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Original Communications

Autopsy Tissue Trace Elements in 8 Long-Term Parenteral Nutrition Patients Who Received the Current U.S. Food and Drug Administration Formulation

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ABSTRACT. Iron, zinc, copper, manganese, chromium, and selenium levels were measured in autopsy tissues of 8 people with short bowel syndrome who received home parenteral nutrition (HPN) and the U.S. Food and Drug Administration (FDA)–approved trace element formulation for an average duration of 14 years (range, 2–21). Iron, zinc, copper, manganese and selenium were measured by inductively coupled plasma methods; chromium, by graphite furnace atomic absorption spectrometry. The levels in the 4 tissues studied, heart, skeletal muscle, liver, and kidney, were compared with levels in 45 controls who died without chronic gastrointestinal disorders. Results showed normal HPN patient values for iron and selenium, mild elevation of zinc, and major elevations of copper, manganese, and chromium. The implications of these results for trace-element supplements in long-term PN adult patients are discussed, and the need for reformulation of commercially available multi–trace element products in the United States is stressed. (*Journal of Parenteral and Enteral Nutrition* **31:**388–396, 2007)

In the early years of parenteral nutrition (PN), physicians hoped they could meet their patients' parenteral trace element requirements by periodically infusing plasma or blood or by contaminants known to exist in the protein hydrolysates then used as a source of amino acids.[1] Over time, and with the use of purified crystalline amino acids, more information accrued about the critical function of these micronutrients, and eventually guidelines for routine parenteral supplements of zinc, copper, manganese, chromium,[2] and later selenium[3,4] were published. These supplements are especially important for patients receiving long-term PN. In long-term nonsupplemented patients, deficiency syndromes of zinc,[5,6] copper,[7–9] chromium,[10,11] and selenium[12–14] have been reported. Although human studies with purified diets suggest a manganese deficiency syndrome can occur,[15] this has never been described in the parenteral setting. However, there are major concerns about the infusion of excess manganese.[16–18]

The task of assessing trace element adequacy or excess in PN patients is not easy. For a few elements, such as iron, functional tests are available that can assess both adequacy and excess. For selenium, erythrocyte glutathione peroxidase activity measures deficiency but not excess.[19] For zinc, copper, manganese, and chromium, functional tests are not yet clinically available.

While measuring plasma or serum trace element levels may indicate deficiency or excess in patients not receiving a trace element infusion, balance studies have shown that plasma or serum values are not reliable indicators of body stores or nutrient adequacy in patients receiving daily trace element infusions.[20–22] Moreover, although patients at home may be stable, if there is an acute phase reaction to infection or inflammation, this causes redistribution of elements, especially zinc, copper, selenium, and iron.[23]

To provide more information about parenteral trace element requirements, we measured iron, zinc, copper, manganese, chromium, and selenium levels in tissues obtained at autopsy from patients who received long-term PN for short bowel syndrome. Their tissue levels are compared with age-matched controls who died without chronic gastrointestinal disorders.[24,25]

MATERIALS AND METHODS

Patients

The autopsy tissues used in this study came from 8 extremely short bowel patients (≤110 cm of proximal small bowel). All patients had been part of the Albany Medical College home parenteral nutrition (HPN) program, which started in 1973. The autopsies were spread over a period of 10 years.

The protocol for measuring trace elements in autopsy tissues was approved by the institutional review board for human studies and given exempt cat-

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TABLE I
Characteristics of the 8 home parenteral nutrition patients

