Nutritional Consequences of Cancer Chemotherapy and Immunotherapy

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Summary

The nutritional consequences of major cancer chemotherapeutic and immunotherapeutic agents are reviewed. In addition, nutritional approaches to cancer treatment are discussed. Effects on host nutrition are related to two primary drug functions, i.e., biochemical interaction with the target tissues and pharmacological action on the host. Treatments with these agents result in profound effects on the gastrointestinal, central nervous, cardiopulmonary, renal, musculoskeletal, hematopoietic, and constitutional systems of cancer patients who have already been nutritionally compromised.

Prevention and treatment of the nutritional consequences of chemotherapy and immunotherapy include specific treatment against particular agents and nonspecific symptomatic or supportive therapy. A modern concept of parenteral nutrition combined with chemotherapy and immunotherapy is one example of a nonspecific approach with a high promise for general use.

More importantly, increasing success in the long-term control of leukemia, Hodgkin's disease, and certain other neoplasms has interrupted the vicious cycle promulgated on the host nutrition by neoplasia and toxic agents. New concepts of chemotherapy, e.g., short intensive treatment instead of prolonged treatment, and surgical adjuvant treatment instead of therapy of patients with advanced cancer, have minimized the nutritional consequences of chemotherapeutic and immunotherapeutic agents.

Introduction

Cachexia and malnutrition are among the major causes of morbidity in patients with advanced cancer. Anorexia, inanition, and progressive weight loss are commonplace.

Therapeutic approaches with chemotherapy, immunotherapy, radiotherapy, surgery, and anesthesia unavoidably affect host cells, often producing a variety of side effects, e.g., nausea, vomiting, oral pain, diarrhea, fever and chills, and further decrease in appetite, physical activity, and body weight. These effects, together with biochemical and histological injuries to major organ systems, may leave the patient with a profound nutritional insufficiency. Treatment is therefore justified only when the patient can recover from its consequences. Otherwise the vicious cycle of cachexia produced by tumor and toxic agents will not end, even if the tumor is apparently regressing. It is important to weigh the risks of treatment versus the possible benefits. Adverse nutritional consequences produced by treatment are a component of the equation. Many of the nutritional consequences of chemotherapy are explained as the result of interference in necessary metabolic reactions ("biochemical nutrition") and pharmacological effects on the host target tissue(s) ("pharmacological nutrition"). For example, the megaloblastic anemia produced by cytosine arabinoside can be readily explained by its biochemical effects selectively on DNA synthesis of erythrocyte precursors. On the other hand, the profound host effects of methotrexate in patients with even mild renal impairment result from the drug's excretion from the host nearly exclusively by the renal route.

In this paper the nutritional impact of commonly used chemotherapeutic and immunotherapeutic agents is reviewed. In addition, the effects of several less commonly used compounds of particular interest are discussed (Tables 1 and 2). Finally, the consequences of nutritional approaches to the treatment of human cancer are summarized. No attempts have been made to detail the nutritional consequences of combination chemotherapy or combined modalities of therapy, dietary manipulation, or hormonal treatment.

Impaired Nutrition due to Decreased Intake p.o. and Toxicity in the Alimentary Canal

Nausea and vomiting following chemotherapy or immunotherapy with antineoplastic agents are mediated by the chemoreceptor trigger zone located in the area postrema of the 4th ventricle (10, 22). Nausea and vomiting are the most common immediate manifestations of administration of many chemotherapeutic or immunotherapeutic agents. Indeed, this complication occurs with almost every major class of compounds including a majority of alkylating agents (e.g., mechloroethamine and cyclophosphamide), the nitrosoureas, folate analogs, purine analogs, pyrimidine analogs, derivatives of triazine and hydrazidine, anthracycline antibiotics (daunorubicin and adriamycin), and other antibiotics (e.g., mitomycin C, bleomycin, actinomycin D, and mithramycin), enzymes (e.g., asparaginase), the simple molecule hydroxyurea and certain immunotherapeutic compounds [e.g., poly(I), Corynebacterium parvum, and

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2 The abbreviations used are: poly(I), polyribonucleosinic, polyribonucleotidyl acid; CNS, central nervous system; BCG, Bacillus Calmette-Guerin.
### Table 1

Chemotherapeutic agents

Recommended as 1st-line drugs for a variety of human neoplasms (137). Some other drugs have also been used as 1st-line drugs alone or in combination. Others are listed for their nutritional implications.

