TOTAL PARENTERAL NUTRITION IN THE CANCER PATIENT UNDERGOING CHEMOTHERAPY

by

ANNETTE KUNIGK
Dipl. oec. troph.
Justus Liebig University, Giessen, W. Germany, 1978

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INTRODUCTION

The growth of cancer in man leads to destruction of tissues and alterations of functions. As a consequence, the process culminates in overt cachexia and death. The manifestation of cachexia, whether due to anorexia, chemotherapy, or factors other than insufficient food intake, may be reversed by sound nutritional support. If the alimentary tract functions adequately, oral feeding is desire however, if the patient is unable to ingest voluntarily other ways of nutritional support must be considered.

The following paper will deal with the application of total parenteral nutrition for the nutritional rehabilitation and maintenance of the cancer patient undergoing chemotherapy.

TUMOR HOST RELATIONSHIP

Anorexia is a common phenomenon in many cancer patients at some time during their illness (1), and is associated with marked weight loss. However, anorexia cannot completely explain the weight loss. Altered mechanisms of metabo lic regulation and lack of efficient patterns of fuel util zation may play a role in cancer cachexia (2).

Knowledge about the partition of energy requirements between host and tumor in a tumor-bearing individual helps to clarify the response of the host to the tumor. In vitro and in vivo findings suggest that the presence of a tumor increases the metabolic rate of the host (3). The metabolic rate increases almost immediately after transplantation of a tumor (4). However, energy expenditure declined in the terminal stage of tumor growth, and the animal became moribund.

To gain an understanding of tumor-host energy relationships, investigations have focused on the following:

1) oxidative metabolism of the tumor
2) energy expenditure of the host
3) the metabolic load imposed on the host by the tumor (3).

Oxidative metabolism of the tumor

Neoplastic cells show a high rate of anaerobic glycolysis (5) and formation of lactate. This results in an increase in Cori cycle enzyme activity and acceleration of gluconeogenesis. Thus, the excessive accumulation of lactate is avoided, which would result in lactic acidosis. This pathway leads to an energy drain of 6 moles adenosine-triphosphate (ATP) per mole of formed glucose. Cori cycle enzyme activity is approximately two- to three-fold greater

in cancer patients than in control subjects (6). Thus, an increased rate of conversion of lactate to glucose has been proposed as a mechanism of the increased energy expenditure and weight loss observed in cancer patients. However, Young (7) concluded from a review of published data, that changes in Cori cycle activity is not a significant cause of cancer cachexia. Less than 10% of the daily energy expenditure can be accounted for by lactate recycling. Assuming that 15% of the total lactate production is oxidized, the resulting high energy phosphate would be sufficient to balance the loss resulting from the conversion of the remaining 85% of lactate to glucose.

Energy expenditure of the host

The most important factor in the determination of energy expenditure is the basal metabolic rate. The basal metabolic rate changes in response to various physiological conditions, such as age, nutritional status, environmental and body temperature and pathological state. A review of studies on the basal metabolic rate of cancer patients revealed that it generally appears to be increased (7). However, a consistent change cannot be observed. There are considerable variations reported among and within the various studies. For example, an increase of the basal metabolic rate in patients with leukemia ranges between 12-120% above normal. Some of these difference are pro-

bably due to methodological variations, but they might also reflect the severity and stage of disease.

Through the growth of malignant tissue, alterations in host metabolism take place, which imply an energy drain on the host resulting in progressive weight loss. Changes in the availability and generation of ATP and alterations in the efficiency of energy utilization might arise as consequences of disease states or therapy. This might be due to changes in energy conserving systems, i.e., the coupling of oxidative phosphorylation and/or a variable activity of ineffective cycles, such as the glucose cycle, the fructose-6-phosphate cycle and phosphoenolpyruvate cycle (Figure 1). The cycling in one direction occurs spontaneously, whereas the reverse reaction requires energy in form of high energy phosphate ATP. As a consequence of these recurrent reactions there is an energy wastage and drain from energy requiring-processes. However, Katz and Rognstad (8) believe that these energy cycles are efficien and that a lack of their efficiency cannot completely explain the energy drain.

A loss of utilizable energy may occur if glucose or other carbohydrate sources are channeled into lipogenic pathways for the temporary storage of energy. Flatt (9) estimated a significant energy cost of 20% using this pathway, whereas Krebs (10) only found a loss of 7% of the

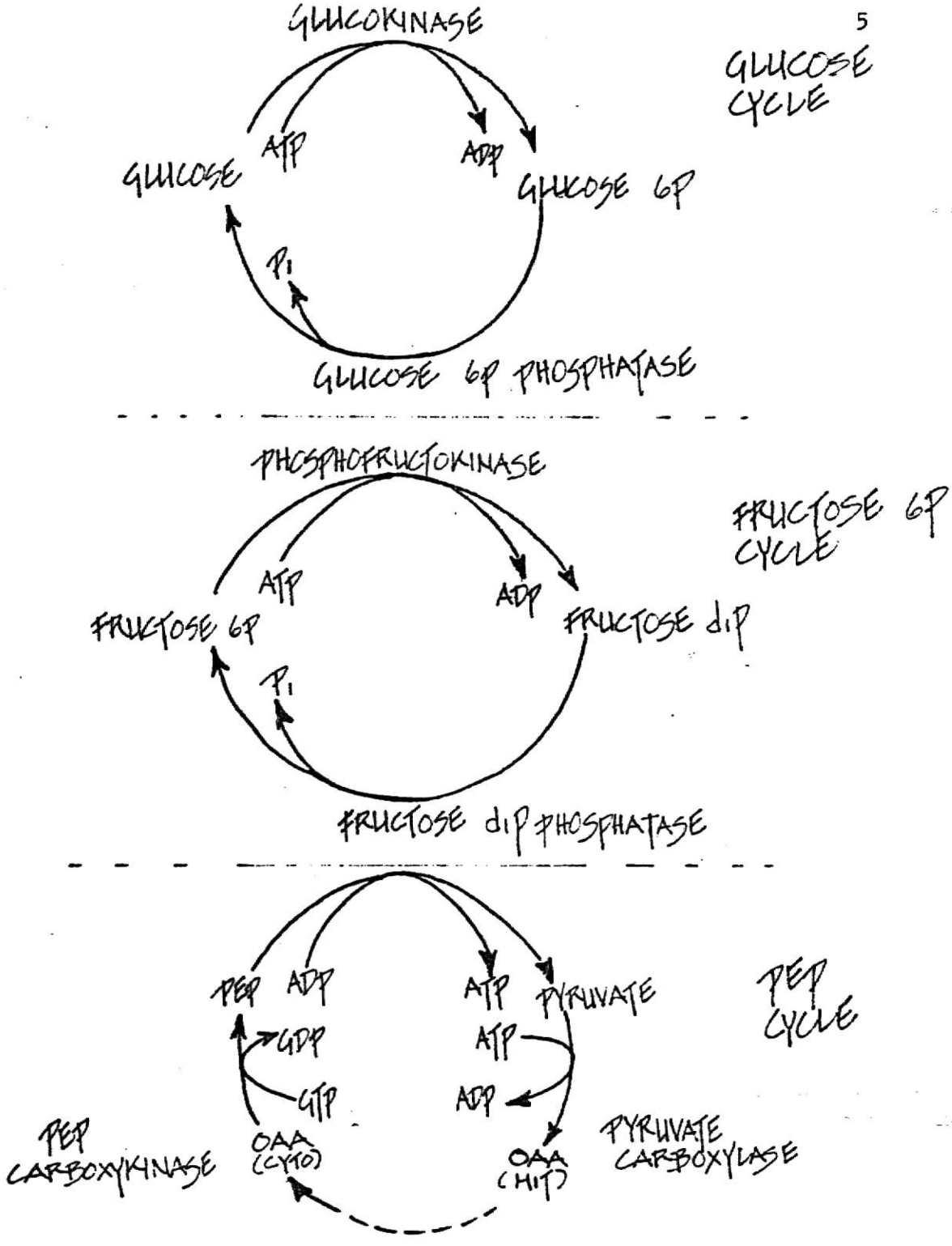


Fig. 1. Important cycles in intermediary metabolism.(7)

OAA, oxaloacetic acid; CYTO, cytoplasmic; MIT, mitochondrial PEP, Phosphoenolpyruvate; Glucose 6P, glucose 6-phosphate; Fructose 6P, Fructose 6-phosphate.

utilizable energy to be stored.

