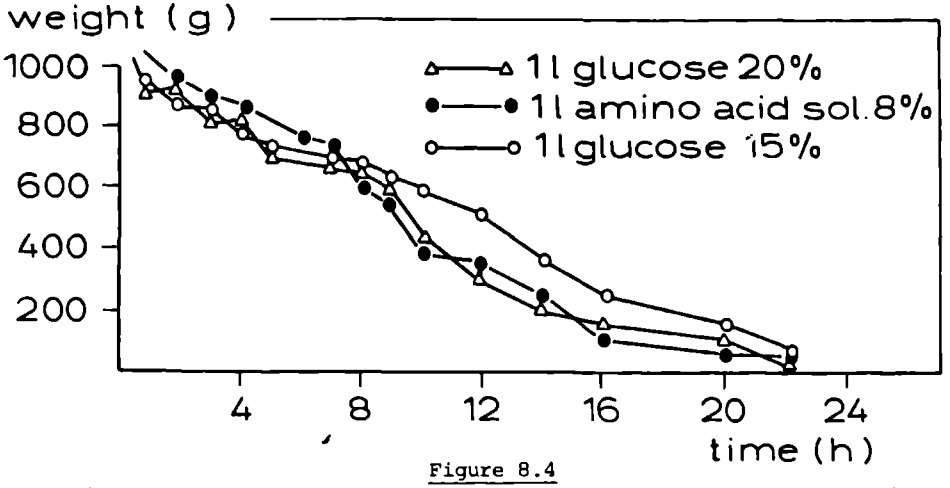


Figure 8.4

Weight drop of three PN-containing bags during simultaneous administration assessed by spring balances.

## 8.5 Discussion

In general, infusion pumps are succesfully used to achieve a constant administration of PN solutions[3,8-11]. Jeejeebhoy et al[12] used a pneumatic pressure system for this purpose. Both energy-dependent pump and pneumatic systems do not simplify PN delivery systems.The Isoflux administration set provides a constant infusion rate at gravity drip. Since flow readjustment during the infusion period is not required, the system markedly relieves the duties of the personnel responsible for the administration of the PN solutions. This phenomenon makes the system especially attractive for patients on home PN, where PN administration mainly takes place during the evening and night. Furthermore, this flow controlling device enables the simultaneous administration of different sterilized solutions making superfluous the use of expensive aseptic compounded PN mixtures.

Two mechanisms increase the safety of the device. First, a one way valve, located just prior to the connecting point (figure 8.1, q) with the vena cava catheter, which prevents inverse blood flow. Second, when the containers have emptied, the upper diaphragm (figure 8.2, d) returns to the relaxed position closing the orifice 1 (figure 8.2) and thus abandoning the risk of air embolism.

A disadvantage of the Isoflux administration set is that only bags empty simultaneously. Bottles, however, empty consecutively because of a different resistance induced by the individually varying air-inlet tubes in each of the bottles. Therefore, we administer fat emulsions in bottles, for instance Intralipid, via the Y-connector q (figure 8.1) before or after the infusion of the PN bags.

In the Netherlands a daily exchange of an Isoflux administration set financially counterbalances the investments required for the purchase of infusion pumps and labor and material costs related to appropriate aseptic mixing of PN solutions.

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Chapter 9

# HOME PARENTERAL NUTRITION VIA ARTERIOVENOUS FISTULAE

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# 9 HOME PARENTERAL NUTRITION VIA ARTERIOVENOUS FISTULAE.

## 9.1 Introduction

In 1968 Dudrick et al[1] demonstrated the feasibility of the vena cava catheter to administer hypertonic solutions for parenteral nutrition. This finding was subsequently confirmed by numerous reports. Especially in the second half of the last decade home parenteral nutrition (HPN) was increasingly used in nutritionally debilitated patients. Vascular access in patients on HPN is generally achieved with vena cava catheters. In this report we present data on 7 patients on HPN via arteriovenous fistulae (AVF).

## 9.2 Patients and methods

Since 1970 twelve patients have participated in the HPN program of this hospital. In seven patients HPN was administered via AVF. In four patients a caval vein catheter was used and in one patient an external arteriovenous shunt. Characteristics of patients on HPN via AVF are presented in table 9.1.

Table 9.1

PATIENT CHARACTERISTICS

| Patient | Sex | Age at start HPN | Indication HPN | Small bowel remnant excluding duodenum (cm) | Frequence HPN administration (days/week) |
|---|---|---|---|---|---|
| 1 | f | 35 | SBS* | 50 | 1 |
| 2 | f | 26 | SBS | 0 | 7 |
| 3 | f | 67 | SBS | 0 | 7 |
| 4 | m | 17 | SBS | 50 | 6 |
| 5 | f | 40 | HOJ° | 100 | 7 |
| 6 | m | 65 | scleroderma small bowel | no resection | 7 |
| 7 | m | 35 | HOJ | 100 | 1 or 2 |

* SBS = short bowel syndrome

° HOJ = high-output end jejunostomy

A short bowel syndrome resulted from surgery for small bowel volvulus in two patients, strangulation ileus in one, and mesenteric infarction in another patient. Two patients with Crohn's disease had a high-output end-

jejunostomy due to frequent intestinal resections including proctocolectomy. One patient had scleroderma of the bowel resulting in severe malabsorption and recurrent paralytic ileus while on enteral nutrition. The average age at the start of HPN was 40.7 years. Alle patients were allowed to eat. Three patients (1, 4 and 7; table 9.1)had normal oral food intake in addition to parenteral nutrition. One patient (2; table 9.1) consumed some nutrients while the other three had hardly any oral nutrition. The solutions for parenteral nutrition were administered during the evening and the night. One of the family members took care of the insertion and removal of a no. 19 butterfly needle in the AVF. After insertion of the needle a small sized sterile gauze is placed beneath the butterfly. To prevent dislodgement the butterfly, the underlying gauze and the needle are thoroughly fixed to the skin using adhesive tapes. One patient (4, table 9.1) completely managed himself in this respect.Altogheter, 8 AVF were used in 7 patients. Two patients had a Cimino fistula, while in the other patients 6 bovine grafts were created. All AVF were located at a forearm with the exception of 2 bovine grafts which had to be placed at a thigh because of inaccesable arm vessels. Patients were instructed to assess fistula function twice daily by palpation of the thrill. To prevent AVF thrombosis all patients were receiving coumarin anticoagulants, mainly intravenously delivered. The effect of anticoagulant therapy was determined by the thrombotest (TT) method according to Owren[2]. Optimal anticoagulation is achieved at a TT level between 5 and 10%.