<table>
<thead>
<tr>
<th>Alkylating agents</th>
<th>MeChloretamine (nitrogen mustard, HN2)</th>
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<tbody>
<tr>
<td></td>
<td>Cyclophosphamide</td>
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<td></td>
<td>L-Phenylalanine mustard (melphalan, Alkeran)</td>
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<td></td>
<td>Chlorambucil (Leukeran)</td>
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<td>Triethylene melamine</td>
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<td>Dibromomannitol</td>
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<td>Alkyl sulfonate</td>
<td>Busulfan (Myleran)</td>
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<td>Nitrosoureas</td>
<td>BCNUa</td>
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<td></td>
<td>CCNU</td>
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<td></td>
<td>Methyl-CCNUb</td>
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<td></td>
<td>Streptozotocin</td>
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<td>Antimetabolites</td>
<td>Folate analogs</td>
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<td></td>
<td>Methotrexate</td>
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<td>Dichloromethotrexate</td>
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<td>Purine analogs</td>
<td>Azaserinec</td>
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<td></td>
<td>6-Mercaptopurine</td>
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<td></td>
<td>6-Thioguanine</td>
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<td>Pyrimidine analogs</td>
<td>5-Fluorouracil</td>
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<td></td>
<td>Cytosine arabinoside</td>
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<td></td>
<td>5-azacytidinec</td>
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<tr>
<td>Derivatives of triazine and hydrazine</td>
<td>Dimethyltriazenoimidazole carboxamide (DTIC, DIC)</td>
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<td></td>
<td>Procarbazine</td>
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<td>Natural products</td>
<td>Antibiotics</td>
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<td>Mitomycinb</td>
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<td>Bleomycinb</td>
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<td></td>
<td>Daunorubicin</td>
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<td>Adriamycin</td>
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<td>Actinomycin D</td>
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<td></td>
<td>Methotrexal</td>
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<td></td>
<td>Vinblastineb</td>
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<tr>
<td>Derivatives of triazine and hydrazine</td>
<td>Vinblastineb</td>
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<td></td>
<td>Asparaginaseb</td>
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<tr>
<td>Enzyme</td>
<td>Asparaginaseb</td>
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<tr>
<td>Heavy metal</td>
<td>Organic platinum</td>
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<tr>
<td></td>
<td>cis-Diaminedichloroplatinum</td>
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<tr>
<td>Hormone</td>
<td>Corticosteroid</td>
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<tr>
<td>Miscellaneous</td>
<td>Hydroxyurea</td>
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<tr>
<td></td>
<td>Methyglyoxal bisguanylylhydrazone</td>
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<tr>
<td></td>
<td>1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane</td>
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</table>

* The abbreviations used are: BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; methyl-CCNU, 1-(2-chloroethyl)-3-methylcyclohexyl-1-nitrosourea.

* Listed for its nutritional implications.

levamisole]. Violent and prolonged nausea and vomiting may occur after administration of procarbazine (16, 46, 109, 118, 120), streptozotocin (13, 112), cis-diaminedichloroplatinum (for review see Ref. 49), and 5-azacytidine (60, for review see Ref. 127), and may be dose limiting. Presently available antiemetics are not wholly effective in the control of drug-induced vomiting. Initiation of phenothiazine medication 1 or more days before the emetogenic drug is helpful.

Nausea, vomiting, and accompanying anorexia not only result in decreased oral intake, but also produce fluid and electrolyte imbalance, general weakness, and weight loss. cis-Diaminedichloroplatinum-induced anorexia may be cumulative, and some patients develop less and less appe-
tite while they are responding to the treatment (52, 53).

There are only a few cancer chemotherapeutic agents which are not associated with nausea and vomiting. These are certain alkylating agents (e.g., L-phenylalanine mustard, chlorambucil, busulfan, dibromomannitol), vincristine, and steroids.

Stomatitis, in the form of oral ulceration, cheilosis, glossitis and pharyngitis, and other mucosal toxicities of the alimentary canal are common with many of the chemotherapeutic agents. The alimentary canal is one of the most vulnerable targets of chemotherapeutic agents. This is probably due to a rapid turnover of the epithelial cells of the mucosa. Rapid cell division at the depths of mucosal crypts produces cells that are pushed in migration up the crypt wall. The squamous mucosa of the oral, pharyngeal, and esophageal surfaces also displays more rapid turnover than skin. Tumors of the alimentary canal usually do not grow as rapidly as do the adjacent normal mucosa (see Ref. 78).

Certain phases of the cell cycle are more sensitive to cytotoxic effects of cancer chemotherapeutic compounds, and even “cycle nonspecific” drugs have greater effects on cells which periodically expose to injury their most vulnerable cell phase. Dose-limiting oral mucosal toxicities occur after actinomycin D (61, 116, 123), methotrexate (see below), and methyglyoxal bisguanylhydrazone (105). Oral mucosal toxicity is unpredictable in patients receiving high-dose methotrexate and leucovorin rescue (33). Severe esophagitis may occur after methyglyoxal bisguanylhydrazone. Severe oral toxicity has also been observed after azaserine, daunorubicin, Adriamycin, and 5-fluorouracil. During infusion treatment with 5-fluorouracil, hematological toxicity is less and oral toxicity may become the dose-limiting complication (114). Mucosal ulcerations are rare with alkylating agents but may be seen with phenylalanine mustard and cyclophosphamide (91).

These toxicities are accompanied by inability to continue adequate intake p.o. and result in dehydration and further deterioration of the nutritional status of the patient.

Constipation and Adynamic Ileus. These are the major toxicities of vincristine. In 1 broad study troublesome constipation was reported in one-third of the patients with a greater frequency, severity, and earlier onset at a higher dose (57).

Malabsorption Syndrome. It is likely that the profound effects of the chemotherapeutic agents on the intestinal mucosa and/or major secreting organs result in the development of malabsorption syndrome. These effects have not, however, been systematically studied during chemotherapy. Positive Shilling tests with and without intrinsic factor compatible with malabsorption syndrome were noted during the nadir of serum albumin and body weight in a patient with acute myelocytic leukemia who was treated with asparaginase (95).

Diarrhea. This is part of the general mucosal toxicity produced by a number of chemotherapeutic agents. Diarrhea is particularly severe after actinomycin D, 5-fluorouracil, and methyglyoxal bisguanylhydrazone. Abdominal pain may accompany it. Diarrhea is also commonly seen after methotrexate, hydroxyurea, nitrosoureas, and 5-azacytidine and less frequently after 6-mercaptopurine, cyclophosphamide, procarbazone, and levamisole. In severe cases, proctitis, mucosal ulceration, bleeding, and perforation accompany diarrhea. Diarrhea alternates with constipation after vincristine treatment. Prolonged uncontrolled diarrhea results in dehydration, electrolyte imbalance, anion, and accelerated mainutrition. Hospitalization may be indicated, and adequate supportive care is essential.