Estimates of Munro (11) demonstrate a close relationship between the intensity of body protein synthesis and rate of energy expenditure in mammals. Young (7) suggests that about one-half of the resting metabolism may be associated with protein turnover. Thus, if a patient is depleted, the replenishment of tissue and organ protein would require an increased energy intake, above that required for normal maintenance. The energy requirement would be comparable to the high energy cost of growth in infants and children (12).

Metabolic load imposed on the host by the tumor

The metabolic load imposed on the host by the tumor must be metabolized and dissipated by the host. The cancer patient may produce lactic acid and other low molecular weight metabolites, i. e., polypeptides, that lead to alterations in the metabolic patterns of the host (13). Changes in various metabolic equilibria and concentrations of metabolites might be the result of allosteric transitions activations, and inactivations of various enzymes in the tissues of the host. These distant metabolic effects are collectively known as paraneoplastic syndromes (14, 15).

The term also implies the release of chemically identifiable toxic mediators (16) that act at sites distant from the anatomic involvement. A toxohormone has been prepared by Yukoni (17). Odell (18) demonstrated release of a number of ectopic hormones produced by the tumor. These humoral syndromes are associated with hypercalcemia, altered gonadotropin production, hyponatremia, hypoglycemia ectopic ACTH-MSH* syndrome, erythrocytosis and others.

EFFECT OF TUMOR GROWTH ON INTERMEDIARY METABOLISM

Few data are available about the regulation of carbohydrate and lipid metabolism and the dynamic interrelationship between glucose, lipid and amino acid metabolism in cancer aptients. Data suggest that there is a disturbance in the normal and homeostatic mechanisms involving the utilization of glucose and lipid in patients with neoplastic disease (19-14).

Carbohydrate metabolism

Cancer patients as a group have abnormal or "diabetic" glucose tolerance (19). There is a relative state of

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*ACTH = Adrenocorticotropic hormone
MSH = Melanocyte stimulating hormone

insulin resistance to endogenous and exogenous insulin, leading to a decreased rate of glucose clearance from peripheral blood. Schein et al. (20) demonstrated that cancer patients show a markedly abnormal curve with a mean 2-hour blood glucose concentration in excess of 160 mg/dl, and a statistically significant higher value for the 1-4 hour period than controls. Plasma insulin levels rose at a slightly lower rate in the cancer patients. A quantitative and qualitative alteration in insulin receptors on peripheral cells may explain the altered glucose tolerance in cancer patients (21). However, Schein (20) found no difference in insulin receptors between the cancer patients and the control group. The abnormalities in carbohydrate metabolism might, therefore, be due to either an alteration in insulin function, such as insulin production, or insulin resistance.

An alteration of carbohydrate metabolism has been proposed as a method of treatment for cancer. Tumor growth can be stopped by the inhibition of the enzyme phosphoenolpyruvatekinase, but this manipulation also causes a significant weight loss in the treated animals as compared to untreated tumor bearing controls (23).

Fatty acid metabolism

Cancer patients show a marked wasting of body fat and an oxidative metabolism consistent with fasting state (1). Increase lipolysis can be explained partially by elevated ACTH (18), which stimulates Cyclic-AMP production and thus lipolysis. Plasma free fatty acids do not differ quantitatively in cancer patients with and without weight loss (6). Waterhouse et al. (19) estimated the rates of free fatty acid and glucose oxidation in normal and cancer patients under basal conditions and glucose loading. Under basal conditions the rates of glucose and fatty acid oxidation in cancer patients did not differ significantly from the controls. However, when a glucose load was given, the oxidation of free fatty acids was suppressed less in cancerous disease. They also compared CO_2 production from labeled glucose and fatty acids in normal subjects and those with cancer. Glucose loading reduced the oxidation of glucose and palmitate in normal subjects but not in cancer patients. The authors conclude that continued intracellular oxidation of free fatty acids occurs despite glucose loading. Cancer patients also showed a slower rate of Krebs cycle activity, which is normally elevated after the administration of glucose.

Amino acid metabolism

Cancer patients show a reduced efficiency of amino acid utilization for muscle protein synthesis. Lundholm (25) investigated protein synthesis in muscle biopsies in vitro The biopsies were taken from a heterogeneuos group of cancer patients and healthy controls. Protein synthesis was significantly reduced in samples from cancerous material as compared to healthy control samples ($p < 0.05$). Protein degradation was 150% higher in malignant muscle samples than in the healthy tissues ($p < 0.025$). Supplementing amino acids (10 times the normal plasma levels) in the incubation medium, Lundholm obtained a nonsignificant increase of synthetic activity in muscle protein biopsies of both moribund and healthy controls.

In vivo findings also give evidence of reduced protein synthesis. Tumor-bearing rats show a reduced rate of myofibrillar protein synthesis in skeletal muscle.
Clark et al. (26) concluded that this impairment is due to a defect in the capacity of the 40S ribosome to promote a postinitiation step in polypeptide synthesis. The cancer acts as a nitrogen trap and extracts amino acids for protein metabolism from the host's nitrogen pool. These amino acids are not recycled, because tumor anabolism exceeds catabolism (27).

Nutritional Implications

Since little is known about the quantitative effects of tumor growth on energy utilization and body energy balance, only crude guidelines can be given for the nutritional management of the cancer patient. According to Waterhouse (19) glucose does not seem to be oxidized directly, but is probably first converted to lipid (7), a high energy conversion affecting total energy requirements. Protein synthesis is reduced in cancer patients (15), but may possibly be stimulated by large additions of amino acids (10 times normal plasma levels)(25). Schein et al. (20) speculate that these metabolic abnormalities characteristic for malignant disease may be potentially controlled by the use of exogenous insulin. Exogenous glucose would be more efficiently utilized as a metabolic fuel to provide energy and conserve fat stores and lean body mass. Cori cycle activity could be reduced, leading to energy conservation for normal tissues as well as a parallel reduction in the oxidation of free fatty acids. Proteolysis could be controlled by enhancing the uptake as well as the retention of amino acids in body protein. This would decrease their use as precursors for gluconeogenesis and a positive nitrogen balance would occur.

CHEMOTHERAPY

Chemotherapy is a major form of treatment in the cancer patient. Effects of chemotherapy are related to two primary drug functions,

- the biochemical interaction with the target tissue, and
- the pharmacological action on the host.