To 6 patients a complete parenteral nutrition scheme including concentrated dextrose and amino acid solutions, Intralipid(R), minerals, vitamins and trace elements, were administered. One patient (7; table 9.1) received solutions containing almost exclusively minerals to prevent fluid and electrolyte imbalance. After its availability in 1978 the parenteral nutrition solutions were administered via a flow controlling device which allows the simultaneous infusion of sterilized dextrose and amino acid solutions in bags at a constant flow rate without the necessity of infusion pumps[3].

## 9.3 Results

The AVF used in our HPN patients were functioning during a mean period of 14.3 months (range 5-54 months).Table 9.2 summarizes the events of these AVF. Despite anticoagulant therapy AVF thrombosis appeared to be the major complication. Three patients had an irreversible bovine graft thrombosis.

Table 9.2

EVENTS OF 8 AVF IN 7 HPN PATIENTS

| Patient | Type AVF | Location AVF | Duration HPN via AVF (months) | Complications |
|---|---|---|---|---|
| 1 | Cimino | arm | 14 | no |
| 2 | BG* | arm | 8 | thrombosis during septic shock |
| | BG | arm | 54 | twice thrombectomy (after 42 and 51 months) |
| 3 | BG | thigh | 5 | lost after extravasation of parenteral nutrition |
| 4 | BG | arm | 13 | thrombectomy after 2.5 months |
| 5 | Cimino | arm | 9 | no |
| 6 | BG | arm | 6 | no |
| 7 | BG | thigh | 5 | thrombosis during insufficient anticoagulant therapy |

* BG = bovine graft

In patient 2 a graft oblitered after 8 months use during a septic shock of non-graft origin. In patient 3 the bovine graft was lost after 5 months as a result of a local abscess and subsequently thrombosis due to extravasation of the parenteral nutrition solutions. However, this graft was located very deep subcutaneously frequently making needle puncture troublesome. In these two grafts an attempt to thrombectomy was not carried out because of systemic or local circumstances. In patient 7 graft thrombosis occurred after 5 months use, while anticoagulant therapy was inadequate (TT 32%). Thrombectomy was unsuccessful in this graft. Another three graft thromboses in patients 2 and 4 were caused by intimal proliferation in the venous anastomosis and could be managed by thrombectomy and local repair after having been used for an average of 32 months. The two Cimino fistula were still patent after 14 and 9 months HPN.

At this moment three patients (2, 5 and 6) are still dependent on HPN via AVF. In two patients (1 and 4) the parenteral nutrition could be gradually tapered off because of increasing absorption of enteral nutrients by their

small bowel remnants[4]. Patient 3 died at the age of 69 because of HPN-unrelated disease. Another patient (7) is temporarily treated with regular saline infusions into peripheral veins untill a recently created AVF can be used.

## 9.4 Discussion

Since 1970 HPN has become an established mode of nutritional support especially for short bowel syndrome patients. Access to the circulation was initially achieved with external arteriovenous shunts[5-7]. However, these shunts tended to obliterate early in patients with chronic intestinal disease[8]. This phenomenon was attributed to the presence of damaged arm veins as a result of previous infusions or venipunctures and to the generally normal coagulation state of these patients in contrast to uremic patients. Accidently, a serious and even fatal arterial hemorrhage may occur due to disruption in tubing during the parenteral nutrition administration. We observed this complication in our first patient on HPN[7].

Scribner[9] did not recommend AVF for parenteral nutrition because of recurrent thrombosis. This statement based on only few cases may have prevented others to use parenteral nutrition via AVF.In table 9.3 experiences with AVF in long-term parenteral nutrition from the literature are summarized[10-18].

Table 9.3

LITERATURE DATA OF AVF IN LONG-TERM PARENTERAL NUTRITION

| Number and type AVF | Reference | Mean usefulness in months (range) | AVF thrombosis (number) |
|---|---|---|---|
| 7 Cimino | 10,13,18 | 38,6 (2,5-86) | 1 |
| 9 Saphenous vein loops | 13,18 | 24,5 (5 -84) | 4 |
| 7* Bovine grafts | 11,12,13, 15,17,18, 26 | 29,2 (5 -84) | 6 |
| 4 PTFE° | 14,16,18 | 3 (1 -5) | 2 |

* Experiences with another 3 bovine grafts are not included because of insufficient data

° PTFE = polytetrafluoroethylene

Altogether, 30 AVF were used in 25 patients. Mean patency of these AVF was 25.5 months (range 1-86). In our patients mean duration of HPN via AVF was 14.3 months. Obviously the best results are achieved with the direct Cimino arteriovenous anastomosis[19]. Nearly similar results are obtained when using saphenous vein loops and bovine grafts. Experiences with polytetrafluoroethylene arteriovenous conduits are too limited for critical evaluation. As in our patients thrombosis was the major AVF complication. None of the authors[10-18] mentioned the use of anticoagulant therapy preventing AVF obliteration, although Baird[18] suggested benefits of aspirin in these circumstances.
Recently Flye[20] reported good results when creating AVF in nonuremic patients on aspirine and low dose subcutaneous heparine therapy. When comparing our results with data from the literature it seems that coumarin anticoagulants do not improve AVF survival. However, we feel that at present data on anticoagulant therapy are too limited to warrant discontinuation of this treatment.

In most studies HPN is administered via vena cava catheters. When initially used at home, the complication rate of these catheters seemed to be acceptable[9,21]. However, in some recent reports[17,22-28] on 675 central venous catheters in 381 patients, catheter problems occurred rather frequently. In all but one[26] of the published series the mean catheter survival time was less than 10 months. The overall percentage of catheter sepsis amounted to 16.4%. Unacceptable catheter migration occurred in 18.6% of all catheters, subclavian or caval vein thrombosis in 8.7% and definitive catheter obstruction in 8.6%. Altogether, in 52.3% of all catheters serious complications were seen.

The perfect vascular access for parenteral nutrition without any complication does not exist. Central venous catheters as well as AVF have their advantages and disadvantages. Vena cava catheters should be the first choice when parenteral nutrition is expected to last relatively short. We applied these catheters in four patients on HPN with incurable intra-abdominal malignancies. When HPN is expected to last a long period or even lifelong, AVF should be considered as a valuable vascular access because of its relatively low complication rate. Besides, the absence of an external device (the catheter) increases the social activities of a person on HPN. The need for another person to insert and remove the needle

appeared to be a minor problem. Some patients are able to completely manage themselves. When ever possible a creation of a Cimino fistulae should be preferred. In case of poor arm veins a bovine graft or a saphenous vein loop can be recommended.

