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NUTRITION AND CANCER: Physiological Interrelationships

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INTRODUCTION

Few areas in medicine have been more exhaustively reviewed than the interrelationships between diet, nutrition, and cancer. There are many issues addressed in such reviews: (*a*) diet and nutrition as a factor in the etiology of

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cancer; (*b*) adequate nutrition as a support modality in the care of the cancer patient; and (*c*) nutrition as a mode of therapy.

The first of those three concerns is not discussed in this review. The diet can be a vehicle for carcinogens and the diet composition may inhibit, promote, or even cause neoplastic growth. The target of the present review is the host with established cancer. Once the cancer is established in the host, the cancer and the host act as a pathophysiological unit. Attempts to use dietary manipulation to support the patient or treat the tumor directly have an underlying set of hypotheses: (*a*) the tumor-bearing host has a different metabolic and nutritional demand than a non-tumor-bearing host, and (*b*) there are differences in metabolism and nutritional requirements between a malignant cell and a normal cell of the same tissue origin. These two hypotheses are frequently only implied, and not overtly stated. An alternative view could be that the presence of a tumor generates only a physical impediment to adequate nutrition or a psychological burden, resulting in anorexia as a symptom of depression or psychological food refusal.

It is the purpose of this review to try to distinguish between these two extremes in view: a malnourished cancer patient is malnourished because of a fundamental physiological consequence of the cancer, *or* a malnourished cancer patient is malnourished because of inadequate food intake for whatever reason, no different from any other malnourished individual.

The literature that could be cited is immense. On occasion, synthesizing reviews by scientists active in a certain area are cited rather than primary sources. Many other papers have been written with more zeal to prove a point than scientific rigor. Furthermore, the transition from frank nutritional quackery to sound nutritional biochemistry is not a step-wise progression but rather a continuum. Even the sound nutritionist can become strident in opposition to food faddism and nutritional quackery (70). One can therefore correctly imply certain interpretations in omissions in this review. This review concentrates on human nutrition and uses animal studies to clarify points in the human situation. There is no doubt that conveniently placed transplanted tumors can have a very different effect than spontaneous tumors growing in an inconvenient location, and therefore many animal experiments are not helpful.

THE EFFECT OF CANCER ON NUTRITIONAL STATE

Introduction

The effect of the presence of cancer on the nutritional state of the host can be divided into several broad categories. These are (*a*) the direct effects of tumor presence, (*b*) metabolic effects of the cancer on the host, (*c*) difficulties with food enjoyment, and (*d*) psychological factors in anorexia. These are discussed in turn. The order of discussion does not imply a specific weighting of factors.

The incidence of overt malnutrition among cancer patients varies widely by time in the course of the malignancy, the specific type and location of the malignancy, and from institution to institution. In children the actual incidence of malnutrition at time of new diagnosis with cancer is not different from that seen in patients with benign tumors referred to the same institutions (45). This cited study was a retrospective study among three institutions. A prospective study in a single institution confirmed this information (27, 28). The incidence is much higher among children with progressive and metastatic disease and may then be as high as 40% in selected groups (156). The data in adults are not as clear. However, even there many patients have no weight loss at time of diagnosis (42). However, once weight loss sets in, it is a poor prognostic sign in children (45) as well as adults (40).

This review does not deal with the details of nutritional support of the cancer patient. However, no matter what the etiology of the malnutrition, vigorous nutritional support of the cancer patient is feasible. As is discussed below, nutritional repletion is not always possible, but without nutritional support, malnutrition becomes an iatrogenic disease. Again, it is beyond the scope of this review to summarize the degree to which chemotherapy contributes to malnutrition. The nausea, vomiting, and anorexia induced by chemotherapeutic agents as well as radiation injury can be very severe. Many reviews exist of this particular phenomenon; only those by Ohnuma & Holland (117) and Donaldson (44) are cited for chemotherapy and radiotherapy, respectively.

Direct Effects of Tumor Presence

The most obvious problem of the presence of cancer is mechanical, when the cancer interferes with intake and absorption of essential nutrients. Large bowel cancer, and cancer of the oropharynx are major causes in weight loss. Therapy is often as debilitating as is cancer itself. Many of such effects are the consequence of radical resection (94). This is especially true when the resection is around the oral cavity and pharynx and esophagus. However, the stomach and small intestines have their own effects on absorption. Colectomy is not as serious a problem, except when the ascending colon is resected where major water and electrolyte homeostasis is maintained (94, 136, 137).