Additional effects of chemotherapeutic compounds on the alimentary canal include jaw pain seen after vincristine (57) and peptic ulcer in patients receiving corticosteroids (65, 166, 210) and peptic ulcer in patients receiving corticosteroids (57).

Table 2

<table>
<thead>
<tr>
<th>Immunotherapeutic agents used in man</th>
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<tbody>
<tr>
<td>BCG</td>
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<tr>
<td>Methanol extraction residue of BCG</td>
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<tr>
<td>C. parvum</td>
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<tr>
<td>Levamisole</td>
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<td>tRNA</td>
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<td>Immune RNA</td>
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<tr>
<td>Thymosine</td>
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<tr>
<td>Antiviral agent used in man with neoplastic disease</td>
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<td>Poly(lC)</td>
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Nutritional Consequences due to Dysfunction of Specific Major Organ Systems Produced by Chemotherapeutic and Immunotherapeutic Agents

The Hematopoietic System. This is another of the most vulnerable targets of cancer chemotherapeutic agents. Hematological toxicities, especially leukopenia and thrombocytopenia, are dose limiting in a majority of cancer chemotherapeutic compounds. This is true for all agents except adrenocortical steroids and most immunotherapeutic agents. Certain drugs active against hematological neoplasms exploit this principle. Although vincristine, bleomycin, and asparaginase are relatively free from hematological toxicity, they induce hematopoietic depression in a few

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Nutritional consequences of long-term administration of adrenal steroid</th>
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<tbody>
<tr>
<td>Modified from Ref. 67.</td>
<td></td>
</tr>
<tr>
<td>Cushingoid appearance</td>
<td>Gastrointestinal\nPeptic ulceration\nAcute pancreatitis</td>
</tr>
<tr>
<td>Endocrine abnormalities \nPolyphagia</td>
<td>Immunological\nInfectious complications\nBacterial, fungal, and tuberculous infection</td>
</tr>
<tr>
<td>Hyperglycemia and glycosuria \nObesity</td>
<td>Psychological\nEuphoria\nInsomnia\nPsychosis</td>
</tr>
<tr>
<td>Fluid and electrolyte disturbances \nEdema</td>
<td>Dermal\nAtrophy (striae)\nAcne\nHirsutism</td>
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<tr>
<td>Hypokalemic alkalosis</td>
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<tr>
<td>Musculoskeletal \nMuscle atrophy and myopathy \nOsteoporosis and vertebral compression fractures</td>
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<td>Circulatory \nHypertension</td>
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patients (57, 93, 97). Profound leukopenia is often accompanied by infection. Fever, chills, anorexia, and increased energy consumption accelerate the deterioration of the nutritional status of the patient.

Anemia, a nutritionally important consequence, is frequently seen after administration of chemotherapeutic agents. Megaloblastic anemia is a predictable toxic effect of chemotherapeutic agents that interfere with DNA synthesis. This complication has been reported with folate analogs (128), 6-mercaptopurine, 5-fluorouracil (12), cytosine arabinoside (122), cyclophosphamide (6), and hydroxyurea (18).

Anemia induced by other agents has been less clearly defined. Anthracycline antibiotics produce anemia (7) and probably normochromic and normocytic anemia (126). Actinomycin D, another agent that binds with DNA, also produces anemia as part of general marrow depression (see Ref. 79). The same appears to be true for high dose cis-diaminedichloroplatinum administration (60 mg/sq m twice weekly) (D. J. Higby, personal communication). Some insignificant anemia was also seen after nitrosoureas (67) and dimethyltriazenoimidazole carboxamide (82). The general mechanism of drug-induced megaloblastic anemia is presumed to be the same as the one that results in megaloblastosis in vitamin B12, and folate deficiencies, i.e., DNA synthesis is retarded in growing cells, whereas the synthesis of cytoplasmic constituents is affected to a lesser degree or not at all (136). However, the "biochemical anemia" produced by drugs may be different from the anemia that results from pure nutritional deficiency. The clinical characteristics of anemia produced by biochemical interference at different stages of maturity from stem cell to erythrocyte have not been well defined. This is in part related to the clinical material; i.e., most patients with advanced cancer and leukemia already have preexisting anemias of various kinds (see Ref. 72), and many have received frequent transfusions of blood components.

The dose-limiting toxicity of mithramycin is a hemorrhagic diathesis produced by alterations of the vascular bed, platelets, coagulation factors, and fibrinolytic activity (88).

CNS. This is influenced by a variety of chemotherapeutic agents (133). Especially noteworthy are intrathecal methotrexate, which can cause meningeal irritation, paraparesis, and encephalopathy (68, 85, 115); procarbazine, which can induce somnolence, confusion, cerebral ataxia, psychosis, and coma (16, 109, 118, 120); vincristine, which at higher doses can produce weakness, insomnia, confusion, psychosis, disorientation, and hallucination (57, 110); asparaginase, which can produce unpredictable lethargy, depression, disorientation, confusion, and hallucination (20, 50, 93-95, 135); 1,1-dichloro-2-(p-chlorophenyl)-2-(p-chlorophenyl)ethane, which can produce somnolence and lethargy (62, 81); cyclocelene, which can produce dizinness, lethargy, hallucination, ataxia, and convulsion (see below); and corticosteroids, which can produce psychosis (Table 3). Administration of high doses of cis-diaminedichloroplatinum (60 mg/sq m twice weekly) can result in confusion, coma, increase in cerebrospinal fluid pressure, and death (D. J. Higby, personal communication). CNS dysfunctions often result in impaired oral intake. Other neurological complications include lassitude, apathy, and confusion following azaserine (37), cerebellar dysfunction from 5-fluorouracil (58, 86, 104), and headache after i.v. levamisole and C. parvum (see Ref. 92). Levamisole also produces insomnia, nervousness, irritability, euphoric sensory stimulation, and more severe psychiatric reactions (92). These complications may also have important nutritional consequences.