Patient number (gender)	1 (M)	2 (F)	3 (M)	4 (M)	5 (M)	6 (F)	7 (M)	8(M)
Diagnosis leading to short bowel syndrome	Bowel ischemia	Crohn's disease	Bowel ischemia	Crohn's disease	Bowel ischemia	Crohn's disease	Crohn's disease	Bowel ischemia
Remaining bowel	80-cm Jejunum, + ½ colon	110-cm Jejunum, no colon	55-cm Jejunum + ½ colon	80-cm Jejunum, no colon	80-cm Jejunum + ¾ colon	80-cm Jejunum, no colon	80-cm Jejunum + ¾ colon	Duodenum + ½ colon
Years receiving PN	12	20	20	20	10	21	15	2
Age at death	29	77	69	60	72	69	78	38
Cause of death	Suspected opiate overdose	Cardiomyopathy and CHF	Catheter sepsis	Catheter sepsis	Broncho pneumonia	Broncho pneumonia	Liver failure	Liver failure
Other disorders	Recurrent catheter sepsis, osteomyelitis	HTN	Chronic renal disease	Kidney failure due to amyloidosis, on dialysis	Kidney failure due to arteriosclerosis, on dialysis	Cirrhosis, HepC		
Interval between stopping full PN and death	0	4 wk	0	0	4 wk	4 wk	2 wk	0
Volume PN L/d	2.5	3.5	2.5	2.2	2.0	3.5	2.5	2.0
Trace elements added/d*								
Zinc, mg	14	14	14	14	11	14	14	11
Copper, mg	1.4	1.4	1.4	1.4	1.4	1.4	1.4†	1.4†
Manganese, μg	700	700	700	700	700	700	700†	700†
Chromium, μg	14	14	14	14	14	14	14	14
Selenium, μg	85	85	85	85	85	85	85	85

CHF, congestive heart failure; F, female; Hep C + = positive hepatitis C; HTN, hypertension; M, male; PN, parenteral nutrition.
*Trace elements added per day receiving HPN. Patients 1 and 4 were receiving HPN 5 d/wk, the others were receiving 7 d/wk. Bowel ischemia in the 2 younger patients (1 and 8) was due to trauma, gunshot wound in 1, and an auto accident in 8. Four of these 8 patients received a blood transfusion at the time of their initial bowel resection. Later in the course, only 3 required parenteral iron, and then for only a few months.
†Discontinued when patient developed elevation of serum bilirubin. Patient 7 died 8 months later; patient 8 died 2 months later.

egory 4 status because it did not involve living persons and the individual's identity is withheld. The study was discussed with 7 of the patients and their families before their demise, and advance permission for autopsy was given and subsequently signed by the nearest of kin. Patient 1 died acutely from a suspected opiate overdose, and his parents gave permission for the autopsy.

Table I lists the patients' underlying disease that led to surgical resection and short bowel syndrome; it also gives the length of the remaining bowel, the years receiving HPN, age at death, cause of death, and interval between stopping full PN and death. Table I also gives the volume of PN in L/d and the trace element amounts added per day of HPN. The trace elements routinely given were zinc, copper, manganese, chromium, and selenium (1.2 mL/d Multiple Trace Element 5 Concentrate plus extra zinc to replace ostomy losses). (The initial formulation was manufactured by Lyphomed, Fugisawa USA Inc, North Deerfield, IL; the current formulation was manufactured by American Regent, Inc, Shirley, NY. Trace element content remained the same and meets the U.S. Food and Drug Administration [FDA]–approved standard.[2]) Iron was given only if the patient had laboratory evidence of iron deficiency. The trace element content of the oral diet of these 8 patients was not monitored, but patients were advised not to take oral mineral and vitamin supplements.

The trace element determinations were done by the Trace Element Unit in Glasgow, Scotland. The results from these 8 short bowel patients were compared with tissue trace element levels in 45 control subjects studied and published earlier by the same laboratory.[24,25] Twelve controls were young healthy accident victims (age range, 18–41 years)[24] and 33 were elderly subjects who died without chronic bowel disease or artificial feeding (age range, 69–94 years).[25]