It is also important to remember that malnutrition feeds upon itself. Malnutrition will result in malabsorption, and therefore is self-accelerating (63). There is no direct effect on intestinal structure and function in cancer patients (140).

In addition, chemotherapy is a major factor in malnutrition. As an illustration, the effect of methotrexate or 5-fluorouracil on the small bowel is extremely rapid and seen with very small cumulative dosages (63). Therefore, the direct effects of tumor presence are as often as not accentuated, or even caused by therapeutic attempts. However, because of the prevelance of bowel cancer,

especially large bowel cancer (104), the nutritional consequences of bowel obstruction can be a very common medical problem.

Finally, there are lymphomas of the bowel that have a profound effect on absorption (123). That subject, fascinating in itself, is beyond the scope of this review.

Metabolic Effects Of Cancer On The Host—Hormonal Effects

PARANEOPLASTIC SYNDROMES Metabolic interrelations between cancer and the host can result in malnutrition. There are two basic ways in which this may occur. First of all, the tumor may exert a direct effect on the host metabolism through hormones or toxic secretions. Alternatively, the host and tumor may have such different metabolisms that the presence of the tumor can result in an imbalanced homeostasis. It is the first of these two phenomena that is discussed at this point.

There is a fine line between true paraneoplastic syndromes and a distant effect through tumor secretions. Paraneoplastic syndromes are defined in this context as the distant effect of the presence of cancer through well-defined humoral secretions. This is almost exclusively limited to the secretion of ectopic hormones. Shills (138), in his textbook *Modern Nutrition in Health and Disease,* lists the many diseases that can cause nutritional-metabolic problems in patients with hormone-secreting neoplasia. Many neoplasias may produce more than one active agent. The hormones that may be secreted include antidiuretic hormone, various steroids, gastrointestinal hormones, such as gastrin, and vasoinhibitory peptide, calcitonin, histamine, parathyroid hormone, catecholamines, and prostaglandins. Lipsett reviewed the subject further (97).

Certain tumors can give severe malabsorption and steatorrhea. In some tumors, such as cause the Zollinger-Ellison syndrome and carcinoid, the associations are very clear. There are other tumors that are uniquely predisposing to malnutrition by unknown mechanisms. These include neuroblastoma and Ewing's sarcoma, especially. Neuroblastoma can give intractable watery diarrhea (106), a syndrome that is also seen in adult ganglioneuroma-pheochromocytomas (152). However, this syndrome is related to differentiated neuroblastic tumors rather than the immature ones (102). The actual malnutrition seen in neuroblastoma is more related to the severe progressive disease. While it is attractive to speculate on the mediation of this effect through catecholamines, this is not really proven. In fact, the less-differentiated tumor often does not make catecholamines.

Ewing's sarcoma also seems to predispose to malnutrition (27, 28, 159). Again, it is not clear that this is through a paraneoplastic syndrome. It is possible that the nutritional demand of a growing adolescent cannot be met in

the presence of cancer, but the same phenomenon is not seen in osteosarcoma (77).

CANCER CACHEXIA The second edition of Robbins' *Textbook of Pathology* states "The most common way in which malignancy leads to death is cachexia: the development of progressive weakness, weight loss, and wasting. Usually, there is a close correlation between the amount of malignant disease present and the severity of cachexia. . . . In this weakened state, cancer patients are particularly susceptible to terminal infections, such as pneumonia, which often precipitates death" (126, also quoted in 158). Many authors feel that the etiology of cachexia is a metabolic distant one. One view is that it is the consequence of the inability of the host to adapt to increased caloric demands. That is discussed below. The other view, primarily promoted by Theologides, states that cachexia is due to metabolites or peptides secreted by the tumor. Theologides (148) proposes that peptides, oligonucleotides and other small metabolites produced by cancer in the tumor-bearing host are responsible for the genesis of cachexia by inducing anorexia. Theologides reviewed the evidence for this proposition on several occasions. He postulates that the effect of these secretory peptides from the tumor could work via the hypothalamus, or by causing a metabolic imbalance through activation and deactivation of host enzymes (149). Williams et al (181) proposed that the molecular base for the mechanism of cachexia begins with a tumor-induced retrodifferentiating change in the liver, causing massive decreases in the activity of alanine aminotransferase. The resulting high concentration of alanine would cause the sequential derangement in gluconeogenesis from lactate, increased secretion of vasopressin, suppression by vasopressin of long-chain fatty acid oxidation and ketone-body production, and finally, an insufficient blood concentration of ketone bodies to regulate branch-chain amino acid oxidation by muscle.