Narcotics given to patients with cancer most frequently affect the CNS and compromise nutrition. Somnolence from drug effects leads to missed nourishment. Constipation from intestinal side effects of narcotics may also diminish appetite.

The Alimentary System. The liver, which plays a critical role in overall nutrition, is often influenced by chemotherapeutic or immunotherapeutic agents, leading to serious nutritional problems. Anorexia is particularly common after hepatic injury. Diffuse hepatocellular damage leads to hypoalbuminemia, a classic form of malnutrition. Liver damage is commonly seen after administration of asparaginase (see below). Glutamine antagonists such as azaserine and duazomycin also cause hepatic impairment (see below). Jaundice occurred in about one-third of the patients who took 6-mercaptopurine in reported series (34, 37). Histologically, bile stasis and hepatic necrosis have been reported. Hepatic dysfunction is also common after methotrexate (see below), nitrosourea compounds (13, 112), mithramycin (14), and 5-azacytidine (4, 127). Several cases of hepatic fibrosis and cirrhosis have been reported in leukemic children and in patients with psoriasis after long-term administration of methotrexate (107). In contrast, intensive courses given to women with trophoblastic neoplasia and in whom remission lasted more than 10 years were not followed by late complications (67). Thus, the exact role of the compounds in the development of this condition has not been completely defined. Dose, schedule, and chronicity may all be critical. Abnormalities in hepatic function tests occur in a small number of patients treated with cytosine arabinoside; however, evidence of definite hepatic toxicity related to this compound is not well established (Ref. 35; for review see Ref. 71). Cyclophosphamide, chlorambucil, and dimethyltriazenoimidazole carboxamide rarely cause hepatic dysfunction.

BCG-induced hepatic dysfunction ranges from mild elevation of alkaline phosphatase and aspartate aminotransferase to clinical jaundice and hepatomegaly (3). Granulomatous hepatitis was documented by liver biopsy in all 3 jaundiced patients treated by intratumoral injection of BCG in Sparks' series (117). BCG administered via the aerosol route appears to avoid hepatic toxicity (45).

Pancreatic dysfunction is produced by asparaginase (see below). Streptozotocin affects islet cells, resulting in hyperglycemia and abnormal glucose tolerance tests. Insulin was required in none (108). Severe hypoglycemia and coma were produced by methylglyoxal bisguanylylhydrazone (105). Exocrine pancreatic function has not been systematically studied during cancer chemotherapy.

The Cardiovascular System. Cardiac damage is a serious complication of anthracycline antibiotics which include both daunorubicin and Adriamycin (see Refs. 7 and 32). Clinically, cardiac toxicity manifests as a frank picture of
congestive heart failure with water retention and electrolyte imbalance. No specific antidote or preventive measures are available at present except limitation of the cumulative dose.

Certain chemotherapeutic agents are local tissue irritants and produce tissue necrosis when extravasated (e.g., vinca alkaloids, most alkylating agents, actinomycin D, and anthracycline compounds). Other compounds are thrombogenic at the local venipuncture site (e.g., bleomycin) (see Ref. 8). Repeated venipuncture results in inability to find suitable peripheral veins for parenteral fluid, electrolyte, and nutritional support, thus exacerbating problems of nutrition in the advanced stages of disease in patients who have had extensive chemotherapy.

The Urinary System. Renal complications lead to varying degrees of the uremic syndrome, with its attendant nutritional disorder. They are particularly apparent after administration of cis-diaminedichloroplatinum, methotrexate (see below), and streptozotocin. cis-Diaminedichloroplatinum (see Ref. 49) produced dose-limiting renal complications. cis-Diaminedichloroplatinum-induced nephrotoxicity manifests clinically as a rise in blood urea nitrogen and creatinine and as decreased creatinine clearance. Histologically, cis-diaminedichloroplatinum appears to cause renal tubular necrosis. Renal toxicity is similar to that seen with other heavy metal poisoning and appears to be dose related, cumulative, and only partly reversible. Renal toxicity of streptozotocin manifests as proteinuria occurring 2 to 3 weeks into the course of therapy. Decrease in creatinine clearance and increase in creatinine or blood urea nitrogen were observed (13, 112). Renal tubular acidosis and Fanconi’s syndrome (aminoaciduria, aminoaciduria, and renal hyperphosphaturia) have also developed in 15 to 20% of patients (13). Fatal renal toxicity was recorded in 5 of 46 patients with islet cell carcinoma. Aminoaciduria also occurs after cycloleucine (see below) (5).

A slight rise in blood urea nitrogen commonly observed after asparaginase treatment represents prerenal azotemia, but in a few cases frank renal failure with marked oliguria has been described. This usually accompanies other severe toxic manifestations (50). Renal complications also occur after other nitrosoureas (30), mithramycin (14), high-dose cyclophosphamide (more than 50 mg/kg body weight) (28), and after immunotherapy with C. parvum (92).