Tissue Sample

At autopsy in New York, 2-×-2-cm cubes (approximately 5 g wet weight) of heart, skeletal muscle, liver, and kidney were removed using clean stainless steel scalpels and forceps. The samples were placed in acid-washed polyethylene containers and stored in a −70°C freezer until all 8 patient samples were collected. The samples were then shipped frozen to the Trace Element Unit, Biochemistry Department, Royal Infirmary Glasgow, Scotland. The frozen samples were allowed to thaw partially and then were trimmed with a titanium scalpel to remove outside surfaces. The samples were then refrozen and freeze dried. Samples of the dried tissue (about 0.2 g) were digested in a quartz pressure vessel with 2 mL of ultrapure nitric acid at 80 bars pressure in a PMD microwave digester (Anton PAAR KG, Graz, Austria) for 10 minutes at power setting 8. The samples were completely mineralized. The digest was made up to 25 mL with deionized water. A sample of NIST 1577b, bovine liver, was included with each batch to test the analytical veracity of the data (see Table II). For iron, zinc, copper, manganese, and chromium, aliquots were diluted (1 + 5) with 18 Mohm water and spiked to 100 μg/L with yttrium as internal standard. The iron, zinc, copper, and manganese solutions were analyzed on a Varian Vista inductively coupled optical emission spectrometer (Fe, 238.2 nm; Zn, 213.8 nm; Cu, 327.4 nm; Mn, 257.6 nm). Chromium was analyzed by graphite furnace atomic absorption spectrometry (Cr 357.9 nm). For selenium, aliquots were diluted 1 + 1 with 2% butanol and spiked to 10 μg/L with rhodium as internal standard, and the solutions were analyzed by inductively coupled mass spectrometry using the 82 Se isotope.

TABLE II
Accuracy and precision confirmed by replicate analysis of NIST 1577b reference bovine liver, Trace Element Unit, Glasgow Royal Infirmary

Element	Nos.	Result	NIST 1577b
Iron	16	184 ± 3.9	184 ± 1.5
Zinc	16	125 ± 3.6	127 ± 16
Copper	16	159 ± 2.7	160 ± 8
Manganese	16	10.21 ± 0.21	10.5 ± 1.7
Selenium	7	0.76 ± 0.013	0.73 ± 0.06
Chromium	7	24.6 ± 1.4	20.3 ± 0.25

RESULTS

Table I describes the clinical characteristics of the 8 short bowel patients; 6 were men and 2 were women. Their short bowel resulted from surgical resection for Crohn's disease in 4 patients, and from mesenteric infarction in the other 4. The table shows their proximal jejunum was 110 cm or less, and 5 patients had partial in-continuity colons. No patient had an ileum or ileocecal valve. Their average duration on HPN was 14 years (range, 2–21 years). At death, their average age was 62 years (range, 29–78 years). Death was due to an HPN complication in 4 patients (3, 4 catheter sepsis; and 7, 8 liver failure) and due to a non-HPN complication in 4 patients (1, 2, 5, 6). Other important comorbidities are also listed in Table I. HPN was continued to within a month or less of the patient's demise. They all received standard amounts of trace elements plus additional zinc, 3–5 mg/L of gastrointestinal loss. The 2 patients (7 and 8) who died from liver failure had their parenteral copper and manganese discontinued when their serum bilirubin levels started to rise.

Figure 1 gives the autopsy tissue levels of iron, zinc, copper, manganese, chromium, and selenium, showing values for controls and HPN patients by number (Table I), using a box plot that identifies the mean (small squares in box), median (line) interquartile range (box), and 90% range (whiskers) for each element. A box plot was used because there was not a normal distribution of control values in all tissues.[24,25]

Specific Elements in Patient Tissues

Iron. Iron was present at normal concentrations in all organs studied.

Zinc. Zinc was present at normal concentrations in heart and muscle, occasionally elevated in kidney, and frequently elevated in liver tissue (5 of 8 patients).

Copper. Copper was present at normal concentrations in heart and skeletal muscle in all patients but very