Some model systems seem to suggest that the anorexia of cancer may be mediated via the central nervous system. A common candidate for the anorexia of cancer, which in turn leads to cachexia, is increased central serotonergic activity. Increased plasma-free tryptophan and 5-hydroxyindoleacetic acid levels are found in tumor-bearing rats who have a high reduction of food intake. However, reduction of food intake is seen without significant differences in these plasma levels, so that increased plasma-free tryptophan and elevated serotonin metabolism may not be the initial dysfunction responsible for nocturnal anorexia (112).

The relationship between plasma tryptophan and satiety has been proposed by others. Krause et al (88) based it on an increased plasma-free tryptophan, but not total tryptophan. They find significantly increased tryptophan and 5-hydroxyindoleacetic acid in brain in tumor-bearing rats as compared to pair fed rats. In another study Krause et al (87) also found increased brain tyrosine. Von

Meyenfeldt et al (162) found that this increase in tryptophan and serotonin was observed in two lines of anorexia-producing tumors and that it preceded the onset of the tumor-induced anorexia. Moreover, the serotonin is not uniformly distributed over the whole brain, but levels are highest in the diencephalon. However, when these same investigators tried to deplete serotonin, utilizing 5,7-dihydroxytryptamine or parachloroamphetamine, cancer anorexia was not affected in the model systems used (30).

One of the candidates for the mediator of a distant tumor effect is an alteration in tissue lysosomal enzymes. In a model of implantable mammary adenocarcinoma, Ferguson et al (51) show that the presence of the tumor induces cachexia and that this is correlated with a change in lysosomal enzyme in the tumor group in liver and muscle. They suggest that these tissue lysosomal enzyme changes may be contributing to tissue alterations seen in the tumor cachectic host. Excision of the tumor does reverse the cachexia (50). After excision, the abnormalities in lysosomal enzyme activity reverse themselves (50).

Through a variety of manipulations that were designed to generate hyperphagic response independent of the hypothalamus, Morrison (108) could dissect the factors that affect the regulation of food intake. There are many redundancies in the feeding control system, so that early impairment can be compensated by hypothalamus-mediated physiological and behavioral mechanisms. In the later stages of tumor growth, compensation no longer seems possible and the feeding control system collapses. Morrison found that this anorexia is more likely due to premature satiety than it is to impaired perception of hunger (110). He proposes that the presence of tumor reduces some meals to zero size and that satiety can occur in the cephalic phase of digestion before any food has been ingested.

While the data are not at all clear about a distant effect, certain model systems do strongly suggest the possibility. A typical example is a model reported by Strain et al (144) wherein a hypernephroma was removed from a man who had lost 30 kg in the two months preceding surgery. The tumor was grown as a nonmetastasizing transplantable xenograph in immune-suppressed mice. The tumor produced a considerable weight loss, greater than 25% in the mice at a stage when it comprised less than 5% of the total body weight. The weight loss was out of all proportion to the decrease in food intake.

Metabolic Effects of Cancer on the Host—Indirect Effects

It is widely believed that the presence of a malignancy causes increased energy expenditure in the cancer patient. Many experiments have been done to prove or disprove this point. Knox et al (84) measured resting energy expenditure by a bedside indirect calorimetry in 200 heterogeneous hospitalized cancer patients. Fifty-nine percent of patients exhibited aberrant energy expenditure outside the

normal range. Thirty-three percent were hypometabolic, 41% were normal metabolic, and 26% were hypermetabolic. The aberrations did not correlate with age, height, weight, sex, nutritional status, tumor burden, or presence of liver metastases. The duration of malignancy seemed to correlate with the incidence of hypermetabolism. The conclusion was that cancer patients exhibit major aberrations in energy metabolism but are not uniformly hypermetabolic.

Studies using smaller patient samples seemed to suggest that there is an increased resting metabolic rate and daily energy expenditure (132). Warnold et al (168) compared cancer patients in separate studies with controls and found an increase in resting metabolic rate and daily energy expenditure. Bozzetti et al (14) found in 65 patients with advanced cancer that resting metabolic energy expenditure was abnormally high in about 60% of the patients. There was a strong correlation between resting metabolic expenditure and weight loss and in between resting metabolic expenditure and variation in serum transferrin. Arbeit et al (3) studied eleven control patients, nine patients with localized tumors and four with diffuse cancer. Patients studied pre- and post-tumor resection all had a postoperative drop in their resting energy expenditure. The resting energy expenditure was significantly correlated with tumor volume. This suggests that the tumor-bearing state exerts a moderate impact on nutritional and metabolic parameters that are related to the extent of disease.