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# Chapter 10

# SUMMARY AND CONCLUSIONS

# 10 SUMMARY AND CONCLUSIONS

## 10.1 Summary

### Chapter 1. Introduction and aim of the study.

Human small intestinal length in vivo probably varies between 2.5 and 4 m. When approximately 1 m or less small bowel is retained after extensive resection, a condition called short bowel syndrome is present. Crohn's disease, small bowel volvulus and mesenteric infarction are the main causes of this syndrome. Since the advent of parenteral nutrition, the prognosis of patients with a very short bowel (less than ± 40 cm jejunum and or ileum left) has dramatically improved. Patients with 40 to 100 cm remaining jejunum and/or ileum can genereally be maintained with oral nutrition due to increased absorption of the small bowel remnant as result of intestinal adaptation. The aim of this study is to report on clinical, biochemical and nutritional aspects of short bowel patients on oral or parenteral nutrition, emphasizing data on absorption of various nutrients and on bone metabolism. Furthermore, some technical aspects concerning long-term parenteral nutrition will be discussed.

### Chapter 2. Short bowel syndrome. Experiences in eight patients.

Eight patients with a mean small bowel remnant of 60 cm (range 40 to 100 cm) were studied during an average of 53 months (range 24 to 87 months) after extensive intestinal resection. All patients took their food orally. Balance studies (fat, N, Ca, Mg, P) were carried out an average of 30 months after intestinal resection.

All patients, except of one, achieved an acceptable nutritional status, Frequent diarrhoea was not noted. Data from body weight, haemoglobin and serum albumin showed optimal intestinal adaptation to occur within two years after discharge from hospital. Mean nitrogen balance was slightly positive (0.1 g/day ± 0.6 SD). Plasma or serum levels of sodium, potassium, calcium, magnesium, phosphate, copper and zinc were unremarkable. Balances of calcium, magnesium and phosphate were about equilibrium. Serum cholesterol was permanently decreased, while serum levels of vitamin E and carotene were sligthly reduced. Mean 25-OH vitamin $D_3$ levels were clearly depressed. The latter observations could be ascribed to the steatorrhoea (mean fat absorption 74% ± 18% SD, normal ≥95%). Patients in whom 15 to 20 cm ileum was retained,

had a normal vitamin $B_{12}$-absorption as time went by. These patients showed also an increase of D-xylose absorption in course of time, which was not or hardly not notable in patients without preserved ileum and ileocoecal valve. The D-xylose test and the Schilling test appeared to be useful parameters in patients with some preserved ileum to evaluate the absorptive capacity of the small bowel remnant. Important psychosocial problems did not occur.

Chapter 3. Intestinal adaptation.

This chapter provides a review of the literature on intestinal adaptation occurring after extensive small intestinal resection. A resection of at least 30% of the small intestine is required to provoke hyperplasia in the bowel remnant. The hyperplastic response in the ileum is much greater than that in the jejunum. Luminal nutrition is the major intestinal adaptation-promoting factor. Nutrients may locally stimulate the release of hormones (especially enteroglucagon) and/or other biochemical substances (ornithine decarboxylase), which in turn initiate the adaptive response. Pancreaticobiliary secretions, whether or not released by cholecystokinin or secretin, probably play some role in intestinal adaptation, although to a lesser extent than luminal nutrition.

Chapter 4. Metabolic bone disease and short bowel syndrome.

Nine patients with a disease-free, mean jejunum-ileum remnant of 52 cm (range 0-110 cm) were studied with regard to calcium and bone metabolism 1 to 5 years (mean 35.3 months) after intestinal resection. Nutrition took place orally in seven patients (oral group), while two patients were dependent on parenteral nutrition for 5 and 3 years respectively (PN patients). Parameters of calcium and bone metabolism as urinary hydroxyproline excretion and plasma or serum levels of Ca, Mg, P, bicarbonate, alkaline phosphatase, albumin and 25-OH vitamin D were measured. A balance study for calcium, phosphate, magnesium and fat was carried out. Finally, a $^{47}Ca$ absorption test was performed and an iliac crest bone biopsy was taken for histology and histomorphometry.

In the oral group (left with 40 to 110 cm disease-free small bowel) patients appeared to be able to maintain an acceptable balance of Ca, Mg and P, despite low 25-OH vitamin D levels.

$^{47}Ca$ absorption was reduced but mean calcium balance was positive probably due to the high dietary calcium content. Slight osteoporosis was found in three patients from this group, aged 59 or more. No signs of osteomalacia or hyperparathyroidism could be detected histomorphometrically.

A slight metabolic acidosis, hypercalciuria, and markedly reduced serum 25-PH vitamin D levels were the most important abnormalities of the PN patients. Calcium balance was slightly negative due to a net loss of calcium in stools. Phosphate and magnesium balance were acceptably maintained. Histology revealed moderate and moderate-to-severe osteoporosis but no signs of osteomalacia or hyperparathyroidism which was confirmed histomorphometrically. Osteoporosis due to negative calcium balance was probably partly related to parenteral nutrition-induced slight metabolic acidosis.

Chapter 5. Iron, zinc and copper balance in short bowel patients on oral nutrition.

This chapter presents data of a five day balance study for iron, zinc and copper in seven patients with short bowel syndrome on oral nutrition. The small bowel remnant of these patients varied from 40 to 110 cm (mean 64 cm), and was radiologically normal in all patients. The study was carried out an average 2,7 years (range 1 to 5 years) after intestinal resection. Balance materials (diets, urine and stools) were measured with neutron activation analysis. Mean iron balance was +28,6 µmol/day (± 10.6 SD). Mean zinc balance was +5.4 µmol/day (±6.5 SD) and mean copper balance +1.5 µmol/day (±2.3 SD). These results are comparable to those reported in healthy controls. Mean net absorption of iron was 12.6% (±1.8 SD), while mean net absorption of zinc and copper was 9.3% (±3.5 SD) and 12.5% (±5.1 SD), respectively. When taking into account integumentary losses of these substances, the balance of each individual trace element remained acceptable. It is concluded that a satisfying iron, zinc and copper status can be achieved in patients after an extensive small bowel resection with a disease-free remnant on oral nutrition.

Chapter 6. Metabolism of orally administered $^{69m}Zn$ in patients with short bowel syndrome as compared to controls subjects.

Zinc metabolism was studied in seven patients with short bowel syndrome (SBS) on oral nutrition using the short-lived isotope $^{69m}Zn$ ($T_{\frac{1}{2}}$ 13.9 hr). Results were compared with data obtained in a healthy control group of comparable age. After an oral dose of $^{69m}Zn$, activity was measured in plasma, erythrocytes, stools, urine, whole body and over a fixed are of the liver and thigh. In addition, apparent $^{69m}Zn$ absorption was calculated from whole body retention data.

In two short bowel patients, results of $^{69m}Zn$ metabolism were comparable to those in the controls. Absorption of fat and D-xylose was also normal or nearly normal in these two patients.