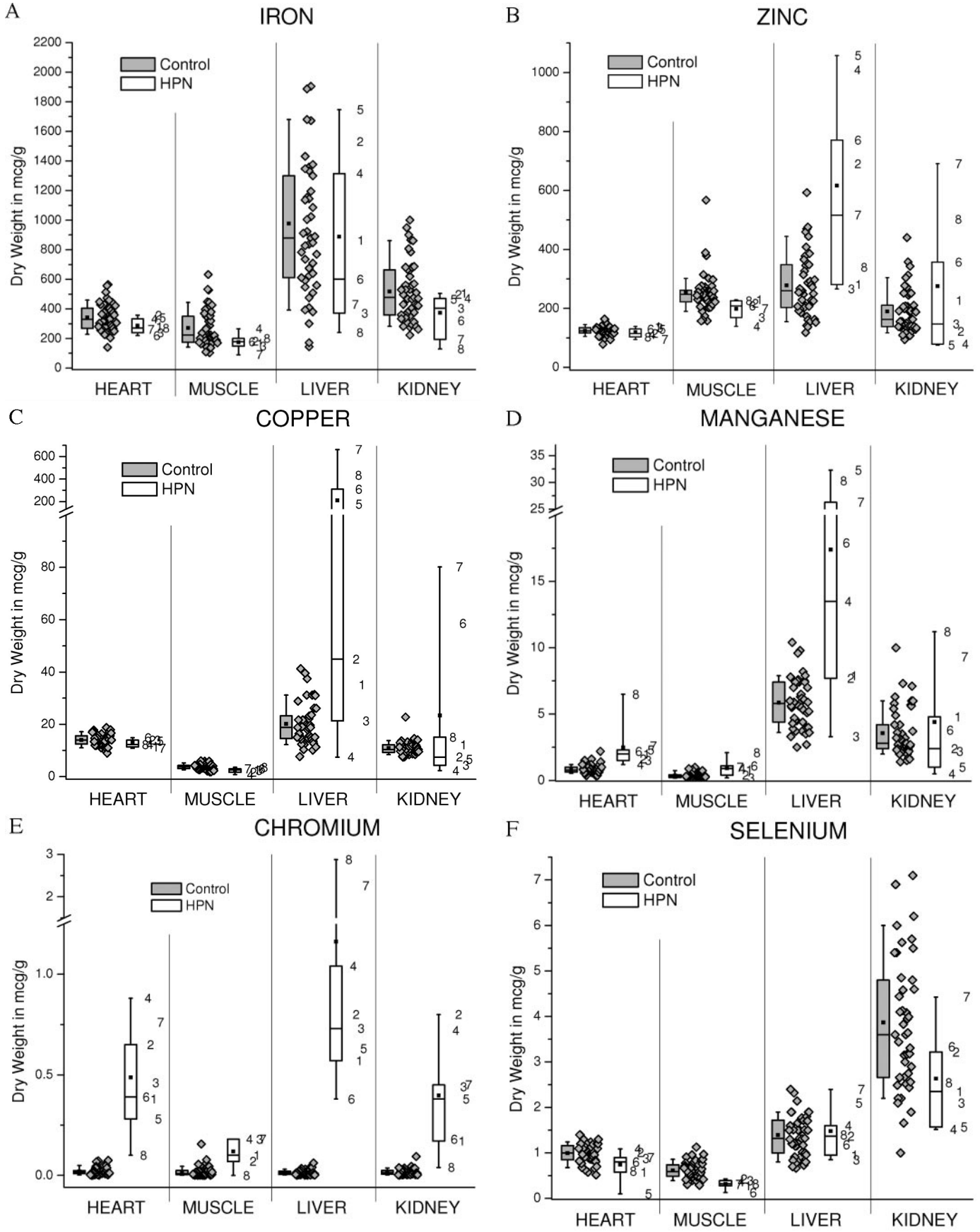

FIGURE 1. Autopsy tissue levels of (A), iron, (B), zinc, (C), copper, (D), manganese, (E), chromium, and (F), selenium, showing values for controls and HPN patients by number, using a box plot that identifies the mean (small square in box), median (line), interquartile range (box), and 90% range (whiskers) for each element.