Many people have diligently searched for correlating metabolic abnormalities. The overall plasma glucose level in patients with cancer is normal. The overall turnover of glucose in normal and cancer patients seems to be normal also (124). There seems to be an increased glycolysis in the tumor and compensating gluconeogenesis in the remainder of the body. Consequently, there is an increased formation of lactate and resynthesis of glucose from lactate. In other words, the Cori cycle is two to four times normal. With this is correlated a small degree of blood lactate level elevations in some cancer patients (74, 75, 169). However, Weinhouse (180) correctly observed that, while tumors do glycolize in vivo at rates similar to those observed in vitro, the homeostatic mechanisms operating in normal humans to maintain the plasma glucose operates without substantial impairment in the cancer patient.

The increased Cori cycle does suggest that there might be an abnormality in the emphasis where the glucose homeostasis is placed. The increased gluconeogenesis might be a point of weakness in the metabolism of a patient bearing cancer. Waterhouse (170) stressed that the metabolic abnormalities probably suggest early consideration of nutritional intervention in the course of malignant disease. However, she also stresses that the increased Cori cycle is often associated with stress and therefore may not be directly related to the cancer. On the other hand, nitrogen wastage and failure to respond metabolically to small glucose loads are also commonly associated with stress and neither of those phenomenon are observed in the advanced cancer patient (170).

A careful study of 12 patients with non-oat-cell lung cancer and six age-matched healthy controls under metabolic ward conditions found increases in protein turnover, glucose production, muscle metabolism in the cancer patients. However, there were no concomitant hormonal changes that might explain these phenomena (69). In children with leukemia and lymphoma similar findings can be cited (81).

There is an additional complication in that the validity of many of the direct and indirect measures of muscle metabolism are called in question. For instance, urinary 3-methylhistidine has been used as an indicator for skeletal muscle breakdown and protein metabolism. The pros and cons of this measure were discussed by Brennan & Ekman (16). Brennan & Ekman point out that 3-methylhistidine turnover in nonskeletal tissue, especially the intestine, is much more rapid than that occurring in muscle. Heber et al (69) used other measures, such as total-body protein turnover measured by the continuous infusion of (^{14}C)-lysine in patients under constant caloric and nitrogen intake. Kien & Camitta (81) used the single-dose (^{15}N) glycine turnover technique. But as long as major methodological questions are raised, it will be impossible to discuss fine distinctions in the detail of the effects of cancer on nutritional status.

These questions are even more difficult in the areas of lipid metabolism. There is an increased glycerol turnover in cancer patients (46). In addition, there are suggestions that there are abnormal fatty acid breath tests in cancer patients (37). However, the data are scant and not very convincing.

If there are primary metabolic abnormalities in the host, the most convincing evidence lies in the increased gluconeogenesis. There are suggestions that there is a decrease in whole-body insulin sensitivity and a decreased glucose tolerance (100). There seems to be a decreased enzyme capacity for glucose metabolism and skeletal muscle as well (99). A suggestion has been made that insulin could help and should be examined as a possible supportive measure in the total nutritional management of cancer patients (131).

Animal model systems seem to support this contention. The Walker 256 carcinosarcoma growing in Sprague-Dawley rats and the Morris 512 hepatoma growing in Buffalo rats both produce cachexia. In both model systems exogeneous insulin results in increased food intake and rate of weight gain of the host (109).

If the distant metabolic effect is primarily the increased Cori cycle activity and the consequent problem in glucose homeostasis, one would expect that interruption of the Cori cycle might be beneficial, and conversely that nutritional support might be less effective than in an equally malnourished patient who is not bearing an active cancer. Attempts have been made to interrupt the Cori cycle with a variety of substances. In a model system where there was significantly increased glucose recycling and increased alanine conversion to glucose,

the administration of 3-mercaptopicolinic acid did result in significantly lower plasma glucose and higher blood lactic acids. This experiment confirmed the Cori cycle acceleration but did not speak in favor of interruption of the gluconeogenesis as beneficial (21).

