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HOME PARENTERAL NUTRITION (HPN)

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Home Parenteral Nutrition (HPN) was first attempted in December 1969 by Shils et al (100) in a woman who had undergone massive small bowel resection for a recurrent desmoid tumor invading the superior mesenteric artery. This patient died about a year later after an unsuccessful bowel transplant. Since that time at least 2000 patients have been discharged on HPN. A young mother started on HPN by Jeejeebhoy in 1971 (51) is still alive and doing well 12 years later. This chapter reviews the current experiences with HPN; information that has accrued about intravenous nutrient requirements, particularly in these long-term and usually stable patients; and the ethical and cost issues that HPN has generated.

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THE CURRENT EXPERIENCE WITH HPN

According to the Registry of Patients on Home Total Parenteral Nutrition[1], 169 hospitals had started one or more patients on HPN by June 1983. This estimate may be low, as there currently is no formal requirement that hospitals or physicians report such patients to the National Registry. Since 1977, the Registry has collected data on all known HPN patients; the most recently released figures describe 394 patients from 89 hospitals started between January 1 and December 31, 1981. These data also include information about 792 patients discharged on HPN prior to January 1, 1981 and offer the cumulative experience of 1186 patients. We summarize this material because it provides the most complete picture of HPN nationwide and in large measure corroborates the published data from single institutions with large HPN programs (9, 29, 38, 50, 104).

Diagnoses of Patients on HPN

In patients starting on HPN in 1981 (Table 1), the most common diagnosis was malignancy (31.2%) with diffuse bowel obstruction, or a cancer treatment sequela, such as radiation enteritis. The next most common disorder was inflammatory bowel disease (28.4%), especially Crohn's with massive small

Table 1 Diagnoses of patients started on HPN in 1981[a]

Diagnosis	Rate of occurrence (%)
Malignancy and its treatment	31.2
With persistent obstruction	15
With persistent fistulae	1.3
Malabsorption from radiation enteritis	7.9
Malabsorption from massive resection	5
Other	2
Total	31.2
Inflammatory bowel disease	31.2
With massive resection	20.5
Without resection	7.9
Total	28.4
Ischemic bowel infarction with resection	10.7
Motility disorders	8.6
Congenital malformation	2.8
Trauma resulting in short bowel syndrome	2.3
Other causes	14.9

[a]Source: Home TPN Registry.

[1]New York Academy of Medicine, 2 East 103rd St., New York, NY 10029

bowel resection. Other diagnoses were ischemic bowel infarction (10.7%), motility disorders (8.6%) such as pseudo-obstruction due to scleroderma, and congenital malformations (2.8%) such as gastroschesis, mid-gut volvulus, or long segment Hirschsprungs. This represents an interesting shift from the period 1977–78 when inflammatory bowel disease and mesenteric infarction characterized about two thirds of the patients started that year on HPN, and malignancy accounted for less than one fifth. This shift suggests several possibilities: first, that extreme short bowel syndrome due to inflammatory bowel disease and mesenteric infarction accounts for a relatively fixed number of patients requiring HPN (106 in 1977–1978 and 154 in 1981); and second, that greater experience with HPN has encouraged physicians to employ this technique more widely and in relatively short-term clinical situations. This explanation is substantiated by the fact that 68.3% of the patients started in 1977–1978 were still on HPN at the end of 12 months, and this figure dropped to 56.8% in 1981.

Age Distribution of Patients on HPN

Table 2 summarizes the ages of patients starting HPN in 1981. About half the patients were between their fourth and sixth decades, 10% were under 10 years, and 10% were over 65 years. In cases involving the very young and the very old, family members probably take the brunt of the infusion responsibility. Screening and supporting these families often becomes more critical and the ethical issues more poignant.

Mortality of Patients on HPN

Of the 394 patients starting HPN in 1981, about three fifths were still on HPN at the end of that year, one fifth were no longer in need of HPN, and one fifth had died. The causes of death are summarized in Table 3, which shows that the great majority of patients died from their underlying disease (95%) and less than five percent died from an HPN complication, such as sepsis. This empha-

Table 2 Ages of patients starting HPN in 1981[a]

Age	Number	Percentage
0–10	41	10.4
11–20	27	6.7
21–30	43	10.9
31–40	58	14.7
41–50	60	15.2
51–60	82	20.8
61–65	43	10.9
Over 65	39	10.0
Total	394	99.6

[a]Home TPN Registry.

Table 3 Causes of death in patients starting HPN in 1981[a]

	Number	Percentage
Patients starting HPN in 1981	394	100
Patients dead as of 12/31/81	82	20.8
Causes of death		
Underlying disease while on HPN	69	16.5
Underlying disease after discontinuing HPN	8	2
HPN complications (sepsis, etc)	4	1
Suicide	1	0.3

[a]Source: Home TPN Registry.

sizes the remarkable ability of most patients and their families to succeed in managing this sophisticated technique in the home setting.

If a patient does not die because of his underlying disease and if death as the result of an HPN complication is unlikely, what is the actual life expectancy for an individual starting HPN? At present, there is no precise answer to this question. Many of the larger, well-established HPN programs have a number of patients who have been on HPN for more than 8 years and, as mentioned above, one patient in Canada has been on HPN for 12 years and is doing well. Of the 1186 patients who began HPN between December 1969 and December 1981, about 25% are dead, implying an average life expectancy of roughly 4–5 years. In the future it will be important to analyze outcome in terms of different disease categories.

Morbidity of Patients on HPN

In 1981 about 25% of the patients sent home on parenteral nutrition had to be readmitted that year for HPN-related problems. Four fifths of these patients were readmitted just once, but for one fifth, there were two or three readmissions. This implies that HPN-related problems requiring readmission are rare for most patients, but a few patients have frequent problems. Unfortunately there is no objective data at present to characterize effectively which patients will do badly. Our experience with 55 HPN patients at Albany suggests that common underlying factors in HPN patients who require frequent readmission are an uncontrolled infected site, such as fistulous tracts in Crohn's; poor family support; or the need for strong and addictive medication.

Table 4 summarizes the reasons for HPN-related hospital readmissions, distinguishing between patients who were mixing their own solutions at home and patients who were being supplied with formulas premixed at the pharmacy. The numbers of patients at risk for complications were similar in both groups (268 and 275, respectively), and the total number of readmissions was also comparable (100 and 109, respectively). As shown in Table 4, complications in these two groups of patients were essentially the same. Most HPN-related

Table 4 Reasons for HPN-related hospital admissions[a]

	Home Mixed Formulas[b]		Pharmacy Mixed Formulas[c]	
	Admissions	Admissions per 100 months	Admissions	Admissions per 100 months
Suspected sepsis	43	2.31	50	2.61
Catheter related problems	20	1.07	19	0.99
Organ failure or dysfunction	3	0.16	4	0.21
Fluid or electrolyte problem	14	0.75	11	0.57
Bone disease workup or treatment	6	0.32	6	0.31
Hypo- and/or hyperglycemia	2	0.10	2	0.10
Other metabolic problems	0	0.00	1	0.05
Psychological problems	2	0.10	1	0.05
Other causes	10	0.54	15	0.56

[a]Source: Home TPN Registry.
[b]268 patients, 100 readmissions.
[c]275 patients, 109 readmissions.

rehospitalizations were due to suspected catheter sepsis or catheter-related problems. Catheter problems included tunnel infections and catheters clotting, breaking, or falling out. The average length of stay in the hospital was 11.3 days for patients on premixed formulas and 18.3 days for patients on home-mixed formulas. This suggests that patients doing their own solution mixing required more in-hospital time to recover and reach a point where they could reaccept a more extensive responsibility.