TABLE III
Parenteral trace elements

	Zinc* Mg	Copper† Mg	Manganese, μg†	Chromium, μg‡	Selenium, μg‡
Adult guidelines					
1979 AMA[2]	2.5–4	0.5–1.5	150–800	10–15	—
1984 NY Acad Med[26] AMA	2.5–4	0.3–0.5	400–800	10–20	50–60
1994 Shils, ME[27]	2.5–4	0.3–0.5	60–100	10–15	40–80
1998 A.S.P.E.N[28]					
2004 A.S.P.E.N[29]	2.5–5	0.3–0.5	60–100	10–15	20–60
Amount received per day by AMC patients	3 plus 3–5 mg/L enteric loss	1.4	700	14	85
Available commercial products					
American Regent (1 mL)§					
Multitrace 4	1	0.4	100	4	—
Multitrace 4 concentrate	5	1	500	10	—
Multitrace 5	1	0.4	100	4	20
Multitrace 5 concentrate	5	1	500	10	60
Abbott/Hospira (5 mL)‖					
4 Trace element	4	1	800	10	—

Data from references 26 and 2.
*Increases with abnormal intestinal losses.
†Decrease or omit with increasing severity of jaundice.
‡Decrease or omit with increasing renal dysfunction.
§American Regent Inc., Luitpold Dr, Shirley, NY 11967. Single-entity trace elements are available.
‖Abbott/Hospira, 100 Abbott Park Rd, Abbott Park, IL 60064.
AMA, American Medical Association; AMC, Albany Medical College.

elevated in liver and kidney, especially in those who died in liver failure (7 and 8).

Manganese. Manganese was elevated, especially in liver and kidney tissues of patients with liver or kidney disease.

Chromium. Chromium had a 10- to 100-fold higher than normal concentrations in nearly all tissues studied.

Selenium. Selenium was present at normal concentrations in all tissues measured.

DISCUSSION

In the United States, the multi–trace element parenteral formula approved by the FDA was described in an American Medical Association publication in 1979.[2] This prescription reflected the scientific knowledge at that time. It was anticipated that modifications would be made as new information became available. Despite a number of studies redefining parenteral trace element needs and several expert conferences[26–29] recommending substantial changes (Table III), the FDA has not yet approved a new formulation. This means practicing clinicians either have to use the outdated multitrace formulation or order each trace element separately.

More updated multitrace preparations are available in Europe and Japan, but these are not licensed for use in the United States.

Assessing trace element requirements in intestinal failure patients dependent on receiving PN is a difficult task because of many confounding factors. First, as the name implies, trace elements occur in minute amounts, and their sampling and measuring require meticulous collection and handling techniques to avoid contamination. Second, in patients receiving trace elements in their nutrient infusion, plasma or serum levels seem to reflect the amount infused and not the tissue status. This unreliability of serum levels has been demonstrated in careful balance studies.[20–22] It is not known how long parenteral trace element supplements must be withheld to make the plasma or serum value interpretable. Third, in addition to prescribed trace elements, studies have shown trace elements are present as contaminants in most nutrient components used to make a PN formula.[30] These contaminants can increase the actual amount delivered by 10%–100%, high contamination being particularly true of manganese and chromium, largely from the processes used in synthesis of crystalline amino acids. Unfortunately, the degree of contamination varies between manufacturers and even between different lots from the same manufacturer.[30] Fourth, careful zinc[21] and copper[22] balance studies have been done in patients fed solely by PN. These studies established the amounts of zinc and copper needed to keep these patients in balance, and the extra amounts required when enteric losses are >300 g/d. However most short bowel patients are encouraged to eat to stimulate bowel adaptation and ward off PN-related cholestasis.[31] Little is known about dietary trace element absorption in short bowel patients, and because eating stimulates enteric losses rich in trace elements, it is not known if eating results in net gain or net loss of these micronutrients.

Because of all these difficulties, we chose to study the cumulative effect by measuring autopsy tissue trace element content of short bowel patients receiving HPN therapy for many years while receiving the FDA-approved multiple-trace-element formulation. This formulation was discontinued in 2 patients who developed a rising bilirubin, and a copper- and manganese-free trace element solution was substituted. These 2 patients died in liver failure a few months later. The trace element tissue concentration of the 8 short bowel patients was compared with the tissue content of 45 age-matched controls studied and published by the same trace element laboratory.[24,25] The control sub-

jects had been receiving an oral diet and died without chronic bowel disease.