In the other SBS patients (abnormal SBS subgroup) the maximum level observed in the plasma $^{69m}Zn$ curve was 2 to 2.5 times lower than that of the controls. In these patinets, calculated apparent absorption was half of that in the normal persons. Data of cumulative faecal $^{69m}Zn$ excretion and whole body retention decline were in agreement with the observed reduced apparent absorption in the abnormal SBS subgroup. Urinary $^{69m}Zn$ excretion was negligible in all studied persons and patients. Uptake of $^{69m}Zn$ in the liver was reduced in the abnormal SBS subgroup, while flux of $^{69m}Zn$ to peripheral tissues (e.g. erythrocytes and thigh muscles) was identical to the control group and adequate. Signs of zinc deficiency were absent. It is concluded that the absorption of zinc in this group of patients was presumably still sufficient. Apparently the liver stored a smaller excess of absorbed zinc in the patients of the abnormal SBS subgroup.

Chapter 7. Home parenteral nutrition. Experience in seven patients.

This chapter reports experiences with home parenteral nutrition (HPN) in seven patients who were fed parenterally for 5 to 54 months (mean 24 months): four patients with a short bowel syndrome, one with a high output jejunostomy, one with complete small bowel obstruction resulting from irresectable tumour growth and one with scleroderma involving the small bowel. In four patients the parenteral nutrition solutions were mainly administered via an arteriovenous fistula, in two patients via a vena cava catheter and in one patient via a Scribner shunt. The infusions took place during the evening and night.

The Isoflux flow controlling device was used to warrant a constant flow rate (see chapter 8). Estimated appropriate amounts of amino acids, glucose, lipids, vitamins and trace elements were administered. Technical problems were primarily related to the vascular access. A fatal haemorrhage from the Scribner shunt was the most serious complication. Catheter complications were relatively often experienced which accumulated especially in one patient. The least number of vascular access complications were met when using an arteriovenous fistula. Metabolic complications included linoleic acid deficiency and fatty liver in the first HPN patient (in 1971) after receiving fat-free solutions during some 18 months. Another patient suffered from anaemia and hypoalbuminaemia of unknown origin. Zinc deficiency was seen three times. Three patients could fully perform their former jobs while on HPN. It is concluded that HPN is an important treatment for patients with a very short bowel or a small bowel without function.

Chapter 8. An accurate flow controlling device to administer simultaneously different parenteral nutrition solutions.

An easily operable, disposable flow controlling device is presented which enables a simultaneous administration of different sterilized parenteral nutrition (PN) solutions at a constant flow rate obtained by gravity drip infusion. The device contains safety mechanisms for preventing air embolism and inverse blood flow. Since flow readjustment during the infusion period is not required, the system markedly relieves the duties of the personnel responsible for the administration of the PN solutions. This phenomenon makes the system especially attractive when PN administration mainly takes place during the evening and night as in patients on home PN.

Chapter 9. Home parenteral nutrition via arteriovenous fistulae.

Vascular access for home parenteral nutrition (HPN) is generally achieved with vena cava catheters. In some 50% of these catheters serious complications can be expected. In this report experiences with arteriovenous fistulae (AVF) for the administration of parenteral nutrition at home are described Altoghether, 8 AVF were used in 7 patients during an average 14.3 months. (range 5-54 months). Four patients had a short bowel syndrome, two a high-output jejunostomy and one patient suffered from scleroderma of the small bowel. Despite anticoagulant therapy bovine graft thrombosis took place in

six instances during 100 fistula-months. Thrombectomy could successfully be performed in three graft thrombosis. No other AVF complications happened. Considering complication rates AVF are valuable alternatives for central venous catheters in HPN.

## 10.2 Some final remarks

Without any doubt one can state that parenteral nutrition has dramatically changed the treatment of patients after an extensive small bowel resection. Sufficient amounts of calories, nitrogen and other essential nutrients can be administered in order to tide over the often troublesome postoperative period. This period is often characterized by massive diarrhoea with severe losses of various important substances, and postoperative complications such as intra-abdominal sepsis. Perhaps even more important is the role of parenteral nutrition for patients who are left with a very short bowel (less than approximately 40 cm small intstine). Generally, adequate provision of nutrients to these patients can only be achieved via the parenteral route. In these circumstances parenteral nutrition can take place best at home. However, some technical and metabolic problems related to long-term parenteral nutrition await further research. For instance, the ideal vascular access has not been found. Furthermore, the appropriate amount of several constituents of parenteral nutrition solutions has not been elucidated. From a metabolic point of view perhaps the most intriguing problem is the influence of parenteral nutrition on calcium and bone metabolism.

The future of patients who are left with some 40 to 100 cm of small bowel is better. They can usually be weaned off parenteral nutrition. When optimal intestinal adaptation had developed no severe problems have to be expected anymore in patients with a diseae-free small bowel remnant. With few exceptions, an acceptable nutritional status is achieved at that time and patients are not disabled by frequent diarrhoea, provided that the colon or a part of it is retained. The absorption of various nutrients such as nitrogen, calcium, magnesium, phosphate, iron, zinc and copper sufficiently takes place in this situation. Steatorrhoea, to a more or lesser degree, almost invariably will be present. It is associated with hypocholesterolaemia and relatively low serum levels of fat soluble vitamins. Frequent meals with a relatively high amount of calories, calcium and phosphate can be advised,

next to lactose restriction and some fat restriction. However, also short bowel patients generally do not comply with dietary fat restriction. There is hardly any place for elementary and MCT-diets. It makes sense to avoid high-oxalate foods and to prescribe oral calcium carbonate in case of hyperoxaluria. When 15 to 20 cm ileum is retained vitamin B12 suppletion is not warranted in most instances. Suppletion of other vitamins is rarely necessary and is only indicated in case of proven deficiency.

## 10.3 Samenvatting

### Hoofdstuk 1. Inleiding en doel van het onderzoek

De lengte van de dunne darm in vivo bij de mens varieert van 2,5 tot 4 m. Indien na een uitgebreide resectie ongeveer 1 m of minder dunne darm overblijft, dan ontstaat een situatie die in de engelstalige literatuur als "short bowel syndroom" wordt aangeduid. De belangrijkste oorzaken van dit syndroom zijn: de ziekte van Crohn en versterf van de dunne darm door b.v. een volvulus of door een afsluiting van de a. mesenterica sup. De prognose van patienten die een zeer uitgebreide dunne-darmresectie ondergingen (minder dan ongeveer 40 cm jejunum en/of ileum over) is aanzienlijk verbeterd door de toepassing van parenterale voeding (hoofdstuk 7). Patienten, bij wie 40 à 100 cm jejunum en/of ileum gespaard is gebleven, kunnen in het algemeen door alleen voeding per os een voldoende voedingstoestand bereiken en behouden (hoofdstuk 2). Dit laatste is mogelijk door toeneming van het absorberend vermogen van het resterende dunne-darmslijmvlies (hoofdstuk 3). Op enkele stofwisselingsaspecten na uitgebreide dunne-darmresecties wordt nader ingegaan in de hoofdstukken 4,5 en 6. Aandacht wordt o.a. geschonken aan de absorptie van een aantal voedingsstoffen en aan de botstofwisseling. Enige technische aspecten betreffende langdurige parenterale voeding komen tot slot aan de orde in de hoofdstukken 8 en 9.