Table 5 shows the outcome for patients readmitted to the hospital for suspected sepsis. Cultures were positive in about two thirds of these cases. This represented an overall sepsis rate for patients on HPN of one episode every four years, a remarkably low incidence when compared to in-hospital parenteral nutrition infection rates (20, 23, 90). As with the inpatient population, home patients have a fairly high incidence of fungal infections, and the fungus is frequently *Candida*. There are several reasons why home patients may be less susceptible to infection than hospitalized patients. First, home patients are usually nutritionally rehabilitated after at least two or three months, and thus it is likely that ther immunocompetence has also improved (85). Second, home patients are invariably cycled, 12 hours on and 12 hours off their nutrient infusion, and this cycling may enable the host to deal with bacteremia and fungemias more effectively. It is well known that high glucose loads can induce extracellular-intracellular phosphate shifts and impair phagocytosis (12), and this relative phosphate depletion is far more common in patients suffering

Table 5 Outcome in patients admitted for suspected sepsis[a]

	Number	Percentage
Suspected sepsis admissions	93	100
Cases of sepsis confirmed by culture	61	65.6
Bacterial	47	
Fungal	13	
Viral	1	

[a]Source: Home TPN Registry.

prolonged starvation (63). A third factor is undoubtedly that home patients are out of the nosocomial environment and away from potential contamination with the more virulent drug-resistant organisms. It has been postulated that subcutaneous tunnelling of long-term HPN catheters may reduce catheter sepsis, but this was not confirmed in a prospective randomized study by Von Meyenfeldt et al (114). In any event, infection in HPN patients is rare, and while aseptic precautions cannot be relaxed, and all HPN patients with fever should be medically evaluated, tunnelled catheters are not usually pulled out until positive cultures have been obtained. Even at that point, if further catheter sites are limited, several centers attempt antibiotic treatment through the line and only pull it if the infection persists. Few controlled studies have been published on this issue (71). There are also reports of urokinase and hydrochloric acid (119) catheter instillations to clear proteinaceous material and improve the chances of clearing the infection without removing the catheter. This course may be dictated by necessity, since many HPN patients have used up their readily available veins for central line placement. On occasion, catheters have been inserted directly into the heart through the right atrial appendage, a procedure that involves major surgery.

Although the Registry does not provide data on the overall hospital readmission rate for HPN patients, a recently published report on 50 HPN patients from the Cleveland Clinic (104) showed that while HPN-related hospital days accounted for about 3% of the patients' total HPN time, hospital days for non-HPN-related problems accounted for 13% of the patients' time. In other words, HPN-related complications accounted for only 24% of all rehospitalization time.

HPN NUTRIENT REQUIREMENTS

Most cachectic HPN patients can be restored to their normal weight in 3 or 4 months. However, it is usually 6–12 months before young patients experience complete return of energy for strenuous physical activity, and many patients and their families comment on delayed recovery of psychological functioning and sexual libido.

Fluid Requirements

For each patient, the parenteral fluid requirement can be calculated by adding the normal daily requirement for a patient of that age (120 ml/kg infant, 40 ml/kg adult), to the abnormal losses; and subtracting the oral intake. For example, a 75 kg man with a high jejunostomy would have a normal requirement of 40 × 75 ml, or 3000 ml, amply allowing for normal losses from urine of 2000 ml and from insensible water of 500 ml. Abnormal losses due to jejunostomy could be 4000 ml, for a total of 7000 ml. Subtracting oral intake of 2500 ml yields a parenteral daily requirement of 4500 ml.

HPN patients must learn how to keep a record of their daily input and output. Unless they have complete bowel obstruction, most patients opt to continue some oral intake even though this stimulates enteric secretions and creates a net fluid deficit. HPN patients should be allowed to start their oral intake before discharge so their parenteral fluid requirements are more realistically established. As can be seen from Table 6, a high jejunostomy loss of 4 liter/day is to be expected in an extreme short bowel patient with oral intake. Anticholinergic medication may reduce this fluid loss to some degree, but an H_2 blocker is more effective (18a), because for at least the first year or two, extreme short bowel patients have hypergastrinemia (82). Oveson et al studied the effect of the oral diet on the fluid, monovalent, and divalent cation loss of extreme short bowel end jejunostomy patients (84). Each patient served as his own control, and for a particular patient all test diets had the same calorie, nitrogen, and sodium contents, were low in simple carbohydrates, and were lactose-free. Each patient's unstimulated losses were measured over 48 hours, and these losses were subtracted from the losses on a low-fat diet (one third of the calories as fat) and two high-fat diets (two thirds of the calories as fat) with P:S ratios of 1:4 and 1:1, given in random order for seven days. There was no consistent effect of these different diets on jejunostomy fluid volumes, and the sodium and potas-

Table 6 Enteric fluid volumes and their sodium, potassium, chloride and bicarbonate content[a]

	l/day[b]	Na	K[c]	Cl	HCO_3
Oral intake	2–3				
Enteric secretions					
Saliva	1–2	10	30	10	30
Gastric juice	2	60	9	90	0
Bile	2–3	150	10	90	70
Small bowel	1	100	5	100	20
Colon	Variable	40	100	15	60

[a]Enteric secretions are also rich in divalent cations (Ca, Mg, Zn, Cu) and their loss is increased by steatorrhea, a high bowel fistula or prolonged suction.

[b]Of the 9 l of oral and enteric fluid presented to the upper small bowel, normally 50% is absorbed in the jejunum, 40% in the ileum, and 10% in the colon. In short bowel patients, the colon can absorb greater amounts, up to 3l/d.

[c]Potassium losses are small except in secretions distal to the ileocecal valve. The colon ion exchange is partly controlled by aldosterone and therefore Na^+ depletion increases K^+ loss in the stool.

ium concentrations stayed remarkably constant. The high-fat diet caused a marked increase in divalent cation loss; conversely, the high-carbohydrate diet often converted a net calcium, magnesium, zinc, and copper loss to net absorption. Substituting polyunsaturated for saturated fat produced no consistent differences in any of the measured losses. It was concluded that if short bowel patients chose to eat a significant amount of fat, and many do, then the exaggerated divalent cation losses had to be replaced by more generous parenteral supplements. In a similar study, Woolf et al (118) also showed that low-fat diets were of no special benefit for reducing ostomy or stool volume. In the Woolf study, however, higher divalent cation losses were not seen with high-fat intakes.

It is important that HPN patients understand that they must have a urine output of at least 1200–1500 ml/day to stay healthy. With a normal urinary concentrating capacity (1200 mosmol/liter), this volume provides a reasonable margin for excreting a renal solute load of ±1000 mosmol/day. For those patients with ileal resection and an incontinuity colon resulting in excessive dietary oxalate absorption (26), renal stones are less likely to form if urine oxalate concentration is kept low. Most experienced patients can recognize relative dehydration and in hot summer wheather will infuse an extra liter or two to replace sweat losses.

Calorie and Amino Acid Requirements

In the buildup phase, most HPN patients require 35–40 kcal/kg/day and 1.5 g/kg of amino acids. After their ideal weight has been reached and muscle mass and circulating proteins such as albumin have been restored to normal, some of the parenteral calories and amino acids can often be gradually withdrawn. In about 30% of the extreme short bowel patients in the Albany program, the remaining bowel adapts to the point where the individual can maintain a stable weight with no parenteral calories or amino acids. However, such patients frequently need partial parenteral support to replace their abnormal fluid losses and avoid recurrent hospitalization for dehydration and electrolyte imbalance.