This autopsy tissue approach has 3 limitations that should be acknowledged before our results are discussed. First, the number of patients studied is only 8; second, the patients' comorbidities and terminal events most likely distorted their tissue trace element accumulation; third, spectrometry measurements do not determine the chemical form of a particular element, its biologic activity, or availability.

Although HPN is initiated in many patients, especially in the United States (estimated prevalence, 120 per million U.S. population in 1992[32]), the great majority are not receiving HPN beyond 2 years, either because of fatal progression of their underlying disease, for example, cancer, or because their short bowel adapts and they resume full enteral nutrition.[33] Long-term users (>2 years) have an estimated prevalence of only 10–15 per million population in the United States[34] and Europe.[35]

Survival in these long-term users depends on their underlying diagnosis. The highest survival rate is described in patients with Crohn's disease.[34] Studies of long-term HPN survivors reveal a high percentage (70%) of short bowel Crohn's patients.[36] In the United States, >50 people are known to have survived >20 years with HPN, and several have survived >30 years.[37] These long-term survivors are distributed in HPN programs across the United Status, and any 1 program follows only a few of these individuals. The Albany Medical Center program started in 1973 and follows 30–40 HPN patients at any point in time; approximately half of these individuals are indefinitely HPN dependent. Because we limited our study to patients cared for by our program to assure their management was consistent and their prescribed trace element supplement was accurately known, it took 10 years to collect autopsy tissue samples on 8 patients.

The issue of how comorbidities and terminal events can alter tissue accumulation is addressed by the detail of Tables I and Figure 1A–F, which combine clinical information about each patient with the patient's individual tissue levels. It is worth emphasizing that the medical disorders experienced by these 8 patients are common in the long-term short bowel HPN population[34] and therefore point to the clinical events that may require trace element modification.

The chemical form of a trace element is important; for example, chromium is thought to be only biologically active in an organic form as part of the insulin receptor.[38] We do not know the relationship between this organic form and the tissue chromium content measured spectroscopically.

Our results seem to confirm the value of a functional test.[39] Parenteral iron supplementation was given only when the patients' hemoglobin, hematocrit, red cell indices, circulating iron, and iron transport proteins indicated iron deficiency and only then after a trial of oral iron supplementation had failed. This occurred in just 3 of the 8 patients, and the parenteral iron was needed for only short courses (2–3 months). Using functional tests to guide supplementation, tissue iron levels of these 8 patients were all within the normal range. The clinical significance of muscle iron values being in the low normal range is not known.

Iodine was not measured in these tissues, but thyroid function tests were checked annually in these HPN patients and remained within normal limits. It should be noted that although iodine was not intentionally supplemented, it may have been absorbed from catheter and wound sites cleansed with povidone iodine. Until recently, povidone iodine was the most commonly used antiseptic for cleaning these sites in HPN patients. Studies have now shown topical chlorhexidine is superior to povidone iodine for bacterial decontamination.[40] This has led to a shift away from iodine use, and this could have implications for the iodine status of HPN patients. Closer thyroid function monitoring may be needed in the future. It is worth noting that iodine (1 μmol/d) has been a standard part of parenteral trace element supplements in Europe for many years.

Zinc, copper, manganese, chromium, and selenium were added to our patients' parenteral formula as a multiple trace element mixture (Table III), with extra zinc to offset abnormal enteric losses. Zinc is the metallocofactor for large numbers of enzymes and is critical for growth, healing, and immune function.[41] Zinc is excreted largely through the gastrointestinal tract and to a lesser extent *via* the kidneys. Wolman et al[21] studied zinc balance in patients solely receiving PN. If enteric losses were <300 g/d, balance was achieved with 3–4 mg of parenteral zinc/d. Gastrointestinal loss of zinc depended on the volume and source of the enteric contents; short bowel patients lost 3.6 mg zinc/kg of fluid lost, and diarrheal patients without small bowel disease lost 15.2 mg zinc/kg of enteric fluid lost. The 8 short bowel patients in the present study had gastrointestinal losses ranging from 2 to 3.5 L/d, as reflected in their parenteral fluid requirement. Their zinc supplementation was 3 mg/d, as approved by the FDA,[2] plus 3–5 mg/kg of intestinal contents, which amounted to a total of 11–14 mg zinc/d, slightly higher than the 6–12 mg/d recommended by Wolman et al.[21] Our zinc supplementation resulted in normal tissue values 60% of the time but tended to produce high liver values, especially in patients with liver or renal failure. This leads us to conclude that parenteral zinc supplementation should be 3 mg/d plus enteral losses, and probably these enteral losses should be measured, not estimated, in short bowel patients with in-continuity colons because these individuals lose a combination of small bowel contents and colonic diarrhea. Close titration would seem to be more important in individuals with liver and kidney disease who are likely to have impaired excretion.

