

INTERACTION OF NUTRITION AND CHEMOTHERAPY
IN THE CANCER PATIENT

by

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INTRODUCTION

Cancer is the second leading cause of death in the United States. In 1979, approximately 400,360 Americans died of cancer (1). Extensive research is being conducted to determine the causes of cancer and to evaluate methods of treatment. Diet and nutrition interact with cancer in various ways. They may play roles as etiologic and conditioning factors in the induction and rate of growth of tumors. In turn, malignant processes may cause anorexia and progressive wasting of the cancer patient. As the mode of cancer treatment has become more aggressive in an attempt to control neoplasia growth, there also has been a rising concern about the effect of treatment on nutritional status. The purpose of this paper is to review the interaction of nutrition and chemotherapy in the treatment of cancer patients.

EFFECTS OF NEOPLASTIC DISEASE
ON NUTRITIONAL STATUS

The growth of cancer leads to numerous alterations of host organs and functions. The overall result is cachexia, a syndrome characterized primarily by weakness, anorexia, and the depletion and redistribution of host components (2). Cachexia has been observed in one-third to two-thirds of patients with various cancers (3). It is the consequence of anatomical alterations, decreased food intake or absorption and altered metabolism. This common response of cancer patients bears no positive correlation to the amount, type, or site of neoplastic tissue and patients may have obvious wide-spread tumors without any of these manifestations. However, when such responses do occur, they are recognized as signs that uncontrolled tumor growth is occurring and unless such cancerous growth can be inhibited, progressive deterioration and ultimate death will occur (4). To better understand the effects of cancer on nutritional status, a closer examination of the components of cachexia is required.

Anorexia

Anorexia (failure of appetite) is a major determinant of cancer cachexia (5). In the cancer patient the reasons for this failure of appetite are highly variable. Early satiety is a symptom in many anorexic patients. Despite being hungry at the beginning of the meal, these patients experience an aversion to more food after the consumption of only a small quantity (6).

Various theories have been proposed to explain the bodily mechanisms affected by cancer that result in early satiety. Alteration of the

second catecholamine mechanism in the hypothalamus provides the basis for the first theory (5). The stress of illness may stimulate release of B-adrenergic and dopaminergic substances leading to suppressed appetite in the cancer patient. The alimentary tract regulation theory indicates that sensations from the oropharyngeal regions, the stomach, and the intestine play a regulatory role by metering the quantity of food eaten on a meal to meal basis (7).

Several other theories include regulation by means of osmoreceptors (8), hormones (9) and the tricarboxylic acid cycle (6). All of these theories, however, leave major questions on the physiology and pathophysiology of hunger and satiety unanswered (10).

Change of Taste

Another factor that can contribute to anorexia is a change in taste. Carson and Gormican (11) compared taste thresholds of cancer patients before cancer treatment and healthy individuals of similar age and sex. Twenty-nine women with breast cancer and ten women and nine men with cancer of the colon were tested. Detection and recognition thresholds for salty, sour, sweet, and bitter tastes were determined using sodium chloride, dilute hydrochloric acid, sucrose, and urea, respectively. Detection threshold was defined as the lowest concentration at which a subject could identify a solution as tasting different from water. The recognition threshold was the lowest concentration at which a subject could correctly identify the solution as tasting sweet, salty, sour or bitter. Higher thresholds reflected decreased sensitivity. Abnormalities observed in patients before treatment involved decreased salt and sweet

sensitivity. For some thresholds, greater abnormalities were observed among men than women, among patients with some types of cancer and among those with a greater extent of disease.

DeWys and Walters (12) correlated altered taste sensations to symptoms of meat aversion, which are frequently recognized in cancer patients. Taste recognition thresholds for salty, sour, sweet and bitter (urea) were tested on 50 tumor patients. The urea-testing results for the cancer patients were divided as to the presence or absence of the symptom of aversion for meat. Of 16 patients who reported an aversion to meat, 12 had a median urea recognition threshold of 75 m moles/liter compared to the median of 300 m moles/liter in the patients without meat aversion. The occurrence of an abnormality of taste sensation has been correlated with tumor extent (12, 11, 5) (see table 1).

TABLE 1
Correlation between tumor extent and
incidence of taste abnormality (5)

Tumor Extent ¹	Normal Taste Threshold	Abnormal
Limited	9	0
Moderate	18	3
Extensive	5	15

¹Tumor extent was scored on a 0 to 3 scale by organ site and the sum of all organ scores was called the tumor extent score. Patients with limited extent had scores of 1-2, moderate 3-4, and extensive 5 or more.

Abnormalities in taste sensation have been correlated with reduced energy intake (5, 13). DeWys (5) observed that patients with an abnormally

low urea threshold or with an elevated sucrose threshold had energy intakes which were significantly lower than those of the cancer patient group with normal taste. Thus abnormalities in taste may discourage food intake and contribute to weight loss and nutritional depletion in cancer patients.