A great deal of attention was paid to the use of hydrazine sulfate as a modulator of glucose recycling. Hydrazine is presumably an inhibitor of gluconeogenesis. Earlier studies were reported that evaluated hydrazine sulfate as a therapeutic agent. These trials have been negative to date (96, 115, 142), though the proponents of hydrazine sulfate vigorously attacked some of those reported negative results (55). The concept was that hydrazine sulfate could change the anabolic profiles in late-stage cancer patients (56). To date only one randomized, placebo-controlled trial has been reported, and that to date only in abstract form (33). This study utilized patients with a diagnosis of advanced cancer and greater than 5% weight loss. After hydrazine sulfate treatment, the authors reported that glucose tolerance was improved in 100% of colon and 57% of lung cancer patients having repeat evaluation. A significant association between improvement in oral glucose tolerance and maintenance of body weight in these hydrazine sulfate–treated patients was reported. In addition, insulin sensitivity seemed improved in such patients (32, 33).

Finally, if a profound defect in metabolic abnormalities were a fundamental component of cancer cachexia, attempts at refeeding would frequently be futile. Here even more disagreement exists. The previously quoted paper by Brennen & Ekman (16) summarizes the evidence, which concludes that individual patients unable to ingest, digest, or absorb food can be nutritionally maintained by intravenous nutrition. Copeland has repeatedly published his vast experience in the use of hyperalimentation in patients with malignancies. A recent review (35) is representative. In that review he cites the evidence for the conclusion that adequate nutritional replenishment should be undertaken prior to the indicated antineoplastic therapy because the malnourished patient has a much narrower safe therapeutic margin for most oncologic therapy. On the other hand, the group under Nixon (113) found that cancer patients compared unfavorably to noncancer patients on receiving hyperalimentation in all measurements of nutrition repletion except triceps skin-fold increments, which suggests that weight gain in cancer patients represents repletion of fat rather than restoration of normally deemed body mass. Elsewhere, these authors summarized common mineral and electrolyte abnormalities that may cause or merely reflect what appears to be a partial block to the restoration of normally deemed body tissue in persons with advanced cancer (95). There is no doubt that in children nutritional repletion is possible even in the face of aggressive tumor growth (160). Furthermore, optimal nutritional support with parenteral nutrition is beneficial to the cancer patients protein economy best stimulating whole-body protein synthesis and decreasing skeletal muscle protein metabo-

lism. There is an insulin-stimulating effect that aids in this protein anabolic effect (22).

Unfortunately, the data on the fundamental question about metabolic aberrations in patients are often clouded by the hope that parenteral nutrition has a therapeutic benefit above and beyond that of nutritional support. A recent point-counterpoint set of papers illustrates this difficulty. Koretz (85) concludes that parenteral nutrition is "oncologically illogical in 1984." He reached that conclusion after evaluation of 17 prospective, randomized, controlled trials that tested the hypothesis that parenteral nutrition will be of clinical benefit in patients receiving chemotherapy or irradiation for various types of malignancies. Apelgren & Wilmore (2) wrote a counterpoint that sounded more in agreement than in dispute. They did point out that diminished morbidity and mortality are not demonstrated for parenteral nutrition. However, that should not preclude an attempt at support of nutritional state of cancer patients.

The human with cancer is a very complicated system. Very few patients are left untreated in order to study their metabolism. Therefore, it is highly unlikely that good data will be forthcoming to settle the issue of an altered metabolism in patients with malignancies. However, Brennan was accurate in pointing out that the system of refeeding the malnourished cancer patients with defined diets will and ought to serve as a way of addressing this question further (17).

Dysgeusia

There is a body of literature that purports to show that there is significant alteration in taste sensation in patients who have cancer. DeWys is active in this area and has reviewed the topic frequently (39, 41). The most significant change appears to be the lower threshold for bitter-tasting foods, which is probably responsible for the aversion to the taste of meat and other high-protein foods frequently observed in cancer patients. In this group of patients too the effect of chemotherapy can be very significant. Carson & Gormican (26) observed that before cancer patients are treated with 5-fluorouracil taste abnormalities included a decrease in sensitivity to salt and sweet tastes, but no change in bitter and sour thresholds. After chemotherapy there were a variety of changes in patients' taste acuity. The change in taste sensations are corrected after intravenous hyperalimentation (128). These changes in taste preference are extremely complex and vary with tumor type, sex of the patient, and specific stimulus used (135). Furthermore, it is extremely difficult to dissect out whether there are psychological conditioning factors associated with the effect of taste sensation changes on anorexia.