Treatment with these agents will result in profound effects on the gastrointestinal tract, the central nervous system, the cardiopulmonary, renal, hematopoietic and musculoskeletal systems of cancer patients (28). Tables 1 and 2 classify cancer chemotherapeutic agents and explain their antitumor mechanism. Also, common side effects are listed. Nearly all chemotherapeutic agents are accompanied by anorexia (28). Common adverse side effects, that affect food intake and nutrient utilization are: abnormal metallic taste in the mouth, mucosal ulcerations, nausea and vomiting, constipation and diarrhea.

The cachectic patient will exhibit a much narrower safety margin for chemotherapy than does the well nourished host in the early stages of metastatic disease. Without nutritional support these patients are considered either untreatable or extremely poor risks for any form of oncologic therapy. Copeland (29) documented a correlation between the nutritional status of the patient and the response to chemotherapy.

Weight gain resulting from total parenteral nutrition or oral nutritional support during chemotherapy resulted in good tumor regression. In contrast, for those patients exhibiting poor weight gain, tumor response to chemotherapy was less and they usually had lower survival rates.

Tumor metabolic pathways might be more susceptible to chemotherapeutic attack, since physical properties of the tumor environment can be changed, which inhibit tumor growth. Methotrexate may be better incorporated into the tumor cell in an acid environment. However, oxidative metabolism seems to be quantitatively limited (30). The drop of tumor pH also activates lysosomal acid hydrolases which stimulate a "cell-suicide" mechanism, known as the "Crab-tree" effect (31, 32). Large amounts of glucose can be given through intravenous means. Besides the "Crab-tree effect, more glucose would finally be available for energy utilization by the host. Meyer found significant tumor regression when the administered nutrient solution was composed of 80% glucose.

TABLE 1
Classification of chemotherapeutic agents and their mechanisms of action (33)

Drug Class	Prototype examples	Mechanism of action	Types of malignancy treated
Alkylating agents	Nitrogen mustard Melphalan Chlorambucil Cyclophosphamide Myleran	Alkylates or interacts with formed DNA	Lymphomas Hodgkin's Disease Multiple myeloma Leukemias (chrome) Ovarian cancer
Antimetabolites	Methotrexate Cytosine arabinoside 5 Fluorouracil 6 Mercaptopurine	Interferes with DNA synthesis	Squamos cell carcinoma Leukemia Osteogenic sarcoma Breast cancer Gastrointestinal cancer
Antibiotics	Adriamycin Bleomycin Actinomycin D Mitomycin C	Mechanism variable including alkylating and direct DNA destruction	Testicular cancer Epidermoid carcinoma Lymphomas Uterine Cancer
Alkaloids	Vinblastine Vincristine	Mitosis inhibitor	Hodgkin's Disease Breast cancer Sarcomas Leukemia and lymphomas
Miscellaneous	Hydroxyurea Procarbazine	Variable	Various types
Hormones	Corticosteroids Testosterone Estrogen/Androgens Progesterone	Unknown	Breast cancer Renal cancer Uterine cancer Prostatic cancer

TABLE 2

Common side effects of cancer chemotherapeutic drugs (33)

System involved	Mechanism of effect
1. Gastrointestinal tract	
A. Nausea and vomiting	Central effect on emesis center of the thalamus
B. Diarrhea	Local mucosal irritation secondary to the direct effect on the bowel
C. Anorexia	1. Central effect on hunger center in the thalmus
	2. Secondary reaction to the nausea and vomiting
	3. Nonspecific metabolic abnormalities.
D. Taste distortion (dysgeusia)	Local mucosal irritation
E. Constipation	Hypomotility of the bowel due to direct effect on the nerve supply (vincristine)
2. Skin and mucosal effects	
A. Dermatitis	1. Erythroderma; pustular or macular rash, desquamation and epidermolysis, all secondary to the direct effect on the skin 2. Allergic reaction mediated through immune mechanisms
B. Stomatitis (mouth ulceration)	Direct effect on cells with inhibition of duplication
C. Alopecia	Direct effect on cells
D. Skin pigmentation	Unknown
E. Nail changes	1. Oncholysis 2. Pigmentation lines secondary to growth arrest
F. Perianal and vaginal ulceration	Direct effect on mucosa

TABLE 2 (concluded)

Common side effects of cancer chemotherapeutic drugs

System involved	Mechanism of effect
3. Hematologic problems	
A. Bone marrow suppression Leukopenia Thrombocytopenia Anemia	Direct effect on the bone marrow stem cells arresting production of peripheral blood elements
4. Urinary tract	
A. Hemorrhagic cystitis	Local bladder irritation (cyclophosphamide)
B. Colored urine	Direct excretion of the drug adriamycin (red); methotrexate (yellow)
C. Impaired renal function	Glomerular or tubular toxicity defect secondary to direct effect
5. Hepatic effects	Fibrosis or hepatitis-like effect, cause unknown
6. Reproduction system	
A. Amenorrhea	Involution of ovarian function and estrogen secretion
B. Impaired spermatogenesis	Involution of testicular function
C. Premature menopause	Involution of ovarian function and estrogen secretion
7. Neurologic effects	Ataxia, paresthesias, paralysis by inhibition of microtubular substance in nerves
8. Miscellaneous symptoms	
A. Fever, chills	Probably allergic reaction
B. General malaise	
C. Flu-like symptoms	

TOTAL PARENTERAL NUTRITION

Total parenteral nutrition can be a valuable adjunct to cancer chemotherapy by improving the nutritional status of the host. The improved nutritional status permits the use of large doses of anticancer agents, reduces toxic side effects of chemotherapy on the gastrointestinal tract and reduces septic complications. Parenteral nutrition is provided through the intravenous administration of nutrients, either through a peripheral vein or central venous catheterization. The provision of nutrients intravenously differs from normal digestion and assimilation of foodstuffs in two primary ways,

1) the usual hepatic and gastrointestinal regulatory mechanisms are bypassed, and
2) nutrients are provided constantly, rather than as intermittent meals.

To compensate for the loss of regulatory mechanisms, parenteral nutrition solutions have been structured to mimic the form in which nutrients are normally absorbed, i. e., carbohydrates are supplied as monosaccharides, and protein as fibrin or casein hydrolysate or as individual amino acids. Lipids are given in emulsions, with particles resembling chylomicrons.

TPN

Application in the cancer patient

Protein calorie malnutrition is a common secondary diagnosis in patients with cancer. It can be a direct consequence of the anorexia of malignancy, chemotherapy, altered host metabolism induced by neoplastic growth, and unknown physiological factors that influence eating behavior (34, 35). The feeding technique established and perfected by Dudrick and coworkers (36, 37) was an enormous step forward in the realimentation of malnourished patients. The site of infusion, either through a peripheral vein or subclavian vein, the infusion rate, and the choice of nutrients must be adapted to meet the energy and protein needs of the patient and his pathologic condition.

Peripheral nutrition in the cancer patient

Intravenous nutrition through a peripheral vein may be adequate to meet nutritional needs of moderately depleted patients, but this form of therapy may be inadequate in the severely depleted cancer patient. The main obstacle to adequate intravenous nutrition is that solutions of high osmolarity are necessary to supply sufficient calorie to achieve a positive nitrogen balance (38). Hyperosmolar solutions are sclerosing if given through a peripheral vein. The osmotic pressure of the blood can be maintained with

the administration of a 5-10% glucose solution. However, the body cannot handle more than 3 liters of water daily. Giving 3 liters of a 5% glucose solution provides 600 kcal while a similar amount of a 10% glucose solution yields 1200 kcal. Thus, sufficient calories cannot be provided to prevent catabolism.