An unresolved HPN issue is the distribution of nonprotein calories between carbohydrate (glucose) and fat. There are several reports of essential fatty acid deficiency occurring in long-term parenteral nutrition patients receiving totally fat-free solutions (33, 87). Although 1–2% of calories as essential fatty acids is apparently sufficient in oral diets (42), parenteral requirements appear to be much higher. One liter/week of 10% Intralipid®[2], providing 2–3% of total calories as linoleic acid, cures and prevents the overt clinical signs of essential fatty acid deficiency; but biochemically, the fatty acid composition of plasma and red-cell membranes stays abnormally low in linoleic acid. This defect is still present in patients in the Toronto program who receive 10–12% of their

[2]Cutter Laboratories, Emeryville, CA

calories as linoleic acid. The biologic significance of this persistent abnormality is not yet clear. Recently a neurologic syndrome was described in a young child on long-term parenteral nutrition receiving linoleic acid but no linolenic acid (43). Since the child had biochemical depletion of the w3 series and improved both physically and biochemically with linolenic acid supplementation, this appears to provide evidence for an absolute human requirement for linolenic acid in addition to linoleic acid (w6 series), and raises some concern about long-term reliance on fat solutions derived from safflower oil.

Several investigators have suggested that hepatic steatosis is less and glucose swings are more moderate if fat provides 20–30% of total calories (74, 75). This is routine in the Canadian programs but less so in the United States, where a parenteral fat calorie costs about four times as much as a glucose calorie.

Weight-stable HPN patients can usually be maintained on 1–1.2 g/amino acids/kg/day. The optimum parenteral amino acid formulation is still a matter of debate and probably depends not only on the ratio of different essential to nonessential amino acids (101), but also on the calorie to nitrogen ratio (94) and perhaps on the colon (48). Recent data from Tanaka et al has pointed to colonic bacterial synthesis of essential amino acids as a possible source of these nutrients in humans (106). A recent report has suggested that taurine may become a required amino acid in patients on long-term parenteral nutrition, and deficiency may result in impaired visual function (32, 72). Taurine has not traditionally been added to amino acid solutions because of a difficult solubility problem. Endogenous synthesis of the dipeptide carnitine may also be limited, particularly in infants; and carnitine deficiency may be a component of the hepatic steatosis associated with parenteral nutrition (34, 92). As discussed in the section on Ethical, Cost & Legislative Issues Relating to HPN, amino acid solutions are the most expensive infusion component for the HPN patient, and therefore it is highly desirable that we establish their exact requirements.

Mineral Requirements

The parenteral requirements for sodium, potassium, chloride, and bicarbonate equivalents (bicarbonate itself induces insoluble salts if added to nutritional solutions) are well understood by most clinicians (see Table 7). The only subtle problem for extreme short bowel patients is their abnormal losses from enteric secretions (see Table 6), which must be computed into the parenteral replacement.

The requirements for phosphorus and divalent cations are less precisely known, and a major issue in this respect is maintenance of bone tissue. Gastrointestinal losses of calcium, magnesium, zinc, and copper are significant in extreme short bowel patients because of diet-induced steatorrhea and because of loss of enteric secretions rich in divalent cations that are normally reabsorbed.

Table 7 Daily parenteral requirements & clinical and laboratory assessment of essential fatty acids, minerals and vitamins

Nutrient	Daily parenteral requirement adult range	Clinical assessment		Laboratory assessment		
		Metabolic function	Deficiency	Test	Normal	Deficient
Essential fatty acids	Uncertain ± 2–4% of calories	Components of all lipid membranes, precursor of prostaglandins	Scaly dermatitis	GLC[a] of plasma or red-cell membrane	Triene:tetraene ratio < 0.4	Triene:tetraene ratio > 0.7
Calcium	15–20 meq	Body content 1.5 kg, bone crystal (99%), blood clotting, nerve and muscle excitability	Osteomalacia Tetany	Atomic absorption or colorimetric	2.2–2.7 mmol/l (8.6–10.8 mg/dl)	< 2.2 mmol/l (8.6 mg/dl) if serum albumin normal
Phosphorus	300–600 mg	Body content 600 g, bone crystal (85%), ~ P bonds, chief intracellular anion	Osteomalacia, hemolytic anemia, ↓ HbO_2 dissociation, ↓ phagocytosis	Colorimetric	0.8–1.5 mmol/l (2.5–4.5 mg/dl)	< 0.8 mmol/l (2.5 mg/dl); severe if < 0.3 mmol/l (1.0 mg/dl)
Sulphur	As S-containing amino acids	Body content 175 g, occurs in methionine, cysteine, thiamine, insulin, chondroitin sulfate, etc.	Unknown	Not routine	No value available	No value available
Potassium	Varies, see Table 6	Body content 160 g, main intracellular cation	Muscular weakness, cardiac irritability, metabolic alkalosis	Flame photometer or ion selective electrode	3.5–5.0 mmol/l (3.5–5.0 meq/l)	< 3.5 mmol/l (3.5 meq/l); severe if < 2.5 mmol/l (2.5 meq/l)
Sodium	Varies, see Table 6	Body content 100 g, main extracellular cation	Circulating blood volume, BP, urine output	Flame photometer or ion selective electrode	135–145 mmol/l (135–145 meq/l)	< 130 mmol/l (130 meq/l) except if H_2O retention is primary problem
Chloride	Varies, see Table 6	Body content 79 g, main extracellular cation	Metabolic alkalosis	Colorimetric	98–106 mmol/l (98–106 meq/l)	< 85 mmol/l (85 meq/l)
Magnesium	10–30 meq	Body content 25 g, cofactor for many enzymes including phosphorylases, phosphotransferases (Na^+, K^+)-ATPase, vitamin D hydroxylases	Tetany, muscle weakness (secondary to hypokalemia and hypocalcemia)	Atomic absorption or colorimetric	0.5–1.0 mmol/l (1.3–2.5 mg/dl)	< 0.4 mmol/l (1.0 mg/dl)