Psychological Factors in Anorexia

Anorexia can have a strong psychological component. The extent of this contributor to malnutrition in cancer patients is not genuinely appreciated. Holland et al (73) gave a detailed review of the psychological aspects of

anorexia in cancer patients. Anorexia is a well-defined component of the psychiatric syndrome of major depression. Holland et al did not find cases with depression in a controlled study (73). The problem of defining depression in cancer patients has been pointed out (47). However, in children, depression can be seen (van Eys, unpublished observations). Bruera et al (19) reported on a study of 72 patients. The malnourished patients had a higher incidence of severe depression and decreased food intake. There was no difference in taste, emesis, or glucose burden to explain the food intake difference.

Even in the absence of true depression, there are episodes of transient anorexia, which can occur at the time of the initial diagnosis or upon learning about recurrent disease. Furthermore, times of pain and discouragement will contribute to anorexia.

There are pseudopsychiatric syndromes that have a specific biochemical cause; in particular, hypothalamic tumors can have devastating consequences on nutritional intake, while appearing to be psychologically or psychiatrically mediated (98). We have observed patients with lack of thirst and hunger as a consequence of hypothalamic tumors. Such patients are not viable without constant support (van Eys, unpublished). On the other hand, the cited case of anorexia nervosa secondary to a hypothalamic tumor can be counterbalanced by a case of our own of anorexia nervosa in a child with a brain tumor in complete remission where it was indeed a purely psychiatric syndrome (157).

An alternative component of psychologically induced anorexia is the problem of learned food aversion. This is best demonstrated in children with cancer. Bernstein (5) demonstrated experimentally that learned food aversions in children receiving chemotherapy were rapidly induced. Using a rat tumor model, Bernstein & Sigmundi (7) could demonstrate that learned food aversion was a component in tumor anorexia and that commonly used antitumor drugs could act as unconditional stimuli to generate learned taste aversions in rats (8). These data refer largely to chemotherapy-induced learned food aversions. Bernstein also summarized the information that seemed to suggest that food aversion can be learned as a result of associating foods with the discomfort of tumor growth (6, 9).

Schmale (133) reviewed the psychological aspects of anorexia in 1979. Little other organized research has been published.

Synthesis of Information

The information presented so far shows a wide range of effects of the presence of cancer on the nutritional state of the host. The data are not conclusive for a biologically mediated effect, unless there is a direct paraneoplastic syndrome present. At best the data are inconclusive; at worse the observed effects are very indirect. Of all phenomenona observed, the general effect on glucose homeostasis is the best documented. Copeland (35) continues to believe that the majority of malnutrition encountered in cancer patients is secondary to a

decrease in nutritional intake related to the anatomical location of the neoplasm or to the adverse gastrointestinal or general systemic effects of oncological therapy. Once large tumor burdens are encountered, nutritional repletion may be difficult and the metabolic differences between the cancer cell and the host cell become important. Our own experience also seems to suggest that most malnutrition in oncology is an iatrogenic disease in most patients (159). The observed cachexia described by Robbins (126) is associated with a very large tumor burden. Therefore, we need to discuss the differences in the metabolism of tumor and host cells and their relationship to the nutritional state of the host.

DIFFERENTIAL METABOLISM OF TUMOR AND HOST CELLS

Cellular Metabolism

WARBURG HYPOTHESIS The consequence of the malignant transformation of cells can vary widely. Some cells are minimally deviated from the normal while others are genetically chaotic cells. In an extensive review of tumor cells, Warburg noted that both animal and human tumors have a high anerobic glycolysis. Furthermore, this glycolysis was only partially eliminated when tissues were incubated in oxygen. In other words, tumors have a diminished Pasteur effect. From this a hypothesis was formulated, generally known as the Warburg hypothesis: "Aerobic glycolysis results if the respiration of growing cells is injured, whether by diminishing its extent or by interfering with the relationship which holds between respiration and fermentation (glycolysis). . .

Interference with the respiration of growing cells is, from the standpoint of the physiology of metabolism, the cause of tumors. If the respiration is disturbed, as a rule, the cell dies. If the cell does not die, a tumor cell results" (166). A wide range of tissues were evaluated by Aisenberg (1), and in general, the phenomenon seems to be borne out. However, there are many that are nonmalignant that have a high anaerobic glycolysis rate. This is especially true for embryonic tissue. Weinhouse has been a strong opponent to the Warburg hypothesis as an important explanation for the deranged metabolism in cancer. A recent review by Weinhouse (180) puts the carbohydrate metabolism of tumors into a more modern perspective.