### Hoofdstuk 2. Zeer uitgebreide dunne-darmresecties. Ervaringen bij acht patienten.

De lotgevallen van acht patienten met een restant dunne darm van gemiddeld 60 cm (spreiding 40 tot 110 cm) werden nagegaan gedurende gemiddeld 53 maanden (spreiding 24 tot 87 maanden) na een uitgebreide dunne-darmresectie. Zij gebruikten allen voeding per os. Balansonderzoek (vet, stikstof,

Ca, Mg, P) werd verricht gemiddeld 30 maanden na de resectie.

Met uitzondering van één patiente waren alle patienten in een heel acceptabele voedingstoestand. Frequente diarree kwam bij geen van hen voor. Uit gegevens betreffende lichaamsgewicht, serum albuminegehalte en hemoglobinegehalte werd geconcludeerd dat binnen twee jaar na ontslag uit het ziekenhuis er sprake was van een optimale darmadaptatie. De gemiddelde stikstofbalans was licht positief (+0.1 g/dag ± 0.6 SD). Plasma of serumspiegels van Na, K, Ca, Mg, P, Cu en Zn waren nauwelijks of niet afwijkend. De balansen van calcium, magnesium en fosfaat waren nagenoeg in evenwicht. Het serum cholesterolgehalte was blijvend verlaagd, terwijl de spiegels van vitamine E en caroteen ook aan de lage kant bleven. De gemiddelde 25 OH vitamine $D_3$ spiegel was duidelijk verlaagd. Deze laatste waarnemingen konden toegeschreven worden aan de vastgestelde steatorree (gemiddelde vetabsorptie 74% ± 18% SD; normaal ≥95%). Een normale vitamine B12 absorptie werd na verloop van tijd gevonden bij patienten, bij wie nog slechts 15 à 20 cm ileum aanwezig was. Bij deze patienten nam na verloop van tijd ook de D-xylose absorptie toe, hetgeen niet of nauwelijks werd gevonden bij patienten zonder ileum. De D-xylosetest en de Schillingtest bleken geschikte parameters te zijn om het absorberend vermogen van het dunnedarmrestant te beoordelen althans bij patienten, bij wie ook enig ileum was behouden. Belangrijke psychosociale problemen deden zich bij deze acht patienten niet voor.

## Hoofdstuk 3. Dunne-darmslijmvlies adaptatie.

Een literatuuroverzicht betreffende dunne-darmslijmvlies adaptatie die ontstaat in aansluiting aan een uitgebreide dunne-darmresectie wordt gegeven. Een resectie van tenminste 30% van de dunne darm is nodig om hyperplasie van het slijmvlies in het restant te bewerkstelligen. Het ileum heeft een aanzienlijk groter vermogen tot hyperplasie dan het jejunum. De belangrijkste factor die de adaptatie bevordert is de voedselstroom door de darm. Het is waarschijnlijk dat voedingsstoffen een locale stimulatie van darmhormonen veroorzaken (met name van enteroglucagon) en/of andere stoffen (het enzym ornithine decarboxylase) waardoor het proces van de intestinale adaptatie in gang wordt gebracht. Gal en pancreasvocht, al of niet gesecerneerd o.i.v. cholecystokinine of secretine, spelen waarschijnlijk ook een rol bij het adaptatieproces, zij het in mindere mate dan de voedselstroom

door de darm.

## Hoofdstuk 4. De gevolgen van zeer uitgebreide dunne-darmresecties voor de botstofwisseling.

Een onderzoek naar de stofwisseling van Ca, Mg, P, vitamine D en bot werd uitgevoerd bij negen patienten met een gemiddeld dunne-darmrestant van 52 cm (spreiding 0 tot 110 cm), 1 tot 5 jaar na een uitgebreide darmresectie. Bij zeven patienten vond voeding per os plaats (orale groep), terwijl twee patienten gedurende resp. 3 en 5 jaar afhankelijk waren van parenterale voeding (PV patienten). Bekende parameters van de calcium- en botstofwisseling, zoals de hydroxyproline uitscheiding in de urine en plasma of serumspiegels van Ca, Mg, P, bicarbonaat, alkalische fosfatase, 25 OH vitamine D (25 OHD) en serumalbumine werden bepaald. Een balansonderzoek van Ca, Mg, P en vet werd uitgevoerd. Tevens werd een $^{47}Ca$ absorptie-onderzoek verricht en werden cristabiopten genomen voor histologisch en histomorfometrisch onderzoek.

De resultaten van de bovenstaande onderzoekingen waren voor wat betreft de orale groep bevredigend. Behoudens verlaagde 25 OH vitamine D spiegels waren andere parameters van de kalk- en botstofwisseling in het bloed bij deze patienten normaal. De absorptie van $^{47}Ca$ was verminderd, doch de gemiddelde calciumbalans was positief, waarschijnlijk dankzij een betrekkelijk hoge calciumconsumptie. De magnesiumbalans was in evenwicht, terwijl de fosfaatbalans licht negatief was. Een geringe osteoporose werd aangetroffen bij drie patienten uit de orale groep die allen ouder dan 59 jaar waren. Aanwijzingen voor osteomalacie of hyperparathyreoidie ontbraken.

Beide patienten, die de voeding voornamelijk parenteraal kregen, hadden een negatieve calciumbalans, een hypercalciurie en tevens een osteoporose die meer uitgesproken was dan bij de patienten uit de orale groep. Ook waren de 25 OHD spiegels flink verlaagd. Mogelijk heeft een lichte metabole acidose bij de patienten uit de parenterale groep de osteoporose bevordert. Zowel de fosfaat- als de magnesiumbalans waren in evenwicht of positief bij de beide parenteraal gevoede patienten. Ook bij deze patienten waren er geen tekenen van osteomalacie of hyperparathyreoidie bij histomorfometrisch onderzoek.

Hoofdstuk 5. De ijzer-, zink- en koperbalans bij patienten met een klein restant dunne darm tijdens voeding per os.