Iron	1–2 mg	Body content 4 g, heme compounds, cytochrome enzymes, iron stores	Microcytic hypochromic anemia, immuno-competence	Atomic absorption or colorimetric	Serum iron > 10.7 μmol/l (60 μg/dl); TIBC > 45 μmol/l (250 μg/dl); plasma ferritin > 30 mg/dl	Serum iron < 9 μmol/l (50 μg/dl), TIBC[d] >54 μmol/l (300 μg/dl); plasma ferritin < 12 mg/dl
Zinc	3–12 mg	Body content 2 g, cofactor for many enzymes including carbonic anhydrase, alcohol dehydrogenase, carboxypeptidase	Growth retardation and hypogonadism: impaired wound healing and immuno-competence	Atomic absorption	10.7–18.4 μmol/l (70–120 μg/dl)	< 7.6 μmol/l 50 μg/dl) if serum albumin normal
Copper	0.3–0.5 mg	Body content 100 mg, cofactor for lysyl oxidase (collagen synthesis), cytochrome oxidase, tyrosinase	Anemia and neutropenia, scorbutic-like osteopenia in children	Atomic absorption	14.2–20.5 μmol/l (90–130 μg/dl)	< 7.9 μmol/l (50 μg/dl)
Iodine	100 μg	Body content 30 mg, component of thyroid hormones	Cretinism/myxedema	Thyroxine (T_4)	315–867 nmol/l (4–11 μg/dl)	<315 nmol/l (4 μg/dl) if binding protein normal
Manganese	2–5 mg	Body content 20 mg, cofactor for lipid, cholesterol, mucopolysaccharide	Abnormal clotting not corrected by vitamin K	Atomic absorption of whole blood	109–182 nmol/l (6–10 ng/ml)	< 90 nmol/l (5 ng/ml)
Chromium	15 μg	Body content 6 mg, part of insulin receptor mechanism	Glucose intolerance	Atomic absorption of plasma	38.5–76.9 nmol/l (2–4 ng/ml)	< 20 nmol/l (1 ng/ml)
Molybdenum	0.1–0.5 μg	Body content 5 mg, cofactor for xanthine oxidase	Confusional state secondary to increased methionine	Colorimetric of plasma	5.2–20.8 nmol/l (0.5–2 ng/ml)	< 5.2 nmol/l (0.5 ng/ml)
Selenium	50 μg	Cofactor for glutathione peroxidase (GP)	Muscle weakness, hemolytic anemia	Fluorometric of whole blood or GP activity of red cell	0.3 nmol/l (0.02 ng/ml)	< .02 nmol/l (0.15 ng/dl)
Cobalt	As Cobalamin	Body content 80 μg, metallocofactor for cobalamin (B_{12})	Unknown in man	Atomic absorption	34–85 nmol/l (2–5 ng/ml)	< 34 nmol/l (2 ng/ml)
Ascorbic acid	100 mg	Microsomal electron transport, tyrosine, tryptophan, and dopamine synthesis, steroid synthesis, hydroxylation of collagen proline and lysine residues; folic acid metabolism	Scurvy, perifollicular hemorrhages, bleeding gums, osteopenia, and subperiosteal hemorrhages; defective wound healing	Colorimetric analysis of a. serum b. leukocytes	 a. 28.4–56.8 μmol/l (0.5–1.0 mg/dl) b. 852–1703 μmol/l (15–30 mg/dl)	 a. < 5.7 μmol/l (0.1 mg/dl) b. < 397 μmol/l (7 mg/dl) ■

Table 7 Daily parenteral requirements & clinical and laboratory assessment of essential fatty acids, minerals and vitamins

Nutrient	Daily parenteral requirement adult range	Clinical assessment		Laboratory assessment		
		Metabolic function	Deficiency	Test	Normal	Deficient
Thiamin	3.0 mg (see text)	Cofactor (TPP) for transketolase pyruvate and ketoglutarate decarboxylase, oxidation of branched-chain ketoacids	High output cardiac failure, polyneuritis	Red cell a. transketolase activity b. TPP stimulation effect	a. 8–15 IU b. < 10% TPP effect	a. < 8 IU b. >20% TPP effect
Riboflavin	3.6 mg	Converted to electron acceptors and donators, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)	Cheilosis, glossitis, seborrheic dermatitis	Red cell glutathione reductase activity	< 1.2 EGR[b] activation coefficient	> 1.2 EGR[b] activation coefficient
Niacin	40 mg	Converted to electron acceptors and donators, nicotinamide dinucleotides (NAD, NADP)	Pellagra: pigmented dermatitis, ulceration of mucous membranes, CNS depression	Microbiologic determination of whole blood, fluorometric analysis of urine metabolites	Niacin: 32.5–73.1 μmol/l (4–9 μg/ml) 2-pyridone/N'methyl ratio > 2.0	< 24.4 μmol/l (3 μg/ml) < 2.0
Biotin	60 μg	Cofactor for carboxylation enzymes where CO_2 is added such as, pyruvate oxaloacetate, acetyl-CoA malonyl-CoA	Alopecia, seborrhaic dermatitis, neuritis	Microbiologic assay of serum	819–2047 pmol/l (200–500 pg/ml)	< 819 pmol/l (200 pg/ml)
Panthothenic acid	15 mg	Converted to coenzyme A	Irritability, burning parasthesias	Microbiologic assay of serum	684–1824 nmol/l (150–400 ng/ml)	< 684 nmol/l (150 ng/ml)
Pyridoxine	4.0 mg	Cofactor (PLP) for many enzymes including transaminases, phosphorylases, amino oxidases	Glossitis, polyneuritis seizures microcytic hypochromic anemia	Red cell GOT	EGOT[c] index < 1.5	EGOT[c] index > 1.5
Folic acid	400 μg (see text)	Cofactor for purine and pyrimidine synthesis and metabolism of serine, histidine, homocysteine, and ethanolamine	Megaloblastic defect of red blood cells and mucous membranes	Microbiologic assay of a. serum b. red cell	a. 6.8–20.4 nmol/l (3–9 ng/ml) b. 405–1362 nmol/l (150–600 ng/ml)	a. < 6.8 nmol/l (3 ng/ml) b. < 227 nmol/ml (100 ng/ml)

Cobalamin	5 μg	Methyl B_{12} involved in methyl donor reactions. 5'-deoxy-adenosyl B_{12} involved in carboxylation reactions	Megaloblastic defect of red blood cells and mucous membranes, central and peripheral neuropathy	Isotopic dilution or microbiologic assay	148–664 pmol/l (200–900 pg/ml)	< 111 pmol/l (150 pg/ml)
Vitamin A	3,300 IU	Light sensitive pigment in retina, epithelial maintenance (retinoic acid)	Night blindess and xerophthalmia, testicular atrophy, keratosis of skin	Colorimetric of fluorometric assay of serum	0.7–2.1 μmol/l (20–60 μg/dl)	< 0.7 μmol/l (20 μg/dl)
Vitamin D	200 IU	Calcium, phosphorus and possibly magnesium absorption from intestine, calcium deposition and mobilization from bone	Osteomalacia (rickets in growing children), muscle weakness	Radioimmunoassay of serum 25-(OH)D	26–208 nmol/l (10–80 ng/ml)	< 13 nmol/l (5 ng/ml)
Vitamin E	10 mg	Prevents peroxidation of polyunsaturated lipids	Hemolytic anemia of newborn, dystrophic changes of retina and posterior column nuclei	Colorimetric assay of serum in vitro, red blood cell peroxide hemolysis	0.02–0.03 mmol/l (0.8–1.2 mg/dl) < 10% hemolysis	< 0.01 mmol/l (0.5 mg/dl) > 20% hemolysis
Vitamin K	300 μg	Involved in synthesis of clotting factors II, VII, IX and X	Bleeding tendency presenting as epistaxis ecchymosis; gastrointestinal, urinary or CNS hemorrhage	No direct assay routinely available	Prothrombin time < 1 second prolonged over control	PT > 2 sec prolonged

[a]GLC = gas-liquid chromatography.
[b]EGR = erythrocyte glutathione reductase.
[c]EGOT = erythrocyte glutamic oxaloacetate transaminase.
[d]TIBC = total iron-binding capacity.

METABOLIC BONE DISEASE Normal mineralization of bone is dependent upon the interaction of several factors, including serum calcium and phosphorus concentration, parathyroid hormone (PTH), and vitamin D. A number of trace elements (aluminum, cadmium, strontium, flouride, vanadium, silicon) may also play a role in bone mineralization while others (copper, manganese) are necessary for formation of normal collagen and mucopolysaccharide (86, 111).

Reports of a metabolic bone disease developing in HPN patients first appeared in 1980 (60, 96). The disease was characterized by hypercalciuria, decreased bone mineralization, and patchy osteomalacia. Serum alkaline phosphatase levels were generally elevated, and serum calcium was normal or slightly increased. Serum phosphorus, immunoreactive PTH (IPTH), and 25-hydroxyvitamin D levels were normal. In a prospective study (96), 75% of patients had biopsy evidence of bone disease but only 30% developed clinical symptoms of insidious onset of bone pain in weight-bearing areas. No identifiable metabolic or biochemical features distinguished those patients with symptoms from those with subclinical disease.