Protein sparing peripheral nutrition

Blackburn et al. (39) postulate effective intravenous alimentation with amino acids without simultaneously infusing glucose. This is based on the concept that glucose-free solutions lead to a decrease in insulin release (40). Available fat stores can be broken down to free fatty acids, which are then used for energy needs. Gluconeogenesis and muscle catabolism are no longer necessary for meeting energy requirements. The intravenous amino acids provide a source of nitrogen for tissue repletion and other body protein synthesis (41). Amino acid infusion alone has been shown to spare body protein more effectively than peripherally administered amino acids with glucose (40, 42, 43). Solutions of crystalline amino acids infused without dextrose produced a marked improvement in nitrogen balance in surgical patients. The mean daily nitrogen balance was -8.9 $\pm$ 1.4 gm/day during dextrose infusion

and -1.2 ± 0.9 gm/day during amino acid infusion at 1 gm/kg ($p < 0.001$). Increasing the infusion level of amino acids from 1 to 1.7 gm/kg further improved nitrogen balance to 1.2 gm/d ($p < 0.01$)(40).

Supplemental peripheral nutrition

In order to provide adequate nutritional support to chronically stressed individuals, calorie and nutrient requirements have to be met. With the use of fat, Intralipid ® *, a nutrient solution of high caloric density can be given through a peripheral vein, because the osmolarity of this solution resembles that of blood. The 10% lipid emulsion solution and a solution containing 5-10% dextrose or fructose are infused at equal rates via a Y-catheter (44, 45) into a peripheral vein. At the intended rate lipid infused amounts to 3 gm/kg/day, and the patient receives 52 kcal/kg/day and 2.1 gm/kg/day of amino acids. With supplemental electrolytes and vitamins these infusions may provide adequate TPN (46, 47). There is the problem of finding veins in a sick malnourished patient, as well as the risk of occurrence of thrombophlebitis.

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* Intralipid ®, Cutter Laboratories

These factors may limit the infusion of adequate nitrogen and calories. Paradis (46) demonstrated lack of clinical response to this system by malnourished patients and a central venous catheter was required in the majority of patients.

Central venous nutrition

Central venous catheterization into the subclavian vein has been adapted for hyperosmolar solutions. The solution is rapidly diluted by the high blood flow in this vein (2 to 5 liters/ minute), thus avoiding the hazards of venous tissue sclerosing. Central venous catheterization permits the infusion of adequate calories, protein and other essential nutrients. Even in hypermetabolic conditions, enough energy can be supplied to prevent negative nitrogen balance and promote new tissue synthesis. Comparisons between this type of alimentation and the protein sparing therapy of Blackburn (39) have shown that the clinical outcome was more favorable with central venous alimentation (48, 49).

NUTRITIONAL NEEDS FOR THE CANCER PATIENT REQUIRING TPN

Energy

The basal metabolic expenditure in a healthy man is approximately 1700 kcal/ day. For each degree Fahrenheit elevation in febrile illnesses, the metabolic rate increases by about 12% (7). Basal metabolic rate increases above 90% have been found in malignancy (7). These high energy requirements can effectively be met by the application of total parenteral nutrition through the central venous route. Sufficient non-protein calories have to be given, if administered amino acids are to be utilize for body protein synthesis. These can be given in form of concentrated glucose solutions (up to 1500 milliosmoles) or intravenous fat emulsion (45).

Chen et al. (50) have advocated an energy to nitrogen ratio between 100:1 to 400:1 or even higher. The middle of the road figure of 200:1 might be used first and the response of the patient observed (50, 51, 52). Nitrogen balance can be achieved with the administration of 35 kcal/kg/day in hospitalized patients (53). However, this amount is probably not adequate to meet the high caloric needs of the cancer patient. Spanier et al. (52) estimated the caloric requirement of the average hospitalized patient to be 46 kcal/ kg/day. However, in the

depleted critically ill patient the infusion of calories in the amount of 56 kcal/kg/day results in rebuilding body cell mass.

Carbohydrates

Glucose is the carbohydrate source most frequently used in TPN solutions. Fructose or other carbohydrate sources are rarely used (54).

There is evidence that the rate of disposal of intravenously infused glucose is less than intragastrically adminstered glucose. Lickley (55) demonstrated a greater increase in immunoreactive insulin (IRI) in intragastrically fed rats compared with those fed intravenously. Also, thei weight gain was greater compared to those rats on intravenously infused glucose. Some of the features distinguishing the response to glucose absorbed from the intestinal tract from that of glucose given parenterally appear to depend on functions in the alimentary tract (59). Portal hyperglycemia due to infusion of glucose did not evoke as much insulin secretion as that due to absorption of glucose from the intestines (57). Since findings have stimulated interest in the roles of humoral agents derived from the gastrointestinal tract in the regulation of the endocrine function of the pancreas. Secretin, pancreozymin, gastrin, cholecystokinin and stimulated glucagon

immunoreactivity have been suggested as influencing the response to enterally administered glucose (56-58). Such findings also suggest that patients receiving intravenous glucose loads would exhibit enhanced tissue uptake and utilization if insulin were administered in the infusion. Since cancer patients also show an abnormal glucose tolerance comparable to patients with diabetes (20), administered insulin would bring about another beneficial effect.

Lipid

Intralipid® is an approved lipid source providing 1.1 kcal/ml. It contains 10% soybean oil, 1.2% eggyolk phospholipids, 2.25% glycerin and water for injection. The soybean oil is a refined natural product consisting of a mixture of predominantely unsaturated fatty acids: linoleic acid 54%, oleic acid 26%, palmitic acid 9% and linolenic acid 8% (59). Its osmolarity resembles that of the blood, and its fat particles are 0.5 μ (60). As a source of essential fatty acids, it prevents biochemical lesions of essential fatty acid deficiency, noticed in patients on long term fat-free intravenous nutrition (61-63) Fat clearance from the blood stream occurs in a manner comparable to the clearing of chylomicrons (64, 65) and is dependent on the presence of lipoproteinlipase. It is

increased following stress and may be accelerated by heparin and insulin. The clearance rate after an overnight fast has been estimated to be 3.8 gm fat/kg/day (65). While clearance cannot be directly equated with fat utilization, studies (66, 67) have documented a favorable weight gain and nitrogen retention with the administration of intravenous fat emulsion in man. Following administration of Intralipid®, an increase in heat production, decrease in respiratory quotient and increase in oxygen consumption, suggest the utilization of fat (64, 65). The emulsion apparently equilibrates with available body lipid for utilization and storage as a basic fuel substrate (68).

The proportion of carbohydrate and fat in the infusion solution

Both carbohydrates and fat provide carbon fragments that can be oxidized in the Krebs cycle. Fatty acid catabolism cannot provide the carbon backbone for the synthesis of nonessential amino acids. Synthesis of nonessential amino acids requires the intermediary products resulting from the metabolism of carbohydrates (69).

Jeejeebhoy et al. (67) conducted a total parenteral nutrition study to compare the effects of a lipid regimen

(83% lipid and 17% glucose) with glucose alone on nitrogen retention and protein synthesis. These nonprotein calories were administered with a constant background of amino acids (1g/kg/day), vitamins and minerals. Changing the source of nonprotein calories resulted in a fall in nitrogen retention, when glucose was replaced by the lipid preparation. Nitrogen retention was achieved again, when glucose replaced lipid. However, the nitrogen balance with both systems was positive to a comparable degree after the establishment of equilibrium and resulted in weight gain and elevation of serum proteins.