Gegevens worden gepresenteerd van een 5 dagen durende balansstudie betreffende ijzer, zink en koper bij zeven patienten, die een uitgebreide dunne-darmresectie hadden ondergaan en de voeding per os tot zich namen. Het dunne-darmrestant van deze patienten varieerde van 40 tot 110 cm (gemiddeld 64 cm) en toonde röntgenologisch geen afwijkingen. Het onderzoek werd gemiddeld 2,7 jaar (spreiding 1 tot 5 jaar) na de resectie uitgevoerd. Er werd gebruik gemaakt van neutronen-activeringsanalyse ter bepaling van de spoorelementen in de balansonderdelen (dieet, urine en faeces). De gemiddelde ijzerbalans was +28,6 µmol/dag (±10,6 SD). De gemiddelde zinkbalans bedroeg +5,4 µmol/dag (±6.5 SD) en de gemiddelde koperbalans +1,5 µmol/dag (±2.3 SD). Deze resultaten komen overeen met literatuurgegevens over balansen van deze spoorelementen, uitgevoerd bij gezonde proefpersonen. De gemiddelde netto-absorptie van ijzer was 12,6% (±1,8 SD), terwijl de gemiddelde netto-absorptie van zink en koper respectievelijk 9,3% (±3,5 SD) en 12,5% (±5,1 SD) bedroeg. Ook wanneer men verliezen via de huid van deze spoorelementen in de beschouwing betrekt, dan blijft de balans van elk van deze drie spoorelementen heel aanvaardbaar bij deze patienten.

Hoofdstuk 6. De stofwisseling van per os toegediend $^{69m}$Zn bij patienten die een grote dunne-darmresectie ondergingen.

Met behulp van $^{69m}$Zn, een isotoop met een korte halfwaardetijd (13,9 uur), werd het metabolisme van zink bestudeerd bij 7 patienten met een short bowel syndroom (SBS), die voeding per os gebruikten. De resultaten werden vergeleken met gegevens van een controlegroep bestaande uit 7 gezonde proefpersonen van gelijke leeftijd als de patienten. Na orale toediening van $^{69m}$Zn werd de activiteit ervan gemeten in plasma, erythrocyten, faeces, urine, boven de lever en het dijbeen en benevens van het gehele lichaam. Uit gegevens met betrekking tot de vermindering van de $^{69m}$Zn-activiteit in het lichaam werd de $^{69m}$Zn absorptie berekend. De resultaten van het onderzoek met $^{69m}$Zn waren bij twee patienten vergelijkbaar met die van de controlegroep. Bij deze twee patienten was de absorptie van vet en de D-xylose normaal of nagenoeg normaal. Bij de andere patienten (abnormale SBS-subgroep) bleek de maximumwaarde van de plasma $^{69m}$Zn-curve twee à twee-

enhalf maal lager dan bij de controlegroep. Tevens was de berekende absorptie van $^{69m}$Zn bij deze patienten ongeveer de helft van die van de controlegroep. In overeenstemming met deze gegevens was de significant hogere cumulatieve uitscheiding van $^{69m}$Zn in de faeces en de significant snellere verdwijning van het $^{69m}$Zn uit het gehele lichaam bij de abnormale SBS-subgroep. De uitscheiding van $^{69m}$Zn via de urine was uitermate gering zowel in de patienten- als de controlegroep. De opname van $^{69m}$Zn in de lever was verminderd in de abnormale SBS-subgroep terwijl het transport ervan naar perifere weefsels (zoals erythrocyten en spieren) identiek was aan dat van de controlegroep. Waarschijnlijk slaat de lever tijdelijk bepaalde hoeveelheid van de overmaart aan geabsorbeerd zink op, een hoeveelheid die dan bij de abnormale SBS-subgroep kleiner was dan bij de controlegroep.

Hoofdstuk 7. Parenterale voeding thuis. Ervaringen bij zeven patienten.

Beschreven worden de lotgevallen van zeven patienten die 5 tot 8 maanden (gemiddeld 24 maanden) thuis parenterale voeding kregen toegediend. Vier patienten hadden een zeer grote dunne-darmresectie ondergaan, één had een jejunostoma, één een totale dunne-darm-obstructie door tumorgroei en bij één patient met sclerodermie bestond er een zeer slechte functie van de dunne darm. Bij vier patienten werden de voedingsoplossingen via een arterioveneuze fistel toegediend, bij twee via een v. cava catheter en bij één via een Scribner shunt. Toediening vond plaats gedurende de avond en nacht. Gebruikt werd het Isoflux toedieningssysteem bij zes van de zeven patienten waarmee het mogelijk is een constante infusiesnelheid te bereiken en verschillende voedingsoplossingen gelijktijdig kunnen worden gegeven zonder hulp van pompen (zie ook hoofdstuk 8). Naast aminozuren, glucose, vet en mineralen werden vitaminen en spoorelementen toegediend. Technische problemen konden hoofdzakelijk aan de toedieningswegen van de parenterale voeding worden toegeschreven. Een dodelijke arteriele bloeding uit de Scribner shunt was de ernstigste complicatie. Problemen met de v. cava catheter kwamen relatief frequent voor, alhoewel deze zich in hoofdzaak bij één patiente voordeden. De minste complicaties werden gezien bij de arterioveneuze fistels. De ernstigste metabole complicaties waren een linolzuurdeficientie en een ernstige steatosis hepatis bij een patiente die thuis ongeveer 1½ jaar parenterale voeding zonder vet kreeg toegediend (in 1971). Een andere patiente hield een, ondanks uitgebreid onderzoek, onverklaarde

anemie en hypoalbuminaemie. Zinkdeficientie werd drie keer waargenomen. Drie patienten waren in staat om hun vroegere werk te hervatten ondanks het feit dat zij afhankelijk waren van parenterale voeding. Geconcludeerd wordt dat parenterale voeding thuis een belangrijke behandelingsmethode kan zijn voor patienten bij wie de toediening van adequate hoeveelheden voeding per os niet of onvoldoende mogelijk is, bijvoorbeeld bij patienten die een zeer uitgebreide dunne-darmresectie ondergingen of patienten met een dunne darm die niet of nauwelijks functioneert.

Hoofdstuk 8. Een eenvoudig en nauwkeurig infuussysteem voor parenterale voeding.

Een eenvoudig toedieningssysteem voor infuusvloeistoffen met een ingenieuze druppelregelaar wordt beschreven waardoor o.a. tegelijkertijd verschillende parenterale voedingsoplossingen kunnen worden toegediend met een constante infusiesnelheid. Het systeem bevat enkele beveiligingen ter voorkomint van luchtembolie en terugstromen van bloed in het systeem. Aangezien de infusiesnelheid na instellen van de snelheid niet meer regelmatig gecontroleerd hoeft te worden, betekent dit systeem een aanzienlijke verlichting voor het personeel dat verantwoordelijk is voor de infusie. Dit geldt in het bijzonder voor toediening van parenterale voedingsoplossingen gedurende de nacht, zoals bijvoorbeeld geschiedt bij patienten die thuis parenteraal gevoed worden.