The original debate between Warburg and Weinhouse is still very instructional (167, 167a, 179). However, while the Warburg hypothesis does not explain malignant differentiation, the fact remains that tumor cells do glycolyze aerobically, and that in face of a high tumor bulk there may be considerable lactic acid production. For instance, in leukemia tumor glycolysis can overwhelm the host and lactic acidosis can become a very severe problem (13). The condition is aggravated by the frequent anaerobic condition inside poorly

vascularized solid tumors. In addition, high glucose parenteral nutrition can precipitate lactic acidosis in children with cancer (103).

Cancer cells often have a strong "Crabtree effect": supplying tumor cells with glucose results in inhibition of endogenous aspiration, which magnifies the dependence on glucose for energy (154). Normal cells usually have no Crabtree effect and maintain respiration from other nutrient sources, even when glucose is supplied. Therefore, the cancer cell utilizes the glucose preferentially. Comparison of the glucose uptake by tumor and host showed an almost complete removal of interstitial fluid glucose by the tumor while the normal tissue exacted only one third of the available glucose, as judged from the circulating blood level (65).

Weinhouse (180) reviewed the potential sites of the deranged Pasteur effect. He discussed the evidence for the switch in pyruvate kinase isozyme patterns as the cause for competition for adenosine diphosphate between respiration and glycolysis. In the same review Weinhouse further calculates that the observed rates of the Cori cycle in human cancer patients are within the bounds that one might expect from usual ranges of tumor glycolytical activity observed in vitro. In other words, Weinhouse assumes from these considerations that human tumors do indeed glycolyze in vivo at rates similar to those observed in vitro and that the usual homeostatic mechanisms operating in normal humans to maintain plasma glucose also operate without substantial impairment in the cancer patient. In other words, the metabolic derangements observed in the cancer patients are normal homeostatic responses.

ADAPTATION TO STARVATION While the Warburg hypothesis may not have an etiological significance, the observations by Weinhouse do suggest that in vivo glycolysis rates are significant. There are therefore differences between the metabolism of a normal and a malignant cell that are fairly generic and that are sufficiently frequently encountered that generalizations are possible. Warburg summarized the observations on tumors as follows: "The anaerobic glycolysis of tumor cells is approximately equal for all tumors. The aerobic glycolysis of tumor cells is on the other hand different. It is the higher, the more malignant the cancer cells are, the faster and more destructively they grow" (my translation) (167b). The literature for the search of such a specific metabolic derangement is even more vast than is the literature on nutrition and cancer. Many investigators have compared normal tissues with derivative malignancies and found quantitative changes in enzyme and antigen compositions. Much of that literature is designed to find key enzymes that could be appropriate targets of selective chemotherapy. To date that possibility has not been realized.

However, another approach to the enzymology of the cancer cells is a review of the causes of the metabolic and nutritional advantage that the cancer cells seem to enjoy in the host. We owe much of the synthesis of the data to George

Weber (171, 172). In carbohydrate metabolism, the quantitative alterations entail a decrease in the activities of the key gluconeogenic enzymes and an increasing rate of the opposing key glycolytic ones. In addition, there is a qualitative change in that there is an isozyme shift manifest in the loss of glucokinase and pyruvate kinase with low affinity in favor of more embryonic hexokinase and pyruvate kinase isozymes with high affinity for their substrates. There are imbalances in the pentose phosphate cycle as well as in purine metabolism. The overall outcome is an enzymic phenotype that may confer reproductive advantages. More importantly however, there is a lack of effect of starvation on hepatoma enzyme activity as compared to normal liver (174).

These data are not limited to the graded sequence of minimal to severely dedifferentiated hepatomas that have been so profitably studied in the past. Various tumor cells and tumor models show these same generalizable deviations (173).

In addition, there seems to be an increased glucose transport in malignant cells over that seen in normal cells. This phenomenon was first described by Michael Weber for rhinosarcoma virus–transformed cells (175). Recently this topic was reviewed by Weber (176). These findings support the notion that there is an additional selective advantage for the growth of tumors that are poorly vascularized and oxygen deficient through their enhanced ability to utilize glucose.

These two selected summaries indicate the possibility that tumor cells do not participate in the normal homeostatic mechanism on the cellular level in response to nutrition. When starved they do not adapt, and when fed, they are in a selective advantage. This phenomenon would be exponentially greater the higher the ratio of tumor mass to host.