When Intralipid® provided 86% of the nonprotein calories and fructose the remainder plus a 7% solution of L-amino acids, this infusion did not rebuild a depleted body cell mass, but only prevented malnutrition in patients (46). Long et al. (70) examined urea nitrogen excretion in five patients who were clinically stable after injury and operation. They found that urea nitrogen excretion was inversely related to carbohydrate intake ($p < 0.01$), and directly related to resting metabolic rate ($p < 0.01$). Fat did not affect nitrogen conservation under the conditions of this study. Long et al. (70) suggested that if the primary clinical goal is nitrogen conservation, carbohydrate calories should be given in amounts approximating resting metabolic rate.

Protein (Amino acids)

Problems have arisen with the protein and amino acid composition of parenteral solutions (71). The optimal amino acid pattern may differ from that of oral consumption. Parenteral mixtures may require large concentrations of the branched chain amino acids. In an orally fed individual the amino acid spectrum emerging from the liver into the general circulation tends to be richer in those amino acids (69).

Two types of amino acid solutions are available: a protein hydrolysate of either fibrin or casein; or a mixture of free amino acids. Both support protein anabolism in experimental animals and human volunteers. In severe catabolis stress free amino acids are preferred. Up to 40% of the total nitrogen of protein hydrolysates is in the form of peptides (59), which are not as effectively used as alpha amino acids (72). Long et al. (73) estimated that 30-50% of the nitrogen available in protein hydrolysates is excreted as urea nitrogen and therefore, lost. Nitrogen retention obtained with intravenous hydrolysates was much less than that achieved in the same patients ingesting equivalent amounts of whole protein. Patel (74) concluded that the deficiency of aromatic and sulfur-containing amino acids in the protein hydrolysates led to the impairment of nitrogen retention. Nitrogen retention was found to be at 240 mg N/kg/day, which is 40%

excess for N-equilibrium in normal adults (73). The essential amino acids should be included at a level of 45-50% (73).

Addition of insulin to the infusate would stimulate the uptake of amino acids into the muscle, favor protein synthesis and would control the rate of amino acid release from the muscle (11).

Vitamins

Vitamins have a definite role in TPN programs, because they are intimately involved in the metabolism of protein, carbohydrates and fat. They function as cofactors in certain enzymatic reactions. Recommended Dietary Allowances (RDA) have been established for some of the vitamins known to be essential for sound nutrition (75). These recommendations are: "the level of intake of essential nutrients considered... to be adequate to meet the known nutritional needs of practically all healthy persons"(75).

However, research in the area of vitamin requirements in the cancer patient is sparse. The cancer patient shows varying degrees of depletion and probably defective mechanisms of utilization of nutrients (7). The relationship of vitamins to cancer is complex. Three types of interactions are possible: the effect of vitamin on tumor growth;

the effect of tumors on vitamin metabolism; and the effect of vitamins on anti-tumor chemotherapeutic agents. In some cases a vitamin inhibits the growth of tumors, whereas in other cases vitamins act as inducers for other kinds of tumors. Some chemotherapeutic agents act as vitamin antagonists, which result in tumor regression (76). These factors will be discussed in the following text.

Vitamins and cancer. Studies on patients with advanced malignant disease have provided biochemical evidence that a significant proportion may be at risk of thiamine deficiency, as judged by decreased transketolase activity (77) Thiamine deficiency leads to an accumulation of pyruvic and lactic acids in tissues and body fluids, which might partl explain the observed lactic acid accumulation in the cancer patient (78). Even on an adequate diet, the thiamine excretion in cancer patients was higher than in controls, which leads to the assumption that the thiamine deficiency may be due to a reduced ability to convert thiamine to thiamine pyrophosphate.

The presence of riboflavin has been reported to reduce the carcinogenity of azo-dyes through their action on the hepatic enzymes responsible for their degradation in vitro (79). In contrast to the inhibiting influence of riboflavin on the formation of hepatic tumors, spontaneous mammary carcinoma in the mouse is dependent on the pre-

sence of panthothenic acid (80).

An increased requirement for folic acid has been observed in patients with cancer (81). Patients with malignant tumors had lower levels of serum folic acid than the controls.

The majority of patients with malignant disease have minimal tissue stores of vitamin C (82). Vitamin C requirements are probably increased in times of stress (83). Cameron et al. (84) reported that high dose ascorbic acid supplements in advanced human cancer may enhance host resistance. One hundred terminal cancer patients were given supplemental ascorbate, usually 10 gm/day, as part of their routine management (85). Their progress was compared to that of 1000 similar patients, matched controls, who received the same treatment except for the supplemental ascorbate. The mean survival time was more than four times as great for the ascorbate subjects as for controls. The authors concluded that ascorbate is of definite value in the treatment of advanced cancer patients. However Alcantara et al. (86) cautions against the use of large doses of ascorbic acid in advance cancer, because some patients do not respond or even may be affected adversely, as evidenced by shorter survival times than controls or tumor hemorrhage and necrosis.

The significance of vitamin A in cancer has been em-

phasized in various studies in which it has been found to have both prophylactic and therapeutic effects on the development of chemically induced papillomas and carcinomas of the skin of mice (87). It might inhibit the induction of the tumor by destroying lysosomes, which release hydrolytic enzymes. A vitamin A deficiency has been associated with malignancy, for example lung cancer (88). Cohen et al. (89) suggest that vitamin A enhances the antitumor effect of certain cancer therapy drugs, such as 1.3-bis (2-chloroethyl)-1-nitrosurea and cyclophosphamide.

Data on the importance of vitamin D in cancer are sparse. However, administration of this vitamin in therapeutic dosage would aid in deposition of calcium in the bone. A common complication of cancer is hypercalcemia (90). Hypercalcemia associated with malignancy may be caused by elaboration of one or more of three humoral substances: parathormone, osteoclast stimulating factor and prostaglandins (91, 92, 93).

There is evidence of vitamin K involvement in tumor growth and metastasis (94). Vitamin K deficiency can be induced by the use of antitumor drugs. Certain surface properties of the tumor seem to be altered by vitamin K deficiency. An agent with strong anti-vitamin K activity is vitamin A. It supports differentiation in epithelial tissues, and has been demonstrated to have strong anti-

tumorigenic activity. Egilsson (95) advocates the use of chemotherapeutic agents, such as dicoumarol, a vitamin K antagonist, for above mentioned purpose.

Vitamins and chemotherapy. Some chemotherapeutic agents exert their action through their antivitamin character, thus creating a specific vitamin deficiency. One example is 6-aminonicotinamide (6-An), a potent niacin antagonist. This agent has strong antitumor activity against mammary adenocarcinoma (96). Shimoyama et al. (97) supported this finding in demonstrating that the tryptophan pathway and the activity of the nicotinic acid mononucleotide pyrophosphorylase was reduced by 6-AN. Antitumor activity may be reversed by nicotinamide. Vitamin A enhances the antitumor effect of an alkylating chemotherapeutic agent (89), probably through alterations of the lipoprotein membranes of tumor cells. As mentioned previously, dicoumarol, a chemotherapeutic agent is a vitamin K antagonist (95).

Vitamins in TPN for cancer patients treated with chemotherapy. The significance of various vitamins in cancer has been briefly described, as well as possible interactions with chemotherapeutic agents. One may summarize that a particular vitamin may act as an inducer for one kind of tumor and as an inhibitor of another kind. This variability in response hinders establishing a uniform basis for cancer patients receiving chemotherapy. However, crude guidelines can be given.