Increased Metabolism

Increased metabolic expenditure also has been shown to be a contributing factor to tissue wasting and eventual cachexia in patients with cancer. Bozzetti et al. (14) showed that resting metabolic expenditure was increased above 20% in 60% of their patients with advanced cancer. They found a significant correlation between resting metabolic expenditure and tissue wasting (evaluated as a weight loss) and a decreased serum transferrin (table 2).

TABLE 2

Relationship among resting metabolic expenditure, weight loss, creatinine-height index, and transferrin (14)

Resting Metabolic expenditure	No. of patients	Weight loss	Creatinine- height index	Transferrin
		%	% standard	gm./100 ml.
+20	27	9.3	-2.2	280
+21 - +40	19	14.5	-1.4	293
+41 - +60	12	17.2	-6.2	239
+61 - +80	7	23.1	-21.6	247

Serum transferrin and creatinine-height index were measured because

transferrin is a sensitive indicator of visceral protein status and creatinine-height index is an indicator of lean body mass. As resting metabolic expenditure increased there was a greater weight loss and a decreased creatinine-height index and serum transferrin. Warnold and co-workers (15) also showed that both the daily energy expenditure and the resting metabolic rate were significantly greater in patients with cancer than they were in controls. Bozzetti et al. (14) pointed out that increased or even normal resting metabolic expenditure, despite weight loss and undernutrition, indicates that many of the adaptive mechanisms normally seen with semistarvation are impaired in patients with uncontrolled cancer growth.

The continued utilization of amino acids for gluconeogenesis indicates a loss of enzyme adaptation for energy conservation. This leads to commonly observed protein-calorie malnutrition in cancer patients (16).

An inability to oxidize a glucose load has been recognized in cancer patients. Waterhouse and Kemperman (17) determined the plasma disappearance and CO_2 production curves after a labeled glucose load was given by single injection to five subjects with cancer. The results were compared to those found in a group of normal subjects on whom identical studies had been carried out. Carbon dioxide production from labeled glucose was much lower in the cancer patients than in the normal controls. These results indicated that the normal metabolic adjustments were severely limited in patients with cancer.

To explain increased energy expenditure and inability to adjust the metabolic rate in a state of malnutrition, various possibilities have been

considered. Utilization of lactate for glucose synthesis is an energy requiring process and an increased rate of resynthesis of glucose in the liver from the lactate produced by the tumor has been proposed as the mechanism responsible for the increased energy expenditure in the tumor bearing patient (18, 19). The increased energy expenditure also could be the result of some alteration in the energy yielding reaction and the coupling mechanism of oxidative phosphorylation (14).

USE OF CHEMOTHERAPY

History

In 1965 Albert (20) reviewed the history of chemotherapy. The term "chemotherapy" was coined by Paul Ehrlich who defined it as the use of drugs to injure an invading organism without injury to the host. Ehrlich's interest and intense research into chemotherapy started in 1899. He saw a need to find chemicals with much stronger affinities for the parasites than for the host. In 1902, Laveran and Mesnil injected arsenic into mice infected with trypanosomiasis. All the mice died, but they died cured which was considered a great advance at that time. In 1904, Ehrlich truly cured trypanosomiasis in mice with trypan red, which thereby became the first man-made chemotherapeutic agent.

Review of Drugs

Chemotherapeutic drugs are classified according to their source and their mode of action in the cell. The major classifications of chemotherapeutic drugs have been outlined by Csaky (21). A review of these major classifications is necessary to understand their principle action.

Alkylating Agents. Alkylating agents interfere with the synthesis

or crosslinking between the chains of DNA, thus preventing proper replication. Examples of alkylating agents include busulfan, chlorambucil, cyclophosphamide, nitrogen mustard, melphalan, cisplatinum, and dacarbazine. These drugs are cytotoxic to all tissues such as intestinal mucosa, corneal epithelium, germinal tissues, lymphatic and hematopoietic tissues.

Antimetabolites. The antimetabolites include the folic acid antagonists and the purine and pyrimidine antagonists. Methotrexate is the major folic acid antagonist and interferes with DNA synthesis by interfering with the formation of adenine. The major purine antagonist is 6-mercaptopurine. Pyrimidine antagonists include cytosine arabinose and 5-fluorouracil which interfere with the formation of DNA synthesis by inhibiting thymidyllic synthetase.

Antibiotics. Actinomycin interferes with cell division by combining with and inactivating the DNA specifically needed for RNA synthesis (RNA polymerase is DNA dependent). Mitomycin C is another antibiotic which acts by depolymerizing DNA; thus there is no cell division. Other antibiotics used include adriamycin D, bleomycin, streptoazotacin, and daunomycin.