The Musculoskeletal System. Musculoskeletal consequences of chemotherapeutic agents are exemplified by muscle atrophy, osteoporosis, and pathological fractures produced by corticosteroids (Table 3). Vincristine can also cause muscle atrophy as a consequence of its neurotoxicity. Methotrexate given over long periods of time can lead to osteoporosis and pathological fractures.

Nutritional Consequences due to Systemic Effects of Chemotherapy and Immunotherapy

Fever and Chills. These are common and immediate side effects of treatment with bleomycin (see Ref. 8), asparaginase (19, 50, 93, 94), BCG (117), i.v. poly(IC) (29), and i.v. C. parvum (92).

BCG induces fever which begins 4 to 8 hr after injection and persists for as long as 24 hr. Pruritus or a rash at the site of injection develops in most patients (3, 117). The methanol extraction residue of BCG (131, 132) produces fever, malaise, and severe local pain at the site of intradermal immunizations that ulcerate (see Ref. 132). poly(IC) (38, 74) is a double-stranded, helical synthetic RNA with a molecular weight of the order of 1,000,000. There is evidence that the size distribution may be biologically important in terms of both toxicity and activity (74). poly(IC) produces fever which appears by 6 to 8 hr and peaks at 24 to 36 hr. Indeed, fever appears to be a prerequisite for the production of interferon (29, 38). C. parvum has been reported to exercise its immunostimulatory effects through the reticuloendothelial system and B-cells, thus differing from BCG (48, 59, 99, 113). It is of note that these chemotherapeutic and immunotherapeutic agents are all macromolecular, and, in certain instances, with the exception of poly(IC), contamination with extraneous pyrogens is possible. Fever has also been associated with the administration of cyclophosphamide, 6-mercaptopurine, and cytotoxic arabinoside. A “flu-like” syndrome has been reported after dimethyltriazenoimidazole carboxamide (66, 79) and BCG (117) with nausea, myalgia, and, occasionally, arthralgia lasting 8 to 9 weeks.

Electrolyte Imbalance. This condition, induced by cyclophosphamide, includes hypernatriemia, which has been regarded as due to inappropriate antidiuretic hormone production. Mithramycin, diazo-oxo-norleucine (89), methotrexate (90), and actinomycin D (21) are known to produce hypocalcemia. Mithramycin is used to treat hypercalcemia (102). Renal impairment produced by other chemotherapeutic agents can also be associated with varying degrees of electrolyte imbalance.

Weight Loss. This is a composite phenomenon in patients who have decreased oral intake, poor intestinal absorption, diarrhea, fever, CNS dysfunction, myopathy, and other causes of negative nitrogen balance. Fluid overload in patients with hypoalbuminemia and hyponatremia often masks important weight loss related to the treatment. Distinct weight loss after treatment with asparaginase may reflect decreased protein biosynthesis (see below).

A syndrome associated with late toxicity of busulfan has been described. It consists of hyperpigmentation, asthenia, hypotension, nausea and vomiting, amenorrhea, and weight loss, sometimes associated with pulmonary fibrosis (72, 91, 98). Although the clinical picture suggests adrenal insufficiency, this has not been documented. The pathogenesis of the syndrome is not well understood, but it may be due to the prosthetic group of the busulfan molecule rather than to its alkylating properties (67). Pulmonary fibrosis produced by busulfan may be nodular or diffuse histologically (69) and can lead to fatal outcome (98). One of the most serious systemic nutritional complications of chemotherapy and immunotherapy is graft-versus-host disease in patients with acute leukemia treated with bone marrow transplantation. In a recent review by Thomas et al. (124), cyclophosphamide treatment plus total-body radiation plus syngeneic transplantation using monozygotic twin marrow, and subsequent immunotherapy with normal
twin buffy-coat lymphocytes and s.c. injections of irradiated autologous leukemic cells produced remissions of from 3 to more than 49 months in 10 of 13 leukemic patients. Intensive combination chemotherapy is being added to the regimen to reduce the total-body burden of leukemic cells before the bone marrow transplantation. In the overall marrow graft experience, despite use of sibling donors matched at the major histocompatibility leukocyte antigen and despite postgraft immunosuppression, graft-versus-host disease has occurred in approximately 70% of successfully grafted patients. Evidently, incompatibility for histocompatibility regions other than the major complex is an important determinant of graft-versus-host disease. Clinically, the principal target organs of graft-versus-host disease are the skin, gastrointestinal tract, and liver. The initial organ involved in almost all cases is the skin, and the disease manifests as a maculopapular rash; in severe cases it manifests as generalized erythroderma with bullae and desquamation. Hepatic and intestinal involvement usually appear several days after the rash. Intestinal involvement is usually manifested as diarrhea but may progress to abdominal pain and ileus. Liver disease is characterized by rises in bilirubin (mainly conjugated), aspartate aminotransferase, and alkaline phosphatase. Fever, wasting, and debility status are also regularly seen. Chronic graft-versus-host disease is characterized by a more indolent clinical course involving the same tissues. A fatal outcome may ensue with profound nutritional impairment.

Adrenal Corticosteroid-induced Malnutrition. The widespread metabolic consequences of corticosteroids are often seen in cancer patients given large doses for prolonged periods. These consequences are summarized in Table 3.

The nutritional impact of newer immunotherapeutic agents such as thymosine, a calf thymus fraction (25, 111), transfer factor (80), and immune RNA (103) has yet to be determined.

Nutritional Consequences of a Specific Nutritional Approach to Chemotherapy

Although few qualitative differences have been observed in the essential nutrient requirements of tumor and normal cells, there are some quantitative differences that are probably dependent on growth rate, and this observation has led to the design of new therapies using inhibitors of glucose, lipids, amino acids, and vitamins.