Hoofdstuk 9. Parenterale voeding, toegediend via een arterioveneuze fistel.

In het algemeen maakt men gebruik van een vena cava catheter bij parenterale voeding. Dit gaat niet zo zelden gepaard met aanzienlijke complicaties. Nagegaan werd in hoeverre dit ook het geval was wanneer arterioveneuze fistels (AVF) werden gebruikt als toegangsweg naar de circulatie voor parenterale voeding. In totaal werd gebruik gemaakt van acht AVF bij zeven patienten gedurende gemiddeld 14.3 maanden (spreiding 5-54 maanden). Vier patienten hadden onvoldoende dunne darm voor een normale absorptie, twee een jejunostomie met ernstig water- en mineralenverlies en bij één sclerodermie-patient was de dunne darm in het ziekteproces betrokken geraakt. Ondanks therapie met anticoagulantia werd zesmaal een thrombose

van een bovine graft vastgesteld gedurende de 100 fistelmaanden. In drie gevallen kon de fistel door verwijdering van de trombus weer hersteld worden. Het aantal en de ernst van de complicaties in aanmerking nemende, kan gesteld worden dat een arterioveneuze fistel een waardevol alternatief is voor de centraal veneuze catheter bij langdurige parenterale voeding.

## 10.4 Enige conclusies tot slot.

Zonder enige twijfel heeft parenterale voeding een belangrijke verandering ten goede bewerkstelligd bij de behandeling van patienten die een uitgebreide dunne-darmresectie moesten ondergaan. Voldoende calorieën, stikstof en andere essentiele voedingstoffen kunnen op zo'n manier toegediend worden om de vaak moeizame postoperatieve fase, die niet zelden gekenmerkt wordt door ernstige diarree en verlies van verschillende belangrijke voedingsstoffen, te overbruggen. Dit geldt temeer in geval van postoperatieve complicaties, b.v. bij ontstekingen in de buikholte.Wellicht nog belangrijker is parenterale voeding voor patienten, bij wie nog maar zeer weinig dunne darm over is (minder dan globaal 40 cm). In het algemeen kan in zo'n situatie alleen via parenterale weg een voldoende aanbod van voedingsstoffen plaatsvinden. Toediening van parenterale voeding kan dan het beste thuis geschieden. Er kleven echter nog een aantal technische en metabole problemen aan langdurige parenterale voeding, die nader onderzoek noodzakelijk maken. De ideale toegang tot de circulatie is bijvoorbeeld nog niet gevonden.De juiste hoeveelheid van enkele voedingsstoffen is ook niet altijd goed bekend. Een fascinerend probleem is het effect van parenterale voeding op de calcium- en botstofwisseling, waarvan nog veel onduidelijk is.

Patienten bij wie nog 40 tot 100 cm dunne darm resteert hebben betere vooruitzichten. Bij hen kan de parenterale voeding uiteindelijk meestal geheel gestaakt worden. Indien de darmadaptatie volledig tot stand is gekomen (na ongeveer één tot twee jaar), dan zijn geen ernstige problemen meer te verwachten. Behoudens een enkele uitzondering zullen de meeste patienten in een redelijke tot goede voedingstoestand komen en zullen zij, vooropgesteld dat het colon of een ruim deel hiervan nog aanwezig is, niet

gehinderd worden door frequente diarree. Onder zulke omstandigheden is de absorptie van verschillende voedingsstoffen zoals stikstof, calcium, magnesium, fosfaat, ijzer, zink en koper voldoende. Wel zal de vetabsorptie vrijwel steeds meer of minder gestoord blijven. Dit gaat dan gepaard met een hypocholesterolemie en relatief lage serumspiegels van vet-oplósbare vitaminen. Frequente voedzame maaltijden, met een betrekkelijk hoog gehalte aan calcium en fosfaat, is dan van belang. Tevens is lactosebeperking in het dieet geboden alsmede enige vetbeperking. Elementaire dieten of dieten waarin het vet grotendeels bestaat uit korte keten vetzuren zijn zelden nodig of nuttig. Het is verstandig voedingsmiddelen met een hoog oxalaatgehalte te mijden en calciumcarbonaat per os voor te schrijven wanneer er sprake is van hyperoxalurie. Indien 15 tot 20 cm ileum behouden is, dan is regelmatige suppletie met vitamine B12 meestal niet nodig. Toediening van andere vitaminen is alleen geindiceerd bij een gebleken tekort.

De schrijver van een proefschrift is veelal een meer of minder ijverig persoon die gegevens, verkregen door het werk van velen, verzamelt, rangschikt en uiteindelijk op schrift stelt. Ik heb niet de illusie op deze regel een uitzondering te vormen. Derhalve is een woord van dank aan allen die direct of indirect aan de totstandkoming van dit proefschrift hebben bijgedragen op zijn plaats.

In de eerste plaats zou ik de verpleging van de afdeling maag-, darm- en leverziekten (B50), destijds onder de bezielende leiding van mevr. A.M.Th. Reitsma-van der Belt, willen danken voor de nauwgezette hulp bij de uitvoering van de balansonderzoeken. Voor wetenschappelijk onderzoek vindt een balansonderzoek tegenwoordig vrijwel steeds plaats in een "metabolic-ward", teneinde de verzameling van de excreta van proefpersonen en patienten zo optimaal mogelijk te doen geschieden. Dat deze onderzoeken echter op een gewone verpleegafdeling naar volle tevredenheid hebben kunnen plaatsvinden, zegt voldoende over de kwaliteit van deze afdeling.

Op het klinisch chemisch laboratorium (hoofd: Prof.Dr. A.P. Jansen) fungeerde mevr. T.M.G. Kamphuys als een ware chef de cuisine bij de verwerking van de balansonderdelen, hetgeen niet steeds een aangename aangelegenheid was. Beste Door, ik blijf je hier dankbaar voor.

Voor het samenstellen en op speciale wijze bereiden van de balansdieten dank ik mevr. H.J.M. Lamers van de dieetdienst en de heer J. Linders van de keuken van het St. Radboud Ziekenhuis.

De medewerkers van het Ir. Reichert laboratorium (hoofd: Dr. F.H.M. Corstens) ben ik veel dank verschuldigd, met name mevr. Drs. W.C.A. Buijs, de heer W. van de Broek, mevr. M. Huybregts-van den Manacker en mevr. G. Nales, die het onderzoek met $^{47}Ca$ en $^{69m}Zn$ op een voortreffelijke wijze uitvoerden.