Plant Alkaloids. Included in this group are the drugs vinblastine and vincristine which act by preventing cell division, specifically by arresting mitosis in the metaphase. Vincristine is more active than vinblastine.

Other drugs. Urea derivatives, which interfere with DNA synthesis, include the drugs, hydroxyurea and urethane. Nitrosoureas, lomustine and streptozocin also interfere with DNA synthesis. Procarbazine hydrochloride,

the enzyme asparaginase, and cortisone and other sex hormones also are used for chemotherapeutic treatment.

Side Effects of Chemotherapy

Nausea and Vomiting. The most common manifestation immediately following the administration of almost all chemotherapeutic drugs is nausea and vomiting (22). Nausea and vomiting associated with chemotherapy are mediated by the chemoreceptal trigger zone located in the area postrema of the fourth ventricle (23, 24). Decreased oral intake, fluid and electrolyte imbalance, general weakness, and weight loss are the nutritional concerns associated with nausea, vomiting, and accompanying anorexia (25).

Schein et al. (26) reported the effects of administering streptozotocin, a naturally occurring nitrosurea antibiotic, to 106 patients with advanced malignancies including Hodgkin's disease, lymphomas, and leukemia. Nausea and vomiting were experienced by 87% of the patients. These symptoms were severe in 11%, moderate in 38% and mild in 38% of the patients. Symptoms usually appeared 1 to 4 hours after drug administration and in large part could not be prevented or controlled by the use of phenothiazine antiemetics.

Broder and Carter (27) treated 52 patients with metastatic islet cell carcinoma with streptozotocin. Acute, often dose limiting, toxicity consisting of nausea and vomiting was observed in 98% of the cases.

Procarbazine, (28, 29, 30), used mainly in the treatment of Hodgkin's disease, also may cause nausea and vomiting. Two other drugs which can be dose limiting because of nausea and vomiting are cis-diamminedichloroplatinum (31, 32), and 5-azacytidine (33). Gottlieb and Drewinko (34)

described patients who vomited for as long as a week following administration of cis-platinum.

Stomatitis. Stomatitis in the form of oral ulceration, cheilosis, pharyngitis, and other mucosal toxicities of the alimentary canal are common with many of the chemotherapeutic agents. Because of a rapid turnover of the epithelial cells of the mucosa, the alimentary canal is one of the most vulnerable targets of chemotherapeutic agents (25).

DiPaola et al. (36) reported that actinomycin D caused ulceration of the gastrointestinal tract of mice. Humphrey et al. (36) evaluated the effects of actinomycin D in 21 patients with advanced cancer. Patients were given a total dose of either 65 or 75 micrograms/kilogram body weight intravenously. The higher dosage level resulted in toxicity manifested most commonly by ulcerations of the lips, tongue and buccal mucous membrane in a large percentage of the patients. Shaw et al. (37) observed oral ulcerations in 3 of 12 children treated with actinomycin D.

Regelson and Holland (38) studied 48 patients with advanced cancer or leukemia who were treated with methyl-glyoxal bisguanylhidrazone at either 5 mg/kg/day or 150 mg/m²/day. For all patients, response was seen only in the presence of significant toxicity which seriously compromised any clinical improvement. Severe oral and pharyngeal ulceration as well as laryngitis, esophagitis, and colitis were among the major manifestations of toxicity.

Pharyngitis and varying degrees of mucosal ulceration were observed in 7 out of 14 patients with advanced lung cancer after treatment with high doses of methotrexate (39). Toxicities, however, could not be correlated with dose level.

Seifert et al. (40) reported mild to very severe stomatitis in 22 out of 34 patients treated with continuously infused 5-fluorouracil for 5 days. This was a dose limiting complication and many of the patients required prolonged intravenous feeding. Severe oral toxicity also has been observed after azaserine, daunorubicin, and adriamycin treatment (25). Mucosal ulcerations are rarely reported in the use of alkylating agents.

As a result of stomatitis, eating becomes very difficult and food intake is decreased. This contributes to dehydration and further deterioration of the nutritional status of the patient.

Constipation. Constipation has been reported to be a prominent problem in vincristine treatment. Holland et al. (41) studied the effects of a series of dose levels in 392 patients with advanced cancer. Constipation was reported on one-third of all patients, with greater frequency, severity and earlier onset in the highest dose group. Three patients sustained adynamic ileus which required medical decompression.

Diarrhea. Diarrhea is part of the general mucosal toxicity produced by a number of chemotherapeutic agents. It is particularly severe in treatment with 5-fluorouracil (40) and with methylglyoxalbisguanyldihydrazone (38). Mucosal toxicity appeared on the average of 7 days after treatment with methylglyoxalbisguanyldihydrazone and continued for an average of 7 days before recovery. Diarrhea also is commonly seen after methotrexate, hydroxyurea, nitrosoureas and 5-azacytidine. Prolonged effects of uncontrolled diarrhea include dehydration, electrolyte imbalance, inanition (lack of food, starvation) and accelerated malnutrition (25, 42).