The etiology of this HPN-associated bone disease remains speculative. Several theories have been proposed, each with some supporting data:

Decreased renal calcium reabsorption Sixty-five percent of patients on parenteral nutrition are in negative calcium balance with the greatest degree of calciuria occurring during the 12 hours of infusion. Hyperinsulinemia (21), carbohydrate loading (69), and high dietary protein intake (2) all stimulate calciuria by decreasing proximal tubular calcium reabsorption in the kidney (22). Since all these conditions can occur with HPN infusions, the role of glucose and protein loading during HPN in the etiology of hypercalciuria warrants further investigation.

Sulfate-induced hypercalciuria The amino acid solutions used in HPN infusions have a substantial sulfur content, and it has been suggested that an increased inorganic sulfate burden may produce the hypercalciuria seen in these patients. As early as 1959, methionine feeding was shown to cause a threefold rise in urinary calcium excretion (67). In recent work, Cole & Zlotkin (16) produced increased calcium excretion and decreased relative calcium retention by the addition of cysteine to parenteral nutrition solutions. The role of sulfur in producing hypercalciuria may be unique to parenteral solutions, as other investigators demonstrated no change in renal calcium reabsorption following oral feeding of sulfur-containing amino acids (7).

Altered vitamin D metabolism Despite normal levels of 24,25-dihydroxyvitamin D (24,25-$(OH)_2D$) and 25-hydroxyvitamin D (25-(OH)D), levels of 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$) have been strikingly de-

pressed (62, 98). This suggests an inhibition of 1-hydroxylation of 25-(OH)D and perhaps a form of vitamin D deficiency. Children with HPN osteomalacia have healed their bone lesions with very high doses of vitamin D (61). Conversely in adult patients, withdrawal of vitamin D resulted in decreased calcium loss, amelioration of symptoms, and improved indexes of bone mineralization (98). The significance of low $1,25\text{-}(OH)_2D$ levels is not clear. It may be that calcium and phosphorus infusion suppresses generation of $1,25\text{-}(OH)_2D$ either directly (110) or via suppression of PTH (40). Decreased 1-hydroxylation is known to occur in renal failure, but renal function was normal in all these patients. Since vitamin D is supplied as vitamin D_2, the circulating vitamin D metabolites are mainly in the vitamin D_2 form (62). It is possible that D_2 and D_3 metabolites are not completely interchangeable in terms of their effect on bone metabolism.

Role of PTH The average HPN patient requires 300–400 mg of calcium infused daily with individual adjustments for excessive losses. PTH suppression has largely been regarded as secondary to calcium infusion, as PTH levels were seen to rise in one patient in whom calcium was withdrawn (62). In addition, low levels of PTH as seen in hypoparathyroidism are not associated with defective bone mineralization.

Role of phosphorus Although low serum phosphate has been associated with osteomalacia (60, 96), in these patients phosphorus levels were maintained in the normal range by infusion of 400–700 mg phosphorus daily. Occasional elevations of serum phosphorus may play a role in suppression of $1,25\text{-}(OH)_2D$ and 1-α-hydroxylase (37).

Role of aluminum Recognizing a similarity between uremic osteomalacia and HPN-associated bone disease, Klein et al (59) examined aluminum status in these patients and the HPN solutions. Aluminum levels in 10% casein hydrolysate solutions was 2313 mg/liter resulting in a substantial load of aluminum in patients using this protein source. These patients had marked elevation of aluminum in serum, urine, and bone. Further studies by Ott et al (83) demonstrated stainable aluminum on bone biopsy in all patients on casein hydrolysate. This was associated with decreased bone formation on surfaces containing aluminum. These data are consistent with the hypothesis that aluminum acts as a toxin, inhibiting mineralization. Since not all HPN patients with bone disease receive casein hydrolysate, it is likely that this is only one of the factors involved in the bone disorder(s) of HPN patients.

Other trace elements It is difficult to exclude the possibility that in the current HPN solutions there is an unrecognized trace element excess or deficiency. Of the trace elements known to play a role in bone mineralization, cadmium and

strontium are present only in trace amounts in HPN solutions (40), fluoride levels are reported to be normal in most HPN patients with bone disease (16), and vanadium and silicon levels remain to be evaluated. Copper and manganese, which are important in collagen and mucopolysaccharide synthesis, have been measured in many patients with bone disease and found to be normal (60, 96).

OTHER MINERALS AND TRACE ELEMENTS Parenteral requirements for *magnesium* are 20 meq/day in adults with normal kidney function and no excessive gastrointestinal or urinary losses (diuretics, aminoglycosides, amphotericin, *cis*-platinum, ethanol). Patients with extreme short bowel and steatorrhea may require 30–40 meq/day. Clinical signs of deficiency include muscle spasms, seizures, cardiac arrhythmias, and refractory hypokalemia and hypocalcemia (89).

Zinc deficiency in long-term parenteral nutrition patients has been reported (54, 65, 81, 116). A depression, poor wound healing, seborrheic dermatitis especially around the mouth, and alopecia are the common signs reported. Immune defects, primarily of cell-mediated immunity, have been observed in zinc-depleted patients. Since zinc is the metallo-cofactor for at least 70 enzymes, including several related to protein synthesis, it is obviously a key nutrient in patient rehabilitation. Recently Cunnane et al demonstrated a role for zinc in linoleic acid desaturation and prostaglandin synthesis (19). This may account for the similarity between an essential fatty acid and zinc deficiency skin rash. In a series of balance studies, Wolman et al (117) showed that gastrointestinal loss of zinc depended on the volume of the contents lost and the source of these contents. The mean concentration in high small bowel contents was 3.6 μg/g and in the distal ileum was 15.2 μg/g. Since normal subjects concentrate intestinal volume about eight times in that bowel distance, the relative loss of zinc in extreme short bowel syndrome is high, although it decreases somewhat in zinc-depleted patients (117). Wolman's results showed that an intravenous zinc intake of 3 mg/day was adequate if stool volume was less than 300 ml/day; but with their much greater enteric losses, short bowel patients required at least 12 mg/day. In normal subjects urinary zinc losses are small; but they can become significant in HPN patients, especially during the nutrient infusion. This may reflect the rapid presentation of infused zinc to the kidney. Urinary losses are further increased because of the chelating effect of sugar-amino compounds if parenteral solutions are heat-stabilized or stored premixed for prolonged periods of time (30).

Copper balance studies in parenteral nutrition patients (97) indicate a requirement of 0.3 mg/day with normal amounts of gastrointestinal excretion and 0.4–0.5 mg/day in the presence of excessive diarrhea or increased losses through stomas or fistulas. This reflects in part the fact that copper is principally excreted in bile; under normal conditions, partial reabsorption occurs, but the

afferent arm of this enterohepatic cycle is lost in extreme short bowel patients. This is equally true for other nutrients with an enterohepatic cycle, such as cobalamin, folic acid, and vitamin D.

In adult patients, copper deficiency has presented chiefly as a leukopenia and microcytic hypochromic anemia (25). Children have had this same hemopoietic picture and osteopenic bone disease (39).

The importance of *selenium* in human nutrition has been recognized in recent years. In animals, selenium deficiency can cause liver necrosis (rat), white muscle disease (sheep), and an exudative diathesis (chicken) (10). In 1979, Van Rij (113) described muscular pain in an HPN patient. This report was followed by others of cardiomyopathy developing in association with selenium deficiency (17, 52) in patients on HPN. Since these early reports, other workers have described similar syndromes (28, 55, 103). The mechanism of injury in selenium deficiency is not completely clear. Selenium is an essential constituent of glutathione peroxidase (GSHPx), which functions to remove H_2O_2 and lipid peroxides, thereby preventing oxidative damage to tissue (120). The accumulation of lipid peroxides has been postulated as the mediator of tissue damage. In addition, a selenoprotein that may play a role in the muscle dysfunction has been isolated from the muscle of lambs (102).