Carbohydrate Antagonist. 2-Deoxy-D-glucose, a glucose antagonist, competes with glucose for phosphorylation by hexokinase and thus diminishes the utilization of glucose by tissues. Inhibition of glycolysis by treatment with 2-deoxyglucose produced inhibition of the growth of mouse and rat tumors. This is in keeping with the high glucose consumption of rapidly growing tumor tissue, independently of whether the glucose is subsequently metabolized by respiration or glycolysis to lactate. 2-Deoxyglucose was given by infusion to 8 patients with various neoplastic diseases (75). The patients developed diaphoresis, drowsiness, headache, generalized flush, and tachycardia, but tumor growth was not affected. The major limitation of this approach is the exquisite sensitivity of the CNS to glucose deprivation.

Lipid Antagonists. Triparanol is a hypocholesterolemic agent that inhibits the conversion of desmosterol to cholesterol. The drug likewise exerts modifying effects on the formation of adrenocortical steroid hormones in man. In 3 patients with metastatic prostate carcinoma, treatment with triparanol produced disappearance of pain, X-ray evidence of healing of bony metastases, and a decrease in acid phosphatase in each case for a year or more (27). There was no clinical evidence that triparanol exerted an estrogenic effect. Eight patients with metastatic breast carcinoma were also treated with triparanol (70). All had prior surgical castration or were at least 10 years postmenopausal. Temporar survival studies were conducted. Treatment with triparanol produced disappearance of pain, X-ray evidence of healing of bony metastases, and a decrease in acid phosphatase in each case for a year or more (27). There was no clinical evidence that triparanol exerted an estrogenic effect. Eight patients with metastatic breast carcinoma were also treated with triparanol (70). All had prior surgical castration or were at least 10 years postmenopausal. Temporar subjective and objective antitumor response was observed in only 1 patient. Two of 4 patients, including the 1 who responded, had a decrease in urinary estrogen excretion, and it was postulated that an inhibition of adrenal estrogen production might have caused the antitumor effects. Alternatively, hypocholesterolemia per se or the accumulation of intermediate steroids or steroid precursors might be causally related to the antitumor effect. Complications of this compound include cataract, alopecia, and dermatosis.

Boxidine, 1-[2-[[4'-trifluoromethyl]-4-diphenyloxy]ethyl pyrrolidine, is a nonsteroidal hypocholesterolemic agent. The compound blocks the conversion of 7-dehydroxysterol to cholesterol, thus producing hypocholesterolemia with an accumulation of 7-dehydroxysterol in blood and tissues. Of 13 patients with advanced cancer of various sites, objective regression of pulmonary metastatic lesions was observed in 1 patient with nonfunctional adrenal carcinoma (43). Side effects include anorexia, nausea, and vomiting. Decrease in serum cholesterol and appearance of 7-dehydroxysterol were also shown.

Amino Acid Antagonists. Cycloleucine, 1-amino-cyclopentane carboxylic acid, is a synthetic amino acid with antitumor effects in experimental neoplasms. Cycloleucine antagonizes the incorporation of valine into protein, probably by preventing the attachment of valine to tRNA (17). In cancer patients treated with cycloleucine results in a reversible, marked amino aciduria primarily involving cysteine, ornithine, lysine, and arginine (15). Cycloleucine has been reported to be effective against leiomyosarcoma (1, 2). It also produced a partial response in a small number of patients with head and neck cancer, colorectal cancer, ovarian carcinoma (125), melanoma (1, 125), and chondrosarcoma (65). Beneficial effects have also been seen in a small number of patients with multiple myeloma (84). Toxic effects of cycloleucine in man include nausea, vomiting, anorexia, diarrhea, weight loss, thrombocytopenia, a fall in concentration of all the serum proteins, and neurological toxicities (1, 5).

Selenocystine has been reported to be an effective agent in the treatment of animal tumors. Inorganic selenium per se could not reproduce the antitumor effect. The compound was thought to act by competing with L-cysteine for incorporation into protein. Two patients with acute leukemia and 2 with chronic myelocytic leukemia were treated with selenocystine daily for 10 to 57 days (130). In each of these patients there was a marked reduction in the circulating leukocytes, and splenomegaly became less pronounced.
However, treatment with this drug produced severe nausea and vomiting, and it was not possible to continue its administration to determine whether remission could be induced. Ethionine, a structural analog of methionine, has been known to impair the growth of experimental tumors. In 6 patients with advanced cancer of various sites, treatment for short periods of time with ethionine and a diet relatively low in methionine led to various toxic manifestations including skin rash, diarrhea, liver damage, renal injury, and psychotic disturbances (134). No significant antitumor effects were observed.

Azaserine, O-diazoacetyl-L-serine, is a glutamine antagonist isolated from cultures of a strain of Streptomyces. It exerts antitumor activity by inhibition of purine and pyrimidine synthesis through the inhibition of amidation reactions utilizing glutamine. Azaserine was tested in 56 patients with various types of cancer (36). Toxicities appeared in 5 to 20 days. The alimentary tract was most prominently involved, with redness of the tongue and buccal mucosa, progressing to ulceration. Nausea and vomiting were commonly observed. One-fourth of these patients developed anorexia, apathy, electrolyte imbalance, and jaundice. These tended to occur in old and debilitated patients. Marrow depression and leukopenia were also observed. Brief partial remission was seen in 3 of 14 children with acute lymphocytic leukemia. Azaserine was tested p.o. in the treatment of multiple myeloma without therapeutic effect (56).