Taste changes. The most dramatic alterations in taste sensitivity

usually occur with radiation therapy. However, 5-fluorouracil treatment caused an increased sensitivity to sweet and some alterations in bitter and sour tastes (43).

Bone marrow depression. The hematopoietic system is one of the most vulnerable targets of cancer chemotherapeutic agents. Leukopenia, a deficiency in the number of leukocytes in the blood, and thrombocytopenia, a decrease in the number of platelets in the circulating blood, are dose limiting toxicities in the use of methotrexate (39), streptozotocin (27), and cis-platinum (34, 31). Leukopenia also was reported after treatment with 5-fluorouracil (40), vincristine (41), bis-guanylhyazone-dihydrochloride (38), busulfan and chlorambucil.

Because of the decrease in production of blood cells by the depressed bone marrow, the patient receiving almost any kind of chemotherapy is very susceptible to infection. The resulting fever, chills, anorexia, and increased energy consumption accelerate the deterioration of the nutritional status of the patient.

Megaloblastic anemia and the effects of folic acid antagonists. Anemia is frequently reported after the administration of chemotherapeutic agents. Chemotherapeutic drugs that interfere with DNA synthesis often result in megaloblastic anemia. This complication has been reported with 6-mercaptopurine, 5-fluorouracil (44), cytosine arabinoside (45) and, especially, the folic acid antagonists, methotrexate and aminopterin (46, 47, 48).

Defective DNA synthesis, producing megaloblastosis, most frequently arises from deficiencies of vitamin B₁₂ or folic acid. Nichole and Welch (49) early demonstrated that the biochemical effect of aminopterin injected

into rats or added to liver preparations in vitro was to prevent the conversion of folic acid to reduced cofactor forms (folinic acid). Broquist et al. (50) further demonstrated that tetrahydrofolic acid could prevent the effects of aminopterin in mice and therefore it was suspected that the effect of the drug was to prevent the reduction of folic acid. Later Waxman et al. (46) agreed by reporting that the folic acid antagonists usually inhibit the enzyme dihydrofolate reductase, which results in blockage of the reduction of dihydrofolate to tetrahydrofolate and its derivatives. As a result, the tissues become deficient in tetrahydrofolate acid. This has the same consequences as nutritional folate deficiency. Depression of thymidylate synthesis follows and therefore failure of new DNA-thymine synthesis results in the arrest of cell division. All actively growing cells whether malignant, normal, or abnormal are affected by these drugs.

The bone marrow and alimentary tract epithelium are the two tissues most affected by folic acid analogs. The toxicity may be more severe and pronounced if patients are in poor condition or have infection or compromised liver or bone marrow function. Previous subclinical folate deficiency commonly observed in patients with neoplastic disease may be related to this increased toxicity (25). Clinical toxicity of methotrexate is more of a direct function of the duration of administration of the drug than a function of the dose of the drug (51, 52).

Liver and pancreas dysfunction. Serious nutritional problems can be the result of chemotherapeutic effects on the liver. Albumin, prothrombin, fibrinogen, and several other serum proteins are synthesized exclusively

by liver cells and extensive liver damage leads to decreased blood levels of these proteins (53). Hypoalbuminemia may occur with a significant destruction or replacement of liver cells.

Liver damage is often observed after administration of asparaginase (54). Einhorn and Davidsohn (55) reported jaundice occurred in 16 of 38 leukemic patients who were treated with 6-mercaptopurine. In eight patients, jaundice cleared up rapidly on cessation of 6-mercaptopurine therapy and there was a recurrence of jaundice in two who were rechallenged with the drug. Hepatic dysfunction also is common after methotrexate (56), streptozotocin (27), mithramycin (57), 5-azacytidine (58), and Bacillus Calmette Guerin (BCG) (59).

The pancreas also is susceptible to damaging effects of chemotherapeutic agents. Pancreatic dysfunction has been reported to result from treatment by asparaginase (54). Streptozotocin treatment was shown to affect the islet cells of the pancreas resulting in hyperglycemia and abnormal glucose tolerance tests (60). Severe hypoglycemia and coma were produced by methylglyoxalbis-guanyl-hydrazone (38).

Renal complications. Renal complications caused by chemotherapy treatment lead to varying degrees of uremic syndrome. The uremic syndrome is characterized by retention of urea, creatinine, and other products of protein metabolism in the blood and tissues; progressive acidosis; inability to excrete a water load within a brief period; and various electrolyte disturbances (61). Renal tubular necrosis was reported as one of the toxic effects of cis-diamminedichloroplatinum when administered in dogs, monkeys, and mice (62). The renal damage caused by cis-diamminedichloroplatinum,

appears to be similar to that caused by heavy metal poisoning in man (34). The renal toxicity appears to be dose related, accumulative and only partly reversible (63).