There is very little selenium present as a contaminant of parenteral nutrient solutions (121) and thus, with unsupplemented formulas, patients on HPN showed a high incidence of low plasma selenium and erythrocyte GSHPx levels. This could develop as early as four weeks after initiation of HPN (64). Balance studies have shown greater retention of selenium as selenomethionine than as sodium selenite (112). This may be explained by recent reports that the presence of copper or high ascorbic acid (1000 mg/liter) concentrations in the nutrient solution leads to precipitation of selenium from selenite, resulting in significant loss of selenium (99). Current recommendations are for 20–50 μg/day of selenium as the organic salt.

Chromium is required for normal carbohydrate metabolism. Inorganic chromium compounds have little or no biologic activity (5) but are converted in vivo to glucose tolerance factor (GTF). GTF functions physiologically to potentiate the action of insulin by facilitating the interaction between insulin and its receptor sites (35). Chromium deficiency has been reported in HPN patients (31, 49) manifested by weight loss, glucose intolerance, and in some cases peripheral neuropathy or encephalopathy. Insulin levels were not elevated. With chromium supplementation, clinical improvement was rapid, occurring within three days. Based on a daily excretion of 5–10 μg chromium/day, it has been recommended that adults on HPN receive 15–20 μg chromium/day.

Molybdenum is the metallo-cofactor for xanthine oxidase and sulfite oxidase (53). In 1981, Abumrad (1) reported a probable case of molybdenum deficiency occurring in a patient on HPN. Clinical signs included tachycardia, tachypnea, severe headache, night blindness, nausea, vomiting, and central sco-

tomas associated with the nutrient infusion. These symptoms were associated with abnormal metabolism of sulfur-containing amino acids and purine compounds, and the metabolic defects cleared following molybdenum supplementation of 300 μg/day.

The parenteral nutrient requirements for *manganese* have not been established. Early studies by Doisy (24) demonstrated a clotting abnormality in a patient with coincident deficiencies of manganese and vitamin K. A similar state unresponsive to vitamin K administration was produced in chicks. Attempts by Leach (66) to repeat these findings have been unsuccessful.

The parenteral requirement for *iodine* is estimated to be about 100 μg/day. Since HPN patients have constant skin contact with antimicrobial iodine-containing solutions, it is likely that they receive adequate systemic iodine by contamination. The obvious functional test is thyroid hormone measurements and these have remained normal in the 55 Albany HPN patients over the past 10 years who receive 100 μg/day of iodine.

Vitamin Requirements

Although there are published guidelines (4) for parenteral vitamin requirements (Table 7), just as there are for trace elements (3), the data on which these recommendations are based are sparse and derived primarily from studies on hospital-based patients receiving parenteral solutions for only a few weeks and by constant 24-hour infusion (13, 57, 70, 80, 105). Such patients are frequently ill with multiple metabolic disturbances and are in various phases of nutritional repletion. Under these circumstances, interpreting circulating vitamin levels is problematic. In contrast, home patients usually are metabolically stable and receive their nutrients over a 12-hour diurnal cycle. This allows for blood sampling during a noninfusion period. In Albany (44), we evaluated the *ascorbic acid, thiamin, niacin, pyridoxine,* and *folic acid* status of eight stable HPN patients (Table 8). Six patients received these vitamins as a twice-weekly bolus; two others, who required only parenteral fluid and electrolytes to remain weight-stable, received none of these vitamins parenterally. All eight patients maintained an adequate vitamin status. Blood thiamin levels tended to be low, but since erythrocyte transketolase activity remained normal, this suggested an adequate functional thiamin status. These results indicated that HPN patients can safely receive these five vitamins as a twice-weekly bolus rather than daily, a possible advantage for home-mixing patients; and that short bowel patients who maintain their weight without intravenous calories and amino acids also assimilate from their diet adequate amounts of these proximally absorbed, water-soluble vitamins. It is important to emphasize that these patients were receiving an older multivitamin preparation[3], which provided nearly five times

[3]5 ml MVI Concentrate®, USV Pharmaceutical Corporation, Tuckahoe, N.Y.

(14 mg/day) the currently recommended parenteral allowance of thiamin (3 mg/day). The adequacy of this smaller dose needs to be evaluated.

Parenteral nutrient infusions have been known to cause acute *folate* deficiency with megaloblastosis and even death (6, 107, 115). Since folate stores normally last at least three months, the acute drop in folate is thought to represent an effect of high methionine on the interconversion of folate metabolites (18, 108). Nichoalds et al (80) showed that hospitalized patients could not maintain a normal serum folate on 300 μg/day but did so on 600 μg/day. Current parenteral recommendations are for 400 μg/day, and as with thiamin, the adequacy of this dose remains to be established.

There have been several reports of *biotin* deficiency in long-term parenteral nutrition patients (68, 73, 76). Biotin deficiency is characterized by alopecia, a rash around the nose and mouth, blepharitis, conjunctivitis, lethargy, depression, and parasthesias. Some biotin-deficient patients may have been expressing a genetic biotin dependency state (56), but others are more clearly deficient because of prolonged biotin-free parenteral nutrition and suppresion of gut flora by broad-spectrum antibiotics (68). Under normal circumstances, biotin synthesized by gut bacteria is probably available to the human host. This may also be true for cobalamin.

We reported the development of clinical night blindness in an HPN patient receiving premixed formula containing 3000 IU/day of *vitamin A* (45). In vitro

Table 8 Vitamins studied, the amount infused semiweekly over 12 hr, the equivalent daily IV dose, and the recommended daily oral allowance and parenteral allowance in eight-stable HPN patients[a]

Vitamin (mg)[b]	Semi-weekly IV bolus	Equivalent daily IV dose	Recommended daily oral allowance[c]	Recommended daily parenteral allowance[d]
Ascorbic acid	500	140	60	100
Thiamin HCl (thiamin)	50 (39)	14 (10.9)	(1.4)	(3)
Niacin	100	28.6	18	40
Pyridoxine HCl (pyridoxine)	15 (12.3)	4.3 (3.5)	(2.2)	(4)
Folic acid	5	1.4	0.4	0.4

[a]Source: Scribner (93).

[b]Five ml MVI concentrate® supplies thiamin and pyridoxine as the hydrochloride salt which provides 78 and 82%, respectively, of the simple vitamin. MVI also supplies vitamin A 10,000 IU, vitamin D_2 1000 IU, riboflavin 10 mg, dexpanthenol 25 mg, vitamin E 5 IU. The 5 mg of folic acid was supplied by 1 ml of Folvite® (Lederle Laboratories, Pearl River, NY). These patients also received 100 μg/week of cobalamin as Rubramin PC® (Squibb, Princetown, NJ) and biotin 60 μg/day (Roche Laboratories, Nutley, NJ)

[c]Recommended dietary allowances. Food and Nutrition Board, Washington DC: National Academy of Sciences, 1980.

[d]Source: American Medical Association (4).

studies showed that the vitamin A disappeared from the stored solution. This loss could be explained in part by sorption of the vitamin onto the plastic container and was probably partly due to oxidation of the vitamin A to a physiologically inactive epoxide. A similar loss has also been described from glass containers (36), and the loss from the solution may be increased by light (95). If the vitamin A is added just before the parenteral infusion is started, little activity is lost and 3000 IU/day sustains normal dark adaptation. This implies that HPN patients receiving pharmacy-mixed bulk orders must learn to inject their vitamin formulation just prior to infusing, the way home-mixing patients do.