Escherichia coli asparaginase exerts its antineoplastic activity by depleting host L-asparagine which is critical for the survival of certain neoplastic cells. Asparaginase is active in inducing remission in about 35 to 60% of patients with acute lymphocytic leukemia (see Ref. 19). This therapeutic effect appears to be related to specific nutritional requirements for L-asparagine by malignant and presumably by normal T-lymphocytes. "Normal" and "malignant" B-lymphocytes do not require L-asparagine in culture (Chart 1) and, in comparison to T-lymphocyte lines, are affected only at 800 to 2000 times higher concentrations of the enzyme (96). The majority of patients with acute lymphocytic leukemia have "null" cells, some of which appear to have been on the path to T-cell differentiation where proliferation of the malignant clone led to the clinical neoplasm. Because there would be a deficiency of T-cell leukemias to account for the asparaginase responses, some of these cells must share the nutritional requirement for L-asparagine. In general, differential nutritional requirements of individual host and neoplastic cells have not yet been clearly elucidated. L-Asparagine depletion by the enzyme treatment results in profound effects on host organ systems leading to a variety of nutritionally important toxicities (19, 20, 50, 93, 94). The toxic effects on liver and pancreas are largely the result of inhibition of protein synthesis in these organs. Patients may complain of nausea and vomiting, chills, and fever within hours of the 1st dose of asparaginase. Biochemical hepatic dysfunction is observed in a majority of patients. Elevation of blood ammonia, a product of the enzyme reaction, has not produced major concomitant neurological problems. Hepatic functional impairment is accompanied by profound hypoalbuminemia, hypocholesterolemia, and diminished clotting proteins (Factors V, VII, X, VIII, and IX, prothrombin, and fibrinogen). Microscopic observation has shown severe fatty metamorphosis of the liver. The endocrine and exocrine functions of the pancreas are also commonly affected by asparaginase, and approximately 5% of adults have overt pancreatitis. Hyperglycemia and hypoinsulinemia without clinical evidence of pancreatitis have frequently been recognized (44). Toxic effects on the CNS appear to be due to depression of necessary amino acids. CNS dysfunction ranging from mild depression and drowsiness to impaired sensorium, psychosis, and frank coma has been noted in adults. Electroencephalograms obtained from patients exhibiting CNS dysfunction have been diffusely abnormal. The CNS dysfunction from asparaginase might be due to a decreased amount of available L-asparagine or L-glutamine or to the increased concentration of L-aspartate and L-glutamate. L-Asparaginase administration in such patients coincided with clinical improvement of mental status (54, 94, 95). Loss of up to 20% of pretreatment body weight was seen after asparaginase treatment (Chart 2) (95). Asparaginase has minimal effects on the bone marrow and is not cytotoxic to oral and intestinal mucosa or to hair follicles.

Vitamin Antagonists. Galactoflavin, 6,7-dimethyl-9-(2'-acetoxeythyl)isoalloxazine, is a potent riboflavin antagonist in rats. Six patients with advanced neoplasms were treated with galactoflavin in combination with a synthetic diet (76). All developed riboflavin deficiency, i.e., weight loss, cheilosis, glossitis, seborrheic dermatitis, and normochromic normocytic anemia. Two suggestive instances of transient clinical improvement were seen.

4-Deoxypyrdoxine is a vitamin B6 antagonist. Three patients with histiocytic lymphoma and 3 with acute lymphocytic leukemia on a vitamin B6-poor diet were fed the antagonist (47). Two of the patients were treated with 4-deoxypyrdoxine, and both developed grand mal seizures. The remaining patients were treated with a smaller dose of 4-deoxypyrdoxine. A slight reduction in lymph node size for a
brief duration was noted in 2 patients with histiocytic lymphoma.

Four patients with acute lymphocytic leukemia who were on a normal diet were treated with 4-deoxypynidoxine for 33 to 80 days (129). Two of the patients developed seborrheic dermatitis, which is taken as evidence of vitamin B	extsubscript{6} deficiency. However, there was no clinical evidence of bone marrow remission.

6-Aminonicotinamide is an antagonist of nicotinamide. It has been shown to be active against a number of experimental tumors. 6-Aminonicotinamide produced 1 regression in 25 patients with renal cell carcinoma. Toxicity appears to take 2 clinical forms. One is a "deficiency" state and occurs as a form of stomatitis which includes buccal ulceration, cheilosis, and glossitis, as well as blepharitis with photophobia and dryness. The other manifestation is neurological, i.e., 8th nerve damage manifested by a gross or audiometrically detectable hearing defect and tinnitus.

Nausea and vomiting are also commonly seen (26, 51).

Methotrexate (amethopterin) is the folate antagonist. Derivatives of tetrahydrofolate function as cofactors for many of the enzymes that are required for the de novo synthesis of nucleotides, purines, and thymidine. Modifying the structure of folic acid by substituting an amino group for the 4-hydroxy group in the pteridine nucleus produced amino-pterin, a very potent and specific inhibitor of dihydrofolate reductase. Both aminopterin and its N°-methyl derivative, methotrexate, proved to be effective chemotherapeutic agents in the treatment of acute lymphocytic leukemia in children. Antifols are also of curative value in choriocarcinoma and related trophoblastic tumors of women. Methotrexate has broad spectrum activity in a modest percentage of cases against squamous cell carcinomas of the head and neck and in adenocarcinoma of the breast (see Ref. 79).