A case of irreversible renal toxicity due to cis-diamminedichloroplatinum was reported by Hardaker et al. (64). The BUN (blood urea nitrogen) reached a maximal level approximately 2 weeks after the start of therapy and never returned to normal. Areas of interstitial fibrosis with lymphocytic infiltrates and tubular destruction were observed.

Methotrexate (65, 51), and streptozotocin (26), also have been reported to produce dose limiting renal complications. Fatal renal toxicity was recorded in 5 of 46 patients with islet cell carcinoma treated with streptozotocin (27).

Amino aciduria, resulting from a blockage by cycloleucine of the renal tubular reabsorption of cystine, ornithine, lysine and arginine was reported by Brown (66). A slight rise in blood urea nitrogen has been observed frequently after asparaginase treatment and, in a few cases, frank renal failure with oliguria has been described (54).

Fever and chills. Fever and chills are common and usually immediate side effects of treatment with bleomycin (67), asparaginase (54), and BCG (59). BCG was observed to have induced fever which began 4 to 8 hours after injection and persisted for as long as 24 hours. Fever also has been reported after the administration of cyclophosphamide, 6-mercaptopurine and cytosine arabinose (25). Fever accelerates all metabolic processes and contributes to the wasting of body nitrogen and energy. Basal energy metabolism is increased by about 13% for each degree Celsius rise in

temperature above normal, 7% for each degree Fahrenheit (68). These increased requirements must be taken into consideration when planning a dietary regime.

Electrolyte imbalance. Mithramycin (69), diazo-oxonorleucine, methotrexate and actinomycin D, have produced hypocalcemia (25). Hyponatremia (low blood sodium) induced by vincristine was reported by Meriwether (70) and was attributed to inappropriate antidiuretic hormone production.

Central nervous system. Neurologic disorders associated with cancer are most frequently the result of metastasis to the nervous system. However, neurotoxicities have been recognized as results of chemotherapeutic treatment. Vincristine can produce weakness, insomnia, confusion, psychosis, disorientation and hallucination (41).

Asparaginase produced unpredictable lethargy, depression, disorientation, confusion, and hallucination (71, 54). Methotrexate (72), procarbazine (30), cycloleucine (66), 5-fluorouracil (73), and corticosteroids also have caused various central nervous system disorders. Central nervous system dysfunctions often result in impaired oral intake (74).

NUTRITIONAL SUPPORT OF THE CANCER PATIENT

Types of Nutrition Support

Nutritional maintenance of the cancer patient before, during, and after treatment represents a continuous challenge. As the result of the cancer or of the treatment, oral food intake is often contraindicated by impaired swallowing, obstruction of the alimentary tract, ileus, fistulas,

coma, severe malabsorption with massive fluid and electrolyte losses, and persistent vomiting. In such cases enteral feeding either by tube or intravenously must be employed (75). When the gastrointestinal tract is not functioning, for example because of an intestinal obstruction or persistent vomiting, the only possible alternative is intravenous feeding.

Effects of Aggressive Nutritional Support

Response rates. Recently much attention has been focused on the effect of nutritional support on the response rates to chemotherapy. Aggressive nutritional support utilizing intravenous hyperalimentation before, during, and after chemotherapy has been reported to positively affect the response to treatment in several studies.

Lanzotti et al. (76) showed a positive correlation between nutritional status and response to chemotherapy in 30 patients with non-oat cell carcinoma of the lung who received the same treatment protocol of bleomycin cyclophosphamide, 5-fluorouracil, methotrexate, and vincristine. Ten of these patients received intravenous hyperalimentation (IVH) at 2000 kcal/day for an average of 22 days starting during the first cycle of chemotherapy. Patient selection was based totally on apparent nutritional need. The least prior weight loss for an intravenously fed patient was 6.5% from normal body weight. Five of the ten patients in the intravenously fed group responded to chemotherapy as compared to none out of twelve of the non-intravenously fed group in the same weight loss category (greater than 6.5%) as seen in table 3.

Issell et al. (77) evaluated the effects of adding IVH to chemotherapy with corynebacterium parvum, isophosphamide, and adriamycin (CIA)

TABLE 3
Comparison of variables possibly affecting
chemotherapeutic response (76)

Variables	IVH ¹ (n = 10)	NonIVH (n = 12)
Mean Age	58.4	59.3
Mean % weight loss	15.9	11.9
No. of patients who received previous therapy	6	3
No. of responses to chemotherapy	5	0

¹ IVH = Intravenous hyperalimentation

in 26 patients with extensive squamous cell lung cancer. Intravenous hyperalimentation was administered for 10 days prior to the first course of CIA in 13 patients and continued up to the start of the second course of therapy for a total of 31 days. Infusion was via a central venous catheter inserted into the middle of the superior vena cava via the sub-clavian vein. The kilocalorie and protein intakes with and without IVH are shown in table 4. To assess nutritional status, patients were weighed and anthropometric measurements were recorded before each course of chemotherapy (see table 5).