The controversies that surround parenteral *vitamin D* have been discussed above, in the section on metabolic bone disease.

Earlier multivitamin formulations (MVI) provided only small doses of *vitamin E* (1.5 mg/day of *dl*-α-tocopherol). Studies by our group in Albany (46) and by Thurlow & Grant (109) showed low serum vitamin E levels in a majority of HPN patients (70%), and many of these patients had abnormal red cell peroxide hemolysis, decreased adipose tissue vitamin E (46), and platelet hyperaggregation (109). In both centers, these problems were corrected in two weeks by 50 mg of intravenous *dl*-α-tocopherol daily. Newer parenteral vitamin preparations provide 10 mg of *dl*-α-tocopherol/day. In a recent study, we found that in 20 HPN patients this amount adequately maintained serum vitamin E levels and normalized peroxide hemolysis (<20%) (Betzhold, J., Howard, L., Chu, R., unpublished data). Does vitamin E deficiency cause a clinical disorder? In 1978, before the larger parenteral doses of vitamin E became available, we observed severe ataxia and pigmentary degeneration of the retina with massive bilateral visual field scotomata in a 64-year-old man with long-standing steatorrhea (47). This patient had received parenteral supplements of cobalamin and all fat-soluble vitamins except vitamin E. His serum vitamin E was barely detectable and his peroxide hemolysis was 100%. Nine months after starting vitamin E supplementation, the patient started to improve neurologically, and after twenty-four months his clinical symptoms were minimal. While a similar syndrome has been described in children (78, 88) and young adults with congenital malabsorption syndromes (27), this case history emphasizes the fact that this syndrome can occur de novo in the adult nervous system. While this is undoubtedly a rare syndrome, its description is significant because it is most likely to appear in patients referred for HPN after a long course of gastrointestinal insufficiency.

Little is known about the parenteral requirements for *vitamin K*. Ten mg of parenteral vitamin K per month has sustained normal clotting function in the Albany HPN patients. It is possible that bacterially synthesized vitamin K can be absorbed through the human colon, as in rats (41).

ETHICAL, COST, AND LEGISLATIVE ISSUES RELATING TO HPN

HPN clearly offers dramatic rehabilitation for patients with severe bowel dysfunction. Patients who ten years ago would have died after prolonged hospitalization now are restored in a few months to productive lives. Nevertheless, starting a patient on HPN is a major physical, psychological, and financial responsibility. It is a decision that involves the patient, his family, and also society at large, since most long-term HPN survivors are ultimately supported in part by public funds. For these reasons HPN patient selection is critical, and the emerging criteria deserve professional and public scrutiny.

Ethical Issues

Should HPN be available to all patients who are unable to survive because of severe bowel dysfunction? Should it be started in children who have no real likelihood of ever being weaned from nutrient infusions? Should there be an age limit for starting HPN? Should HPN be withheld in rapidly progressive diseases with no possibility of long-term rehabilitation?

In many respects, HPN or the "artificial gut" has a status similar to renal dialysis, or the "artificial kidney", before Title 19 funding. Before federal money was directly available, communities assigned the distribution of limited dialysis resources to committees with lay, religious, and medical representation, and certain criteria for age and prognosis were developed for patient selection. It may be reasonable to suggest that a similar approach be used for HPN.

Table 9 lists the patient selection guidelines used by many programs. Since HPN places a heavy responsibility on the patient and his family, the rehabilitation it affords must be perceived by these individuals as appropriate. For the patient who experiences unrelenting pain, is bedridden, or is mentally incompetent, intervention with HPN would not seem reasonable. Families likely would reject the obligation, and nursing homes rarely have the capacity to provide such specialized care.

Table 9 Criteria commonly used for selecting HPN candidates

Potential for meaningful rehabilitation
Patient's desire and ability to accept responsibility for aseptic infusion techniques
Ability of family or friends willing to support patient
Availability of medical backup for both acute problems and long-term supervision
Financial resources so the patient can afford HPN without great distress or anxiety

Ethically, the most difficult areas are cancer patients and infants with severe bowel dysfunction. At the Cleveland Clinic (104), no patient with metastatic cancer or a life expectancy of less than one year is given HPN therapy. In Albany, several patients with metastatic bowel obstruction or fistulae have been sent home on HPN, especially where there may be some response to chemotherapy, the patient is young and needs to put his affairs in order, is relatively pain-free, and is likely to live at least six months. For bowel-obstructed cancer patients with a shorter life expectancy, a central line for simple hydration may also be justified if the patient and the family prefer to manage the terminal period at home.

Randomized prospective studies (8, 91) do not show that nutritional support improves longevity in cancer patients unless surgery is required, in which case preoperative total parenteral nutrition improves postoperative morbidity and mortality in malnourished cancer patients (79) just as it does in other cachectic states (77). Longevity may not be the most critical issue to a patient with a limited life expectancy; an improved sense of well-being and time spent at home may be valued more highly. At present few studies provide guidance for these difficult decisions.

The issue of the infant and HPN is equally problematic. Most eligible infants have some form of extreme short bowel syndrome (11, 14) and a significant potential for adaption and hypertrophy of the remaining segment. Successful adaption depends on what segments remain. The infant with massive jejunal resection but some ileum and the ileocecal valve usually does well. Unfortunately, with gastroschisis, mid-gut volvulus, long segment Hirschsprungs, or massive resection for necrotizing enterocolitis, frequently only the proximal jejunum is spared. In this situation, ultimate bowel compensation is far less certain. It is important to present as clear a picture as possible to the infant's family (58). Perhaps such discussion should be preceded by an exploration of the family's social and fiscal resources, so that parents who cannot provide such demanding care are not subject to guilt-related pressures. If a child is sent home on parenteral nutrition (6 of the 55 HPN patients discharged from Albany are children), more elaborate home planning is essential. For example, in very young children, we have found that a catheter tunnelled onto the back may be a great advantage, preventing the child from pulling at his line and contaminating the catheter. Most parents need a respite facility where they can safely leave the child for short periods. While there are many clinical situations where temporary relief by trained personnel can make a domicilary effort succeed and avoid the more costly alternative of rehospitalization, such resources as yet are not well developed for HPN families.

In our experience HPN is not successful even in adult patients if the support of family or close friends is missing. It may seem unfair that an individual's fate

should depend so strongly on having this social support, but in Albany the 10% of patients with poor social support account for over 50% of the readmissions.

The central goal in HPN is restoration of physical well-being and independence for the patient. While a physician has to accept overall medical responsibility, nurses and pharmacists play important roles in supporting the HPN patient. In order to maximize independence wherever possible, the patient should accept full responsibility for his infusion technique, with members of the family taking over only in special circumstances such as an intercurrent illness or deterioration from the underlying disease. If nurses are asked to visit these patients at home and become involved with their infusion techniques, such nurses should also be trained by the in-hospital team so that the patient does not receive conflicting advice and so that communication channels to the responsible physician are well maintained. HPN patients and their families must be educated about the acute and potentially life-threatening problems that can develop at any time. For example, if the patient rolls over in bed at night and disconnects the infusion line, he is immediately at risk for bleeding, air embolism, reactive hypoglycemia, and infection, especially if he panics and reconnects a contaminated line. In such circumstances, the patient or the family must act immediately. Only later is there time to review this management with the medical team at the hospital. For these reasons, the phase of in-hospital education is extremely important and cannot be relegated to the post-discharge visits of nurses or pharmacists. Whether interval retraining is appropriate has not been studied. Many patients do cut corners once they are familiar with their infusion technique. However, the low sepsis rate in HPN patients (one episode every four years) argues against the need for mandatory retraining. Perhaps an annual outpatient workshop or occasional supervision of the patient at home is appropriate. Because of the low incidence of HPN-related complications, only multicenter studies can answer these questions.