The bone marrow and alimentary tract epithelium are the 2 tissues most affected by folic acid analogs. Bone marrow toxicity manifests as reticulocytopenia, anemia, leukopenia, and thrombocytopenia. After a single i.v. dose of methotrexate the bone marrow begins to recover in 10 to 14 days. The toxicity may be more severe and pronounced if patients are in poor condition or have infection or compromised liver or bone marrow function. This increased toxicity may be related to the subclinical folate deficiency commonly observed in patients with neoplastic diseases, particularly with cancer of the head and neck. Low pretreatment levels of serum folate appear to predispose patients to the toxic effects of methotrexate, but correlation with the degree of tumor response has not been good. Oral mucosal toxicity occurs as redness, pain, and ulceration. Diarrhea is seen occasionally. Skin rash occurs in approximately 10 to 20% of patients treated with therapeutic doses. Nausea, anorexia, and, less commonly, vomiting are noted during or after methotrexate administration, especially with large doses. Subclinical injury is particularly noteworthy, and repeated doses could prove catastrophic since methotrexate is excreted almost exclusively by the kidney. Liver damage is rarely noted after moderate doses because of rather rapid clearance, but hepatic fibrosis and cirrhosis have been reported after long-term administration of methotrexate (see above).

Clinical toxicity of methotrexate is almost a direct function of the duration of administration of the drug and, to a lesser extent, a function of the dose of the drug (121). This is shown distinctly in high-dose treatment with methotrexate followed by leucovorin rescue which extends the usefulness of this compound in other types of solid tumors with, in general, remarkably little hematological toxicity (33). This has been particularly therapeutic in osteogenic sarcoma (41, 64). At high doses methotrexate appears to exert its therapeutic effects by entering into the tumor cells by filtration, diffusion, or by other passive mechanisms rather than by carrier transport alone (41). The clinical toxicity has been correlated with the drug concentration in the circulating blood. New data indicate that administration of high-dose methotrexate (more than 50 mg/kg) is accompanied by excretion of significant amounts of the metabolite 7-hydroxy-methotrexate (63). The lower aqueous solubility of the 7-hydroxy metabolite may have significant toxicological importance.

**Trace Metals and Electrolytes.** Many of the metals found in trace quantity in normal and neoplastic tissues are known to be essential for certain biological reactions. The biological role of some metals that are often present in tissues is not known. In some cases their presence may simply represent contamination from the environment. Forst (42) has indicated that most antitumor drugs can act as chelating agents and has speculated that this property may be important involved in chemotherapeutic action. 3-Ethoxy-2-oxo-butyraldehyde bis-thiosemicarbazone (kethoxal thiosemicarbazone) is a copper chelating agent. Thirty-four patients treated with this compound developed dose-limiting neurotoxicity, e.g., paresthesias, myalgia, motor weakness, and hallucinations. Nausea, vomiting, and bone marrow depression were also observed (106).

Regression of malignant tumors was observed in magnesium and potassium depletion induced by diet and hemodialysis (101). This observation will undoubtedly stimulate continuing investigation into the effects of minerals and electrolytes on tumor growth.

**Perspectives**

Years ago when chemotherapy was considered the last...
resort for the hopelessly ill patient with advanced cancer, antitumor drugs were frequently given too late to be effective. Even active drugs were often indicted for shortening the lives of cancer patients. This is understandable when one recognizes that the list of complications of chemotherapeutic and immunotherapeutic agents is long and the nutritional impact is formidable. The risks, however, must be viewed in proper perspective. Most of the complications listed are reversible and resolve in a matter of weeks. The risks of cancer chemotherapy and immunotherapy are small compared to the natural consequences of untreated cancer on the host. The most drastic reactions described rarely occur in day-to-day management. Many nutritionally important untoward effects can be prevented or treated non-specifically with antiemetics, analgesics, anti diarrheal agents, antibiotics, and transfusions of blood components during the initial critical phase of chemotherapy and immunotherapy to maintain an appropriate nutritional status.

Cancer patients who were placed on an elemental diet rich in calories, amino acids, and vitamins before and during treatment with 5-fluorouracil and, in some cases, radiotherapy showed no drug-related rectal lesions and maintained their pretreatment body weight (11). Chemotherapy in combination with parenteral nutrition is well tolerated (23, 24) in cancer patients who are nutritionally depleted and who would otherwise have been deprived of adequate antitumor chemotherapy for fear of complications from malnutrition and inanition. Suggestive evidence has been presented that nutritionally less deprived patients are more likely to respond to chemotherapy (77). Specific antibodies have been used to counteract toxic effects of the chemotherapeutic agents. Leucovorin against methotrexate, deoxyctydine against cytosine arabinoside (100), thymidine against 5-ido-2'-deoxyuridine (83), and L-asparagine against asparaginase (54, 94, 95) are some examples. Additionally, increasing success in the long-term control of acute leukemia (55), Hodgkin's disease (31) and other lymphomas, and certain carcinomas and sarcomas has severed the vicious cycle promulgated on the host by neoplasia and toxic agents. Indeed, with the use of appropriate induction regimens, certain diseases can be brought under sight (see Ref. 40). These findings indicate that intermittent treatment is superior to continuous treatment (see Ref. 40). These findings should lead to short-term intensive combined modalities to attempt tumor debulking, remission induction, or cure, rather than long continuous treatment with nutritional maintenance.

More importantly, the concept of chemotherapy has changed from last resort in the treatment of advanced disease to surgical adjuvant in the treatment of breast cancer (9, 39) and other neoplasms. Chemotherapy is now given to patients who show no evidence of disease, who are ambulatory and maintain normal activity, and who thus have normal appetite and nutrition. Chemotherapy is given to these patients with minimal nutritional consequences.

As cancers become more definitely characterized and understood, the nutritional treatment of tumor and normal tissues may be more effectively approached.

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