Anthropometric measurements in this study included arm muscle circumference and triceps skinfold. Arm muscle circumference is measured with a tape at the midpoint between the scapula (bony protrusion on posterior of upper shoulder) and the ulna (bony point of elbow) with arm bent at elbow at 90° angle and palm up. Triceps skinfold is also measured at

this midpoint of the upper arm. The examiner grasps a verticle pinch of skin and subcutaneous fat between the thumb and forefinger. The skinfold is gently pulled away from the underlying muscle tissue and measured using a caliper.

During the first course of chemotherapy, patients fed by IVH had an increase in body weight and arm muscle circumference and less of a decrease in triceps when compared to patients not fed by IVH who had decreases in all three parameters. There was very little difference in weight change between the IVH group and the nonIVH group in the second course of treatment. Arm muscle circumference and triceps were again decreased more in the nonIVH group as compared to the IVH group. Bone depression, the dose limiting factor in CIA treatment, was observed less in the patients receiving IVH. A significant decrease in nausea and vomiting was found for the IVH group. The differences in toxic effects between each group were not maintained over subsequent courses of therapy when both groups received CIA alone. The results of this study suggested that IVH provides a means of giving high chemotherapeutic doses with the intent of increasing tumor response and patient survival.

An increased tolerance for 5-fluorouracil has been demonstrated in rats maintained on IVH (78). Administration of 15 mg/kg/day of 5-fluorouracil intraperitoneally for 7 days killed 80% of the rats fed orally, whereas only 30% of the rats given IVH were killed by the same dose of 5-fluorouracil. Minimal diarrhea, melena (darkening of the stools by blood pigments), and fur loss occurred in the intravenously-fed group,

TABLE 4

Total nutritional intake from all sources
during first course of chemotherapy (77)

	IVH ¹		NonIVH	
	Median	Range	Median	Range
Kcal	170	120-238	81	57-125
Nitrogen	270	167-320	133	102-161

¹ IVH = Intravenous hyperalimentation

TABLE 5

Relation of nutritional parameters to administration
of intravenous hyperalimentation (77)

	IVH		NonIVH	
	Median	Range	Median	Range
First Course				
Weight change ¹	+7	+1 to +11	-1	-9 to +3
Arm muscle circumf. change ²	+6	-2 to +13	-4	-8 to +1
Triceps ³	-2	-11 to +28	-6	-26 to +29
Second Course				
Weight change ¹	0	-7 to +4	+1	-7 to +7
Arm muscle circumf. change ²	+1	-11 to +3	-5	-8 to 0
Triceps ³	-8	-16 to +16	-5	-22 to +12

¹ % of stated normal weight ² % of standard ³ % of standard

compared to frequent occurrence of these symptoms in the orally-fed group.

Aggressive nutritional support was credited by Copeland et al. (79) for an increased response rate in patients with metastatic colon cancer. They reported that 16 patients given a loading course of 5-fluorouracil while on IVH had a 31% response rate, while only 1 out of 10 of comparable patients not on IVH responded.

Nutritional status. Aggressive nutritional support may increase net response rates by making nutritionally debilitated patients eligible for chemotherapy they could otherwise not tolerate. Valdivieso et al.¹ collected nutritional assessment data on fifty-one patients receiving chemotherapy for oat cell lung cancer. Twenty-three patients received IVH while twenty-eight did not. Patients were evaluated pretherapy and after course two of treatment. Intravenous nutritional support resulted in weight gain, increased triceps skinfold and increased arm muscle circumference (table 6).

Copeland et al. (80) observed patients with a variety of solid tumors who were given IVH. All of the patients had an initial weight loss of greater than 10% and a serum albumin of less than 3.0g/100 ml. (normal level = 3.5g/100 ml.). The overall response rates to chemotherapy among this group of patients was 36%.

Tumor growth. Concern has been expressed that aggressive nutritional

¹Valdivieso, M., Freeman, M.B., Frankmann, C.B. & Beck, J.E. (1981) Significant nutrition parameters in oat cell lung cancer patients during chemotherapy. (Abstracts) 64th annual American Dietetic Association meeting, Philadelphia, Penn., pp. 117-118.