TPN programs mainly use carbohydrates as the primary energy source. Sauberlich (98) could clearly demonstrate on human volunteers that a close relationship exists between the requirement for thiamin and the amount of calories derived from carbohydrates in the diet. The glucose oxidative pathway requires thiamin pyrophosphate as a coenzyme in transketolase reactions (99). The demand for thiamin in a predominately carbohydrate diet must therefore be high, Since thiamine deficiencies have been reported in cancer patients, the requirement for this vitamin in cancer patients is possibly higher than currently established recommendations by the American Medical Association (AMA) for intravenous feeding (Table 3).

Likewise, the amino acid source (either as protein hydro lysate or amino acid solution) in the TPN mixtures affects the utilization and urinary excretion of the vitamins, riboflavin and pyridoxine. The role of those vitamins in the various metabolic pathways of amino acids is well known (75). There is an increased utilization of the nitrogenous material from the L-amino acid solution as compared to the hydrolysate. Only 3% of the nitrogenous material of the amino acid solution was recovered in the urine, whereas the nitrogenous material of the protein hydrolysate was only 60-80% used, although the amount of protein nitrogen was comparable in both solutions. The increased utilization of

TABLE 3
Comparison of the composition of multivitamin infusion solutions with recommendations and current investigated data

VITAMIN	RDA[1]	AMA[2]	MVI[3]	MVI[4]	NICHOALDS[5]
Vitamin A (IU)	5000*	3300	3300	10000	4200
Vitamin D (IU)	4000	200	330	1000	420
Vitamin E (IU)	15	10	1.65	5	2.1
Vitamin K (mg)	-	-	-	-	-
Ascorbic Acid (mg)	45	100	465**	500	210
Folacin (ug)***	400	400	300	-	600
Niacin (mg)	20	40	33	100	42
Riboflavin (mg)	1.8	3.6	3.3	10	4.2
Thiamine (mg)	1.5	3.0	16.5	50	21
Pyridoxine (mg)	2.0	4.0	4.95	15	6.3
Cobalamin (ug)***	3.0	5.0	30	-	15
Panthothenic acid (mg)	(5-10)	15.0	8.25	25	10.5
Biotin (ug)	(150-300)	60.0	-	-	-

1 = Recommended Dietary Allowances, oral alimentation for children age 11 and above and adults; does not include requirements for pregnancy and lactation (75)

2 = American Medical Association (100)

3 = Multi Vitamin Infusion, USV Laboratories, 10 ml vial, daily dose

4 = Multi Vitamin Infusion, USV Laboratories, 5 ml concentrate, " "

5 = Nichoald's modified formula (101)

* assumes 50 percent of intake of carotenes, which is less available than the vitamin

** an extra amount of 100 mg/l was added by the hospital pharmacy

*** not part of the MVI solution

( ) RDA not established; amounts considered to be adquate in usual dietary intake

the L-amino acid solution was accompanied by a decreased excretion of pyridoxine and riboflavin, demonstrating the higher requirement for these vitamins, when using amino acid solutions.

Vitamin E requirements increase with the use if Intralipid®. As described previously, Intralipid® is a source of unsaturated fatty acids. In animals the dietary requirement for vitamin E increases when the uptake of polyunsaturated fatty acids increases (75), since the vitamin prevents the oxidation of these compounds.

A beneficial effect of administered fat-soluble vitamins will not take place if circulating plasma-binding proteins are low, as is commonly seen in cancer patients (65). The plasma-binding proteins are necessary for the transport of fat-soluble vitamins in the blood stream (69).

Although a long period of time is required to deplete the adult of fat-soluble vitamin stores (72), the cancer patient may have depleted liver stores resulting from prolonged periods of inadequate alimentation. Thus, it is necessary to include fat-soluble vitamins (A,D,E) in a TPN program.

The liver may also play a conserving role for the water-soluble vitamins. Observations on the urinary excretion of the vitamins, riboflavin and pyridoxine, in a patient who received all the vitamins orally or mixed with the TPN solution, gave the following evidence. Water-soluble vitamins

are more effectively utilized when administered orally than through intravenous administration. On intravenous administration 58-67% of the unbound pyridoxine was excreted. However on oral feeding only 16-35% of unbound pyridoxine could be detected. With parenteral nutrition there appears to be a greater degree of excretion of vitamins through the kidneys (72).

A commercially available "Multi Vitamin Infusion" (MVI)* is available for use in TPN solutions. However, the U.S. Food and Drug Administration (FDA) has declared it: "ineffective as currently formulated" (100). In particular there is a need for research on vitamin requirements under special pathological conditions such as cancer. The latest recommendations of the American Medical Association (AMA) (100) for multivitamin infusion solutions are listed in Table 3. For comparison the current RDA's for oral needs are summarized. Table 3 also includes data of a study of Nichoaldes (101), who evaluated a modified MVI solution for its ability to maintain normal circulating plasma levels of vitamins A, C, E, B_{12}, folic acid and riboflavin. This modified formulation yielded normal blood levels of all tested vitamins within two weeks of initiating TPN therapy However, the investigators did not specify the conditions for which the patients were hospitalized, and thus no conclusions can be drawn regarding applications to the cancer patient.

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* MVI, USV Laboratories

When determining vitamin requirements, nutrient losses in the infusion material have to be kept in mind (102, 103). Moorhatch found that vitamin A (as acetate) 7.5 mg/l displayed 66.7% sorption to a plastic test strip in 24 hours. The presence of 5% dextrose and 0.9% sodium chloride increased the extent of sorption. However, the following vitamins did not reveal significant sorption to a Viaflex test strip in 24 hours: Ascorbic acid, niacin, pyridoxine, riboflavin, thiamine, vitamin D and vitamin E.

Electrolytes in TPN

A parenteral feeding program would be inadequate if electrolytes were not simultaneously administered. When longer periods of TPN feeding are applied, the risk of electrolyte imbalances or even inefficient utilization of nutrients may occur (104).

No one single formula will provide adequate electrolyte supplementation for every patient. Therefore, urine and serum electrolyte concentrations must be monitored, and additions and substractions made depending on the clinical situation. Cancer patients undergoing chemotherapy offer new problems. An important property of chemotherapeutic agents is probably their chelating effect on minerals (28).

Many of the metals are known to be essential for bio-

logical reactions in normal and neoplastic tissues (105). Table 4 summarizes the baseline requirements for electrolytes according to lean body mass, as recommended by Shils and Wretlind (106, 107). These recommendations serve as guidelines which can be altered for the specific patient. Adjustments must be made based on electrolytes already present in basic commercial infusion solutions (Table 5).

Since cachexia is a common phenomenon in the cancer patient (1, 2), special considerations must be given those elements required to rebuild lean body mass. Potassium is essential for the formation of lean body mass and deposition of protoplasm. For protein synthesis 3 mEq of potassium are required for every gram of nitrogen retained (108). Some evidence suggests that potassium is needed for the entrance of glucose in the cell (109). It is an essential activator of many enzymatic reactions involved with the transfer of high energy phosphate in carbohydrate metabolism. Thus sufficient potassium for a cancer patient will probably have a beneficial effect on glucose tolerance.

Magnesium is also an important intracellular cation needed for the deposition and formation of lean body mass. For new tissue synthesis, magnesium has to be provided at 0.5 mEq for every gram of nitrogen retained (108).