Copper is the metallocofactor for enzymes involved with connective tissue cross-linking, iron metabolism, electron transfer, and noradrenalin synthesis.[42] It is chiefly excreted through the bile. Copper balance studies in PN patients done by Shike et al[22] found daily parenteral requirements were as low as 0.3 mg/d in patients with normal gastrointestinal losses and 0.4–0.5 mg/d in patients with increased gastrointestinal losses. The FDA-approved formulation recommends 0.5–1.5 mg/d. This was calculated in the 1970s from a

normal dietary intake and percent estimated absorption.[2] Our patients received 1.4 mg/d. This amount resulted in high liver values, especially in patients 7 and 8 who died in liver failure, and patient 6 who had underlying cirrhosis from hepatitis C. In fact, these patients had liver values comparable to Wilson's disease (>250 μg/g dry weight[43]). Our results suggest the Shike et al[22] recommendation (0.4–0.5 mg/d) is a more appropriate dose, and that parenteral copper withdrawal should begin long before the bilirubin starts to rise, perhaps as soon as liver-associated enzymes (amino transferases and alkaline phosphatase) increase more than 2 times their normal value.[44] If no intentional copper supplement is added, it would be important to watch for clinical signs of copper deficiency (leucopenia, microcytic hypochromic anemia, and defective bone mineralization[42]), and under these circumstances, a low serum copper level would be a helpful indicator.

Manganese is the metallocofactor in arginine, pyruvate, and superoxide metabolism.[45] Like copper, manganese is chiefly excreted in bile. Clinical manganese deficiency has not been confirmed, but excess has led to neurologic symptoms of hyperirritability and extrapyramidal disease in children. These neurologic symptoms correlated with increased signal intensity in the basal ganglia on magnetic resonance imaging (MRI).[16,17] These MRI abnormalities slowly disappeared after manganese supplements were stopped. The high levels of manganese shown in our 8 patients, especially those with liver and renal disease, suggest manganese, like copper, should be removed as an additive when liver-associated enzymes rise >2 times normal. Our patients were not studied by MRI; however, none had clinical signs of Parkinson's disease. Fell et al[16] noted that in addition to neurologic abnormalities, liver dysfunction also improved in their affected children once manganese supplements were withdrawn. This suggests hypermanganesemia may be one of several factors contributing to PN cholestasis. The FDA-approved formulation[2] recommends 150–800 μg manganese/d, and our patients received 700 μg/d from their multiple trace element supplement. Takagi et al[46] found not adding manganese led to whole-blood manganese results below the mean of the reference range, whereas supplementing 55 μg/d maintained a level within and across the reference range. The current recommendation[27–29] of 60–100 μg manganese/d appears to be more appropriate but may still be too high because manganese is a common contaminant of many parenteral nutrient additives,[30] and possibly manganese should not be routinely added to any parenteral nutrient solutions.