TABLE 6

Relation of nutritional parameters to administration
of intravenous hyperalimentation²

Parameters	IVH	Control
Weight	+ 5.7	- 6.4
Triceps Skin Fold ¹		
J	+ 9.6	- 14.4
F	+ 10.2	- 15.2
Arm Muscle Circumference		
J	+ 2.3	- 6.8
F	+ 6.4	- 5.6
Mean Kcal Intake	+961	+341
% RDA	+ 49.2	+ 14.6

¹ (J) Jelliffe, (F) Frisncho (Two standards of measurements)
support might harm the host by promoting growth of the tumor. Steiger et al. (81) studied tumor growth in 31 female Lewis-Wistar rats with subcutaneously transplanted rat mammary tumors. The subcutaneous location of the tumors allowed for accurate 3-dimensional measurements and computation of tumor volumes. The rats were fed intravenously and were allowed unrestricted activity in their cages via the use of a special harness and fluid infusion swivel apparatus. One group of rats received a diet containing 30% glucose and 5% amino acids. Another group received a 5% amino acid solution with no carbohydrate, and the third group received a 5%

²Valdivieso, M., Freeman, M.B., Frankmann, C.B. & Beck, J.E. (1981) Significant nutrition parameters in oat cell lung cancer patients during chemotherapy. (Abstracts) 64th annual American Dietetic Association meeting, Philadelphia, Penn., pp. 117-118.

glucose intravenous solution with no amino acids. Mean body weights and tumor sizes were nearly identical at the start of the 10 day infusion period. There was a significantly greater tumor growth in the well-nourished hyperalimentated group compared to the malnourished group receiving 5% glucose (table 7). Tumor growth in the group receiving 5% amino acids also was greater than in the group receiving 5% glucose. Those diets having amino acids enhanced tumor growth even in the presence of marked weight loss. In this study the amino acid content of the diet appeared to be the nutritional stimulus for tumor growth, independent of general nutritional status.

TABLE 7

Relation of weight change to diet (81)

I.V. diet	Change in body weight
	g
5% amino acids - 30% glucose	+27 \pm 11
5% amino acids - no glucose	-51 \pm 9
5% glucose - no amino acids	-41 \pm 11

Daly et al. (82) evaluated the effects of oral and intravenous nutritional repletion on tumor growth and host immunocompetence in malnourished rats. Sixty adult purified protein derivative positive Buffalo rats, inoculated with Morris hepatoma 5123, were fed a regular diet for 14 days and then were switched to a high carbohydrate, protein-

free diet for 14 days. Then they were divided into three groups: group 1 received an intravenous diet of 25% dextrose and 4.25% amino acids, group 2 was fed the regular oral protein diet ad libitum, and group 3 remained on the oral protein-free diet. The average weight gain or loss for groups 1, 2, and 3 were +14 gm., -17 gm., and -23 gm., respectively. Intravenous hyperalimentation resulted in significant body weight gain and a slight but not significant increase in absolute tumor weight when compared with rats fed the regular oral protein diet. The tumor weight:body weight ratios were unchanged by any of the three dietary regimes used following protein depletion. Neither IVH nor regular diet stimulated tumor growth out of proportion to host nutritional repletion. Although the absolute tumor size did increase in the nutritionally repleted rats compared to the rats on the protein free diet, the repleted rats were much stronger and healthier and would be predicted to better tolerate antineoplastic therapy.

Cell cycle specific drugs such as 5-fluorouracil have the most effect in rapidly dividing tissues. Therefore Copeland et al. (80) hypothesized that if nutritional support could induce an increase in the growth fraction of tumors, it might be possible to optimize the use of cell-cycle specific chemotherapeutic agents.

Failure of Progressive Nutritional Support to Produce Significant Results

Much concern recently has been expressed at the failure of many of the previously mentioned studies to identify those components of outcome that can be attributed to nutrition per se versus what should be attributed to the disease process or to conventional forms of antineoplastic

therapy (83). In fact, not all studies agree with the positive results of aggressive nutritional support that have been previously mentioned. Jordan et al (84) studied 65 patients with advanced adenocarcinoma of the lung who received chemotherapy treatment. Twenty-four received no IVH, 19 received simultaneous IVH beginning on day 1 and continuing through the first course of treatment (median 25 days), and 22 received pre-chemotherapy IVH beginning 10 days prior to treatment and continuing through the first course (median 35 days). There were no significant differences in survival among the three treatment groups. Survival was prolonged in patients with less than 6% pre-treatment weight loss, in patients who were responding to treatment and in patients with stable disease. Five of 16 responding patients remained alive for greater than or equal to 18 months. Protection from chemotherapy-induced gastrointestinal and hematologic toxic effects by IVH was minimal. The researchers concluded that the routine use of IVH as an adjunct to chemotherapy in patients with adenocarcinoma of the lung does not appear to be justifiable. Findings, similar to those of Jordan et al. (84), on the effects of IVH and chemotherapy in patients with stage 3 testicular cancer, were reported by Samuels et al. (85).

Nutritional Repletion Problems Reported

Sloan et al. (86) suggested that nutritional outcome is linked more directly with the state of disease than it is to the cancer therapy or to the type of nutritional support. They described several cases where malnourished patients who were receiving total parenteral nutrition experienced weight loss, a decrease in total protein and albumin and finally death.