Het Interuniversitair Reactor Instituut te Delft zorgde voor de levering van het $^{69m}Zn$. Dr. C.J. van den Hamer, werkzaam in dit instituut, volgde steeds met veel belangstelling de resultaten van dit onderdeel van het onderzoek en gaf bovendien geregeld nuttige adviezen, waarvoor ik hem graag wil danken. Van Ir.A.A. van Barneveld, eveneens van het Interuniversitair Reactor Instituut, kreeg ik een aantal nuttige suggesties betreffende de betekenis van sommige uitkomsten van de $^{69m}Zn$-studies.

Dr. W.J. Visser (laboratorium voor de botstofwisseling, kliniek voor

inwendige ziekten, Academisch Ziekenhuis te Utrecht) verrichtte met grote deskundigheid het histologisch en histomorfometrisch botonderzoek. Bovendien leverde hij, in samenwerking met Dr. J.A. Raymakers, nuttige kritiek op het manuscript van hoofdstuk 4, waarvoor ik hen beiden dank.

Uiterst prettig heb ik samengewerkt met Drs. J.H. Bakker van de afdeling klinische farmacie, vooral wat betreft de samenstelling en bereiding van de parenterale voedingsoplossingen. Hans, onze veelvuldige discussies over dit onderwerp blijven een inspirerende herinnering.

De bepalingen van 25 OH vitamine B in het serum geschiedden op het laboratorium maag-, darm- en leverziekten door Dr. A. Tangerman en mevr. A. van Schaik.

Bij het verzamelen van de literatuur was de medische bibliotheek behulpzaam (hoofd: de heer E. de Graaf). Aan de zelden van humor gespeende uiteenzettingen van de heer de Graaf denk ik nog steeds met plezier terug.

De heer C. Nicolasen van de afdeling medische illustratie vervaardigde met veel zorg de tekeningen voor dit proefschrift. De afdeling medische fotografie (hoofd: de heer A. Reynen) zorgde voor een adekwate afbeelding hiervan.

De heer Th. van Winsen droeg op nauwkeurige wijze zorg voor correctie van de Engelse taal.

Mevr. P. Mey-Fuhlrott, secretaresse van de afdeling maag-, darm- en leverziekten, typte snel en accuraat de vele versies van de verschillende hoofdstukken. Zij vormde buitendien een onmisbaar, organisatorisch trait d'union tussen Nijmegen en Sittard. Gelukkig bleek zij ondanks alle drukte toch nog steeds in staat om mij nauwkeurig op de hoogte te houden van haar ontdekkingsreizen door culinair Nederland.

Hanneke, mijn echtgenote, wenst niet bedankt te worden voor de vele avonden en weekenden die zij, ondanks mijn aanwezigheid, in betrekkelijke stilte heeft moeten doorbrengen. Ik vind het fijn dat de sfeer in huis nauwelijks of niet geleden heeft onder de werkzaamheden die nodig bleken voor de voltooiing van dit proefschrift.

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# CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren te Maasbracht op 6.11.1948. In 1966 behaalde hij het diploma HBS-b aan het Bisschoppelijk College te Roermond. Hierna volgde tot 1974 de studie geneeskunde aan de Katholieke Universiteit te Nijmegen. Op 1.9.1979 werd de opleiding tot internist binnen de Kliniek voor Inwendige Ziekten van het St. Radboud Ziekenhuis te Nijmegen voltooid (opleider Prof.Dr. C.L.H. Majoor). Hierna volgde de opleiding tot gastroenteroloog aan de afdeling maag-, darm- en leverziekten van het bovengenoemde ziekenhuis (opleider Dr. J.H.M. van Tongeren). Ook fungeerde hij nog tijdelijk als chef de clinique op de afdeling reumatologie (hoofd Prof.Dr. L.B.A. van de Putte). Vanaf 1.5.1983 is hij werkzaam als gastroenteroloog in het Ziekenhuis de Goddelijke Voorzieningheid te Sittard in samenwerking met Dr. L.P. Bos, gastroenteroloog en H.N.L.M. Bron, Dr. A.M.J. Moers, Dr. J.L. Visser en Dr. Th.W.M. van de Wiel, allen internist.

Hij is gehuwd met Hanneke van Slijpe. Zij hebben een zoon, Titus.

STELLINGEN

1 Ook zonder dunne darm is veelal een acceptabel leven mogelijk.
dit proefschrift

2 Indien na een uitgebreide dunne-darmresectie nog slechts 20 cm ileum is behouden, dan is een normale vitamine B12-absorptie mogelijk.
dit proefschrift

3 Patienten met een uitgebreide dunne-darmresectie kunnen een calcium- en fosfaat-verrijkt dieet aanbevolen worden.
dit proefschrift

4 Het Isoflux toedieningssysteem voor parenterale voeding is een waar ei van Columbus.
dit proefschrift

5 Indien parenterale voeding gedurende zeer lange tijd nodig is, dan vormt een arterioveneuze fistel een goede toegangsweg naar de circulatie.
dit proefschrift

6 Teveel vitamine B6 is ook niet goed.
Schaumburg H, Kaplan J, Windebank A et al. N Engl J Med 1983; 309: 445

7 De absorptie van koper kan in bijzondere omstandigheden door antacida geremd worden.
Van Kalmthout PM, Engels LGJ, Bakker JH et al. Dig Dis Sci 1982; 27: 859

8 Het innemen van mexiletine tijdens de maaltijden blijkt de bijwerkingen van dit geneesmiddel te beperken. In de bijsluiter van mexiletine wordt hiermee echter geen rekening gehouden.
Dimarco JP, Gavan H, Ruskin JN. Am J Cardiol 1981; 47: 131

9 De muziek van John Coltrane (17.7.1967†) blijft (voorlopig nog) van ongeëvenaarde kwaliteit.

10 Indien tijdens endoscopie zwart gekleurd slijmvlies in de maag wordt waargenomen bij een patient die een geconcentreerde zuuroplossing heeft gedronken, dan moet ernstig rekening worden gehouden met een op handen zijnde maagperforatie.
Engels LGJ, Klaassen L, Yap SH et al. Ned Tijdschr Geneeskd 1982; 126: 1996

11 Het werken op een polikliniek met medische dossiers bestaande uit losbladige vellen papier, waarop de gegevens chronologisch genoteerd worden, verhoogt niet het overzicht en inzicht in het ziektebeloop van patienten.
(mededeling HMLM Bron en LP Bos, eigen waarneming)

12 Vrijwel alle grote vernieuwers van de jazz vertonen een discontinuiteit in de continuiteit ten aanzien van de traditie, doch eveneens een herbronning op die traditie.
De jazz-traditie speelt een doorslaggevende rol bij iedere belangrijke vernieuwing van deze muziek.

LGJ Engels
Sittard-Nijmegen