Although HPN patients have to deal with their own acute emergencies, medical support must be available constantly, and if the patient is more than an hour away from his supervising physician, it is essential that a more local physician agree to accept emergency responsibility. The geographic distribution of the 169 hospitals currently training HPN patients has not yet been published. One hopes these hospitals are sufficiently widespread to make HPN training potentially available to all US patients. Since only a few of these centers have laboratories capable of measuring both macro and micro nutrients, some regional plan for annual or biennial nutrient assessment available to all HPN patients is desirable, at least until parenteral nutrient requirements are better understood.

The ethical issue of the age at which HPN should be started is not easy to resolve. Two octogenarians in the Albany HPN program live comfortably with

their families. As in the pediatric age group, elderly patients rely heavily on family involvement; hence the need to explore, in advance, the family situation and develop respite care arrangements is particularly important.

Perhaps there are no absolute criteria for who should receive HPN—only general guidelines and a need to examine each situation on its own merits. This responsibility is best handled by an experienced HPN team consulting with those who are closest to the patient. Since HPN is an elaborate undertaking, it should not be presented to the patient until the background feasibility assessment has been done and the outlook for a successful undertaking appears good.

Cost Issues

Compared to the number of hospital-based parenteral nutrition patients, the number of home patients is small. However, because of their chronicity, these home patients use large quantities of parenteral nutrient solutions. These solutions, and the tubing and bags needed to deliver them, account for 95% of the costs of the patient at home. Table 10 summarizes these costs in 1981 for the 89 HPN programs reporting to the Registry of Patients on Home Total Parenteral Nutrition. As shown in Table 10, a HPN program costs about 20% more if the solutions are premixed by a hospital or commercial pharmacy. In 1981 about half the patients at home used such premixed solutions. Since there is no difference in complication rates between patients on the home-mixed versus pharmacy-mixed solutions (see Table 4), special justification is needed for providing patients with the more expensive premixed solutions. In 1973 when the Albany program started, the hospital pharmacy mixed our HPN patients' solutions in bulk, and the patients collected their supply every two weeks. In 1976 when the program had grown to ten patients, the pharmacy could no longer reasonably perform this function and home mixing was introduced. To our surprise this added task was not perceived as particularly difficult by the patients, who rapidly got their solution mixing time down to 10–15 minutes per day. More important, complications did not increase; in fact, as an added advantage, patients stayed knowledgeable about their various additives and could readily make formula changes if told to do so. In 1981, of the 89 programs reporting to the Registry, 31 used pharmacy-mixed solutions exclusively. This suggests that the type of program was determined more by the physicians' lack of experience with home mixing than by specific patient need. Registry data shows that mean training time required before discharge is longer for patients learning home mixing (30.4 $\pm$ 17.8 hours) than for those being provided with pharmacy-mixed solutions (21.6 $\pm$ 16.9 hours), and as mentioned in the section on The Current Experience with HPN, hospital readmissions tend to last a few days longer for the home-mixing patient (18.3 days compared to 11.3 days). These differences in hospital costs might justify pharmacy mixing for the rather short-term patient. In Albany we have used

Table 10 Annual cost of HPN in 1981[a]

Individual items	Mean Cost ($)	Range ($)
Infusion pump	2,057	0–18,000 (Free loan)
Supplies		
Home-mixed solutions	37,237	14,560–96,000
Pharmacy-mixed solutions	47,338	16,560–127,032
Physician or clinic fees	412	52–2,000
Laboratory test fees	538	75–1,200
Total annual cost of HPN ($)		
Home-mixed solutions	39,311	
Pharmacy-mixed solutions	49,939	

[a]Source: Home TPN Registry

pharmacy mixing for the elderly patient who has trouble measuring out additives with syringes and for the patient who has frequent sepsis. This accounts for only 10% of patients in the program, however.

Most programs provide their patients with disposable equipment to minimize the risk of infection. Controlled studies are needed to determine whether any of this equipment could be recycled safely. Even more important in terms of potential dollars saved is accurate assessment of parenteral nutrient requirements (See section on HPN Nutrient Requirements), especially the amino acids, hypertonic dextrose, and parenteral fat solutions which, in Albany patients, account for 40%, 12%, and 10%, respectively, of the overall HPN cost.

Long-term cost saving should be important to patients and professionals alike. The wide variation in annual cost between different programs ($14,560–127,032 in the 1981 Registry report) suggests a need for some type of peer review, because unnecessary expense certainly invites federal and third-party restrictions.

Legislative Issues

Because HPN is expensive and if extended for many years exceeds most private health insurance coverage, most long-term survivors must ultimately depend on federal funds. Moreover, the federal funding (Medicare) for persons under the age of 65 requires that the patient be designated totally disabled for a 24-month period to become eligible for social security benefits and medical assistance. If the patient who needs HPN has no private insurance and no fiscal resources with which to survive the 24-month period, then he is often temporarily eligible for a small supplemental income and state-administered medical assistance (Medicaid).

A Catch-22 problem for many HPN patients is the designation "totally disabled." The experience in both our program and the Cleveland program is that 80% or more of the noncancer patients can resume work or caring for their families. Despite such rehabilitation, few HPN patients can resume their original job or even less exacting work because their huge medical expenses and potential for acute medical setback make them too great a liability for employers.

It would be rational to treat HPN patients like renal dialysis patients, providing Title 19 compensation for their extraordinary medical expenses while encouraging their social and psychological recovery by promoting, whenever possible, their return to work. Unfortunately the federal experience with renal dialysis is that government funding enormously expanded dialysis programs and escalated the costs far beyond what was initially conceived. Currently there are 70,000 dialysis patients nationwide, costing $1.8 billion per annum. Because of this experience, Congress has been understandably reluctant to place similar chronic medical disorders, such as HPN, in the Title 19 category. This reluctance may also reflect a concern by legislators over the current lack of agreement within the medical profession about which patients qualify for HPN. This uncertainty particularly relates to patients with cancer.

For those HPN patients whose physical rehabilitation and private health insurance allow them to return to work, the social benefits are normally substantial. Thus it would seem imperative that federal and state funding mechanisms should also be developed to help HPN patients on Medicaid or Medicare to achieve reentry into the work force without penalizing and destabilizing them by withdrawing support for their extraordinary health costs.

In California, a Senate bill (Senate Bill No. 1263) has been passed to extend medical benefits to cover hyperalimentation costs. This is free for a totally disabled person in a family unit with a net worth of less than $5,000 and charges the person 2% of the cost for each $5,000 of additional net worth up to $250,000, at which point the person is liable for 100% of the cost. If the individual can work, he is still eligible for MediCal support after first applying for any available private health insurance. Such a person is liable to pay 1% of the cost for each $5,000 of family unit net worth up to a maximum of $500,000.

In New York State a similar bill, introduced in April 1983 (Senate Bill 5751), is currently in the Social Services Committee. This bill may take many years to become law, but it is an important start.

It is hoped that these fiscal and legislative issues will soon be solved so that many parenteral nutrition patients can return to fully productive lives. Such patients need the assurance that their medical costs are covered, so that terrible financial anxiety is not added to the psychological and physical burdens they already carry.

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