Nixon et al. (87) took serum protein (albumin), creatinine/height ratio and anthropometric measurements of 15 undernourished patients with advanced cancer and of 10 noncancer undernourished controls during IVH. Intravenously-fed cancer patients showed significantly less improvement than the noncancerous controls in body weight, albumin, creatinine/height ratio, and mid-arm muscle area (table 8). In contrast triceps skinfold measurements were similar for the two groups. Nitrogen retention was similar in the cancer and noncancer patients, but the cancer group retained significantly less magnesium and phosphorous. These findings indicated a partial block in repletion of lean body mass or abnormal composition of newly deposited lean body mass when undernourished patients with advanced cancer receive hyperalimentation.

TABLE 8

Responses to hyperalimentation in
cancerous vs. noncancerous patients (87)

	Wt. gain	Albumin	Creat./ height	Midarm	Triceps
	Kg	g/dl	% of standard		
Noncancer	8.9	0.5	10	11	8
Cancer	5	0.1	4	4	10

Problems and Criticism of Nutritional Support Programs

In a panel report from a National Institutes of Health (NIH) workshop on cancer, the controversy about the actual merits of nutritional support for patients undergoing different types of oncological treatment was

discussed (88). One problem in evaluating the success of nutritional support that was pointed out was the fact that in the seriously ill cancer patient, nutritional support is rarely the only modality of treatment. Therefore to distinguish between effects of different treatments has been difficult and perhaps not accurate. The panel members agreed that the anorexia that accompanies malignancies can be reversed by successful oncological therapy and that anorexia due to malnutrition should respond to nutritional support. However, very few studies have separated these two components.

Recommendations for Future Research

The members of the NIH workshop panel on cancer (88) made various research recommendations for the future. They recognized a need for rigorous studies to distinguish the effects of nutritional support on lean tissue repletion versus simple supplementation of body fat stores. In addition, they agreed that studies of the effects of nutritional support should concentrate more on functional indices of wellbeing of the host at the cellular, tissue, organ, and whole body levels. They recommended that long-term studies of the effects of nutritional support should distinguish between two types of patients: 1) patients in whom malnutrition is established at the time of presentation and 2) patients in whom there is no nutritional deficit at the time of presentation, but in whom a nutritional deficit can be expected as a result of antineoplastic therapy. The effects of nutritional support on tolerance and efficacy of therapy should be examined, especially in the second group. Finally, the panel emphasized the need for long range studies with careful documentation of the characteristics of the patient, his tumor, and his therapy at each follow-up assessment.

SUMMARY

Nutritional status of the cancer patient is negatively affected by a variety of factors. The malignancy may have detrimental effects such as anorexia with early satiety or changes in taste. Increased bitter and decreased salt and sweet taste sensitivity have been noted in some cancer patients. An increased metabolic expenditure was demonstrated in many cancer patients with resulting weight loss and tissue wasting. Altered glucose and amino acid metabolism has been attributed to the cancer state although mechanisms for these metabolic changes are not clearly understood.

Chemotherapy as a cancer treatment, utilizes drugs that have specific inhibitory action in healthy as well as malignant cells. Chemotherapeutic drugs, classified according to their source and mode of action in the cell, include alkylating agents, antimetabolites, antibiotics, and plant alkaloids. Some side effects of chemotherapy which decrease food intake and deteriorate nutritional status include nausea and vomiting, stomatitis, constipation, diarrhea, and taste changes. Other effects include bone marrow depression, megaloblastic anemia, liver, pancreas, and kidney dysfunction, fever, chills, electrolyte imbalance, and central nervous system disorders.

Aggressive nutritional support via intravenous hyperalimentation of nutritionally depleted cancer patients has been shown in some patients to improve nutritional status, increase response to drugs and prevent weight loss. Other studies have indicated that intravenous hyperalimentation does not improve the patient's response rate or protect the patient from

toxic side effects of the drugs. Nutritional outcome was linked more directly with the state of disease than to the cancer therapy or the nutritional support.

Future recommendations include long range studies with careful documentation of the characteristics of the patient, his tumor, and his therapy at each follow-up assessment.

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INTERACTION OF NUTRITION AND CHEMOTHERAPY
IN THE CANCER PATIENT

by

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Nutritional status of the cancer patient is negatively affected by a variety of factors. The malignancy may have detrimental effects such as anorexia with early satiety or changes in taste. Increased bitter and decreased salt and sweet taste sensitivity have been noted in some cancer patients. An increased metabolic expenditure was demonstrated in many cancer patients with resulting weight loss and tissue wasting. Altered glucose and amino acid metabolism has been attributed to the cancer state although mechanisms for these metabolic changes are not clearly understood.

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