Since malignancy is often associated with hypercalcemia (90-93), the administration of extra calcium must be moni-

BLE 4
seline 24-hour nutrient requirement in tissue synthesis (106, 107)

Nutrient	Patient's lean body weight (kg)							
	50	55	60	65	70	75	80	85
otein (gm)	63	67	70	74	80	84	88	92
lories (non-protein)	2700	2850	3000	3150	3300	3450	3600	3750
a^+ (mEq)	100	100	100	100	100	100	100	100
(mEq)	52	56	60	64	70	72	76	80
g^{++}(mEq)	6	6.4	6.8	7.2	7.6	8	8.4	8.8
a^{++}(mg)	477	494	516	538	560	582	604	627
l^- (mEq)	100	100	100	100	100	100	100	100
(mg)	492	515	539	562	600	608	632	655

TABLE 5
Electrolyte content of commercial TPN Products (59)

Electrolyte	Aminosol[1]	Amigen[2]	C.P.H.[3]	Travamin[4]	Freamine[5]
Acetate (mEq/l)	-	-	-	-	20
Chloride (mEq/l)	?	22	?	22	45
Phosphate (mM/l)	-	30	-	30	-
Calcium (mEq/l)	-	5	-	5	-
Magnesium (mEq/l)	-	2	-	2	-
Sodium (mE/l)	13	35	39	35	10
Potassium (mEq/l)	17	18	18	18	-
Comment	a	b	a	b	a,c

1: by Abbott; 2: by Baxter; 3: by Cutter; 4: by Travenol
5: by McGaw

a deficient in calcium, magnesium, phosphate, potassium and sodium

b deficient in calcium, magnesium, potassium and sodium

c high chloride

Table 6 lists the role of electrolytes in TPN, their main function in metabolism and recommended concentrations for intravenous nutrition solutions.

TABLE 6
The role of electrolytes in TPN (108, 69)

Electrolyte	required for	recommended concentration (106)
Potassium	maintain intracellular tonicity normal contraction of smooth muscle; transport of glucose and amino acids across the cell membrane; protein synthesis	90-240 mEq/24 hrs 40 mEq/l
Magnesium	protein synthesis for new cell formation	24-45 mEq/24 hrs 8 mEq/l
Phosphate	protein synthesis for new cell formation; balance Ca/P ratio in blood; deposition of glycogen in the liver	60 mEq/24 hrs 20 mEq/l
Sodium	equilibrium between extra- and intracellular fluid compartments	60-150 mEq/24 hrs 40 mEq/l
Calcium	bone mineralization; functional integrity of nervous and muscular system; blood clotting	9-11 mEq/24 hrs 10 mEq/l
Chloride	acid base balance as part of extracellular fluid	100-120 mEq/24 hrs 40 mEq/l

tored carefully.

Adequate supplementation of phosphate ions is mandatory, because of commonly observed hypophosphatemia during TPN. Hypophosphatemia leads to a reduction of the levels of 2,3-diphosphoglycerate and adenosinetriphosphate (ATP) in red blood cells with a resulting shift to the left in the oxy-hemoglobin dissociation curve (110) leading to tissue hypoxia. Similarly hypophosphatemia with intravenous nutrition has been associated with a reduction of ATP in leukocytes causing depression of chemotactic, phagocytic, and bactericidal activities of the granulocytes, leading to inability to combat infection (111).

The nutritional status of the host with respect to selected electrolytes may affect tumor growth and metastasis. Depletion of magnesium and potassium in the rodent adversely affected the growth of transplanted tumor cells (112). Parson and coworkers (113) observed some tumor regression, gain in weight and relief of symptoms in terminal cancer patients with low plasma magnesium (0.8 mg/dl) and potassium (3 mmole/l). Low magnesium and potassium serum values were obtained by diet modification and/or hemodialysis (112). However, benefit was greatest with a higher than normal intake of calories and protein. The authors indicated that they have no conclusive evidence that the depletion of potassium and magnesium are responsible for the spontaneous regression of tumors. The removal of other

toxic factors through dialysis might have played a role as well. However, these observations will indoubtedly stimulate continuing investigation into the effect of minerals and electrolytes on tumor growth.

Trace elements

In recent years the importance of trace elements in the normal and abnormal functioning of metabolic processes has become progressively more apparent (113). Dietary deficiencies result in imbalances, which are correlated with acute and chronic disease states (114-117). The rationale for adding trace elements to TPN solutions is as follows (118, 119):

1) they fulfill important biochemical and physiological functions;
2) deficiencies of certain elements have been reported, especially on prolonged TPN (120-125);
3) patients in a catabolic state, like the cancer patient, are likely to have an increased demand.

Present knowledge of only fluorine, chromium, manganese, iron, cobalt, copper, zinc, selenium, molybdenum and iodine allows an evaluation for human nutrition (75). Table 7 list their metabolic functions and requirement for TPN (126). In Table 8 recommendations for individual trace element solutions for parenteral infusion are given (126, 127).

Hauer et al. (128) investigated trace element profiles in TPN solutions and found inadequate amounts in zinc, copper, iron and magnesium as compared to the recommendations. These researchers suggest monitoring serum and urine concentrations of trace elements in each patient receiving TPN.

There is evidence that utilization or redistribution within the body may affect plasma concentrations of trace elements in some patients (129, 130). Neither an increase in urinary excretion nor a primary decrease in plasma-binding proteins appeared to be a major factor in lowering plasma trace metal concentrations in patients undergoing TPN (129).

Plasma proteins are essential for the transport of trace elements in body fluids. Copper, for example, is bound to plasma albumin before the element is incorporated into various proteins and enzymes (116). Since cancer patients have low circulating levels of plasma proteins, especially albumin and transferrin (130), carriers of the elements are insufficient, allowing excretion of needed nutrients. This might explain the high urinary loss in catabolic stress situations (120).

Of particular importance for the cancer patient might be the addition of chromium and zinc to the infusion solution. Chromium increases glucose tolerance in patients. A

TABLE 7
Trace elements in TPN (126, 127)

Element	functions is	recommended daily dosage
chromium	glucose tolerance	15 mcg
cobalt	constituent of vitamin B_{12}	5 mg/d other than amount from vit. B_{12}
copper	hemoglobin formation activator of enzymes	1 mg
fluoride	prevention of dental caries	1-2 mg
iodine	thyroid function	1-2 mcg/kg
iron+	red blood cell production coupling of oxidative phosphorylation	1-2 mg
manganese	protein synthesis reproduction and growth activator of enzymes	1-2 mg
zinc	activation of enzymes for protein metabolism vitamin A metabolism	2-4 mg

+ iron is not added to TPN solutions because of incompatibilities and precipitation reactions. It is usually administered intramuscularly.

TABLE 8
Recommendations for individual trace element solutions[+] (126)

	Ionic Concentration	Salt Concentration	%W/V
Zinc, mg/ml	1.0	4.39[#]	0.439
Copper, mg/ml	0.4	1.57[*]	0.157
Chromium, ug/ml	4	20.5[@]	0.00205
Manganese, mg/ml	0.1	0.308[ø]	0.0308

[+] the specific hydrate form of the salt employed is determined by the manufacturing procedures and requirements.

[#] Zinc as: $ZnSo_4 \cdot 7H_2O$; molecular weight (mol wt), 287.56; Zn^{++} = 22.74

[*] Copper as; $CuSO_4 \cdot 5H_2O$; mol wt, 249.69; Cu^{++} = 25.45%

[@] Chromium as: $CrCl_3 \cdot 6H_2O$; mol wt, 266.45; Cr^{+++} = 19.5%

[ø] Manganese as: $MnSO_4 \cdot H_2O$: mol wt, 169; Mn^{++} = 32.5%

chromium-nicotinic acid complex, "glucose tolerance factor", facilitates the interaction of insulin with insulin receptors at the cellular level (124). Latest research indicates a role of zinc in the immunological system (131). Especially in the cancer patient, immunocompetence is important for tumor inhibition and regression. Zinc deficiency is characterized by impairment of sensory perception, poor wound healing, diarrhea, mental depression, paranasal, oral and perioral dermatitis and alopecia (114). These signs resemble in every way those observed in cancer patients undergoing chemotherapy (28, 33). One might speculate, therefore, that some chemotherapeutic agents exhibit chelating effects, making the element unavailable.