Chromium, in an organic form, facilitates the attachment of insulin to its peripheral receptor sites, promoting glucose oxidation, lipogenesis, glycogenesis, and amino acid transport.[47] In 1977, Jeejeebhoy et al[10] reported chromium deficiency in a patient receiving HPN for 5 years. She presented with glucose intolerance and weight loss and improved on 20 μg chromium/d. Other investigators have reported high serum chromium values in PN patients,[48] and our 8 patients all had high chromium tissue levels. Moukarzel et al[48] demonstrated a strong inverse correlation between parenteral chromium intake and glomerular filtration rate in children receiving PN, and recommended a reduction in chromium intake. The FDA-approved formula[2] provides a chromium supplement of 10–15 μg/d, and our patients received 14 μg/d; this amount has not been modified by recent expert opinion[26–29] despite the high levels described. This is because the chemical form of chromium is critical and tissue chromium levels may not reflect the adequacy of the chromium glucose tolerance factor. Jeejeebhoy[49] has suggested the only convincing way to assess chromium deficiency is to demonstrate abnormal glucose clearance responding to chromium supplementation. We have no evidence that our patients' high chromium levels were associated with toxicity. In fact chromium poisoning has only been described in industrial settings (stainless steel welding) where chromium is airborne, and in the Cr^6 valency.[50]

Selenium has an important role in several selenoproteins; the best characterized are the glutathione peroxidases, which use reduced glutathione as the hydrogen donor to limit free hydrogen peroxide and to prevent peroxidation of membrane phospholipids.[51] Human selenium deficiency has been described in areas of China with low selenium soil content (Keshan disease).[52] It presents as a cardiomyopathy in children and women of childbearing age. A similar syndrome of cardiomyopathy, skeletal muscle pain, and weakness has been described in long-term PN patients not supplemented with selenium.[12–14] Balance studies suggest the parenteral requirement is 60–120 μg/d.[3,20] Our 8 long-term short bowel/HPN patients received 85 μg/d of selenium, and this achieved normal tissue levels in the older subjects. Younger adults seem to require somewhat higher amounts to achieve the higher tissue levels characteristic of their age group.[24] Selenium has a fairly narrow therapeutic margin, and intakes >350 μg/d are associated with nausea, vomiting, hair loss, irritability, fatigue, and a peripheral neuropathy.[51]

The autopsy tissue findings in these 8 long-term HPN patients in large measure support the modifications to the FDA approved formulation[2] proposed by parenteral trace element experts in 1984,[26] 1994,[27] 1998,[28] and 2004[29] (Table III). Our findings confirm that the FDA-approved formulation is too high in copper and manganese, and our study and the MRI studies in children[16,17] suggest a strong potential for serious copper and manganese toxicity with the current FDA formulation. The FDA's most fundamental obligation is to protect the population from harmful drug effects.

The accumulated scientific data point to a serious need for a consensus conference on parenteral trace element requirements, with FDA participation, leading to a reformulation of the multiple trace element products available for use in the United States. An improved formula would likely have worldwide influence. Hopefully, a reformulation can be achieved without such a heavy financial penalty that current commercial producers opt to remove all multiple parenteral trace element products from the market.

Some knowledgeable clinicians in the United States, recognizing the potential for toxicity with the available

TABLE IV
The multiple-trace-element formula recommended by the authors for adults receiving long-term parenteral nutrition

Element	Amount per day	Comment
Zinc	3–6 mg	2 mg/kg of enteral loss for a total of 6–12 mg/d
Copper	0.3–0.5 mg	Discontinue when serum aminotransferases and alkaline phosphatase levels are >2 × normal. Check serum Cu levels every 6–12 mo thereafter.
Manganese	30–60 μg	Discontinue when serum aminotransferases and alkaline phosphatase levels are <2 × normal. Check serum Mn levels every 6–12 mo thereafter.
Chromium	5–10 μg	Check HbAIC every 6 mo
Selenium	60–100 μg	Higher dose in adults <40 y

multiple trace element products, have recommended ordering each trace element separately. This adds time and cost to an already expensive product and has great potential for increasing compounding errors. A compromise solution may be FDA approval of a new basic multiple trace element preparation to which additional trace elements can be added for patients with increased trace element losses such as zinc. The authors' suggestion for a basic multiple trace element formulation is described (Table IV). Hopefully, these suggested amounts could provide a springboard for discussion by a consensus panel in the near future.

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