COMPLICATIONS OF TPN

Total parenteral nutrition has been accepted widely as a important measure for the realimentation of a malnourished patient, which includes the cancer patient. However, experience has made some negative aspects of this regimen evident. Advantages and disadvantages have to be compared, and the true benefit/risk ratio determined. Table 9 outlines potential complications of TPN therapy. They can be organized into mechanical and metabolic complications, and those derived from contaminations of the infusion site.

Dudrick (36, 37) advocated meticulous care and a strict protocol to reduce the incidence of complications. Following his principles most complications can be avoided.

TABLE 9
Complications of total parenteral nutrition (136)

HAZARD	POSSIBLE EXPLANATION
I. Mechanical Complications	
pneumothorax damage of intrathoracic structure thrombosis	due to incorrect placement of the catheter; nonsterile surgical insertion; sclerosis of venous structure (133-135)
II. Metabolic Complications	
Glucose metabolism	
- hyperglycemia; glycosuria, osmotic diuresis, nonketo-hyperosmolar dehydration; coma	rapid infusion of hypertonic glucose inadequate endogenous insulin; glucocorticoids.
- postinfusion hypoglycemia	continuing high endogenous insulin production, due to the increased stimulus of the pancreas by high carbohydrate infusion (135, 136).
Amino acid metabolism	
-hyperammonemia	excessive ammonia in the protein hydrolysate solution; deficiencies of arginine, ornithine, citrulline in crystalline amino acid solutions; Hepatic disorder (137, 138)
- hyperchloremic metabolic acidosis	due to excessive amounts of chloride ions in crystalline amino acid solutions; excess amounts of cationic amino acids in relation to anionic amino acids in the infusate (138).

TABLE 9
Complications of total parenteral nutrition (concluded)

HAZARD	POSSIBLE EXPLANATION
Mineral metabolism	
- hypophosphatemia with decreased erythrocyte 2,3-diphosphoglycerate	inadequate phosphorus administration; increased demand for glucose metabolism (139, 140)
- increased affinity of hemoglobin to oxygen	due to left shift of oxygen dissociation curve of hemoglobin (110);
- hypocalcemia	inadequate calcium administration; reciprocal response to phosphorus repletion, hypoalbuminemia (130)
- hypercalcemia	hypercalcemia of malignancy; excessive vitamin D administration (90-93)
Trace mineral metabolism	
- Zinc deficiency	due to inadequate administration in the infusion solution (120-123)
- Copper deficiency	
- Chromium deficiency	
Electrolyte metabolism	
- hypokalemia	increased requirement for protein anabolism; inadequate administration; diuresis (109)
- hyperkalemia	excessive potassium administration
- hypomagnesemia	increased requirement for protein anabolism and glucose metabolism;
- hypermagnesemia	excessive administration

TABLE 9
Complications of total parenteral nutrition (concluded)

HAZARD	POSSIBLE EXPLANATION
Essential nutrient deficiencies	
essential fatty acid deficiency	
- serum deficiencies of phospholipid, linoleic and/or arachidonic acids; serum elevations of 5,8,11-eicosatrienoic acid	inadequate essential fatty acid administration; inadequate vitamin E administration (75, 141)
hypovitaminoses	
- low serum folate levels	increased requirement (81);
- ascorbic acid	increased requirement; due to stress; tissue synthesis (82)
Hepatic disorders	
- elevation in SGOT, SGPT* and serum alkaline phosphatase	enzyme induction secondary to amino acid imbalance; excessive glycogen and/or fat deposition in the liver (135, 142)
- hepatomegaly	
III. Contamination	
Sepsis	lack of sterile technique may result in contamination of both the catheter and the infusion material (143, 144). Decreased immunocompetency of the host (131)

* SGOT = serum glutamic-oxalacetic transaminase
SGPT = serum glutamic-pyruvate transaminase

SUMMARY

The growth of cancer leads to profound alterations of host organs and functions. The overall result is cachexia a syndrome characterized primarily by weakness, anorexia and depletion of host components.

Two major effects may play roles in cancer cachexia: reduction in protein synthesis and inefficient patterns of fuel utilization, with lipid sources predominating.

Therapeutic approaches with chemotherapy unavoidably affect host cells and produce a variety of side effects on organ systems further decreasing appetite and body weight. These effects may leave the patient with profound nutritional deficiencies.

The manifestation of cachexia, whether due to anorexia of malignancy, side effects of chemotherapy, or factors other than insufficient food intake (paraneoplastic syndrome), must be reversed by vigorous nutritional support. The cachectic patient will exhibit a much narrower safety margin for chemotherapy than does the well nourished host.

The nutritional status of a cachectic patient, whose gastrointestinal tract is not in condition for adequate nutrition, can be successfully restored and maintained through the intravenous administration of nutrients. Central venous catheterization of the subclavian vein

has become the favored route for the administration of sufficient energy and protein to promote tissue synthesis. Commercially available nutrient solutions for total parenteral nutrition are applicable. However, only crude guidelines can be suggested for the levels of energy intake and optimum relationships between protein and energy requirements for the feeding of the cancer patient.

Likewise, incertainty remains about the quality and quantity of vitamins to be administered. Since one particular vitamin may act as an inducer for one kind of tumor, and act as an inhibitor for another kind of tumor, this variability in response hinders establishing a uniform basis for vitamin solutions for the cancer patient. Also, interactions of vitamins with chemotherapeutic agents occur, as a basis for their antitumorigenic effect.

Prolonged periods of TPN feeding may lead to electrolyte and trace mineral imbalances and thus, metabolic abberrations and inefficient nutrient utilization. Additions or substractions to the infusate of any of these essential nutrients are recommended according to serum and urine concentrations and the clinical situation of the patient.

Besides all the advantages of this important therapy for the realimentation of a malnourished patient, a variety

of complications have been reported. However, advantages of a total parenteral nutrition regimen for a cancer patient on chemotherapy outweigh possible side effects, which are avoidable by meticulous care and a strict protocol of the therapy.

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TOTAL PARENTERAL NUTRITION IN THE CANCER PATIENT UNDERGOING CHEMOTHERAPY

by

ANNETTE KUNIGK
Dipl. oec. troph.
Justus Liebig University, Giessen, W. Germany 1978

AN ABSTRACT OF A MASTER'S REPORT

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ABSTRACT

The growth of cancer leads to profound alterations of host organs and functions. The overall result is cachexia, syndrome characterized primarily by weakness, anorexia and depletion of host components.

Therapeutic approaches with chemotherapy affect host cells and produce a variety of side effects on organ systems further decreasing appetite and body weight. These effects may leave the patient with profound nutritional deficiencies.

The nutritional status of a cachectic patient. whose gastrointestinal tract is not available for adequate nutrition can be successfully restored and maintained through the intravenous administration of nutrients. Commercially available nutrient solutions for total parenteral nutrition are applicable. However only crude guidelines can be given for the levels of energy intake and protein requirements and the intake of other essential nutrients.

Possible side effects of a total parenteral nutrition regimen, are avoidable by meticulous care and a strict protocol of the therapy.