Differences in Tumor and Host Cell for Nutritional Requirements

The differences in carbohydrate metabolism sketched out above, are paralleled in a difference in ability to utilize nonglucose substrates. Then the question can be legitimately raised whether there is a disadvantage in attempting to refeed the malnourished cancer patient in that the tumor cell might take advantage of this refeeding above and beyond the normal cell. A corollary question would be whether specific composition of the refeeding nutrient mix might be used to the advantage of tumor therapy. The latter is discussed below. However, the question of whether feeding the cancer patient will accelerate the demise of the patient from the cancer is a hotly debated topic that deserves some detailed review.

There are no current methodologies known through which nutrition can be expeditiously directed to the host and not to the tumor. The unbridled growth nature of tumors makes it likely that they behave very much like a pregnancy,

with preferable utilization of proferred nutrients. There is an extensive literature on the effect of nutrition on tumor growth. That literature deals primarily with transplantable tumor models in experimental animals. Japanese investigators found that the mitotic index of malnourished rats with implanted lung cancer is much lower than that of adequately fed rats, which in turn was lower than that of rats fed through hyperalimentation (82). When only glucose and electrolytes were infused, there was a significant amount of weight loss. Tumor growth decreased and the tumor showed massive necrosis (67). Compared to animals who received inadequate nutrition, the tumor cell size is reported to be larger, and it seems as if the increase in size is due to hypertrophy, but not to hyperplasia of tumor cells (68).

On the other hand, there are claims in the literature that intravenous hyperalimentation is beneficial in and of itself in patients with tumor. For instance, Ota et al (118) suggested nutritional regimens such as intravenous hyperalimentation can cause protein repletion in the malnourished host and simultaneously decrease tumor utilization of alanine and aspartic acid for energy production. However, many more studies seem to suggest that hyperalimentation results in larger tumors and not necessarily in prolonged survival of the animals when compared to protein-depleted animals (54, 150). In addition to bigger tumors, an increased mitotic activity after hyperalimentation is seen in American studies as well (25). Furthermore, whether oral or intravenous food was used, tumor growth (as measured by changes in volume, weight, DNA content, or nitrogen content) is unaffected by the various nutritional regimens, though the host does respond differently to the different regimens (60).

There is an indication that protein manipulation can change the pattern of metastases (24). However, the greatest claim is always made that protein calorie manipulation might increase the tolerance to chemotherapy (36). For instance, Weber et al (177) suggest that protein-free diets do not significantly affect metastases, but hemorrhagic cystitis after cytoxan is much more common in protein-free groups compared to rats on regular diets. In these experiments there was no direct effect on outcome of chemotherapy but there were delays because of the side effects of chemotherapy. Chemotherapy is sometimes self-cycle specific. Infusing amino acids to enhance tumor growth seemed to result in potentiation of tumor response to methotrexate without increasing host toxicity (151). The catabolic effect of 5-fluorouracil can be significantly enforced by intensive nutritional support of animals (143). Methotrexate metabolism is significantly altered in malnutrition (64, 159).

There are many more papers that bear on this problem. The above-cited are representative of the kind of arguments brought forth, without being an exhaustive summary of the polemic that has raged in the surgical and oncological literature. The arguments extend to human cancer management. Papers by Copeland have already been mentioned. Reviews by Copeland (34) on in-

travenous hyperalimentation and chemotherapy consistently maintain that hyperalimentation is helpful in such patient and that no adverse effect is seen. However, in patients with extensive large bowel cancer, hyperalimentation seemed to have an adverse effect on overall survival (95, 114). A complete review of total parenteral nutrition in the cancer patient was published by Brennan (18).

No matter what the outcome of the specific question of stimulation of tumor growth will eventually be, the fact remains that nutritional support seems to be neither counterproductive nor specifically helpful as far as tumor therapy is concerned. A previously published conclusion on the effect of nutritional status on response to therapy still stands: poor nutritional status is reversible, whether therapy is given or not, and initial malnutrition presages poor outcome. However, reversal of the nutritional state does not affect outcome unless the antineoplastic therapy is inherently effective (158).

Nutritional Sensitivity of the Immune System

The immune system is very sensitive to malnutrition. There is a clear association of immunodeficiencies with the protein calorie malnutrition syndrome (90). Poor nutrition is implicated in the progression of infection, and those infections worsen nutritional status by loss of nitrogen and depletion of body protein. Contrary to animal studies, in humans with protein calorie malnutrition the humoral element of the immune response remains relatively intact while the cell-mediated component is markedly impaired (80, 111). At the same time, there is a benefit of chronic undernutrition, both in overall longevity, cancer incidence, and immune status (31, 59).

Good et al (58, 59) pointed out that the difference between the human and experimental system could in part be due to zinc deficiency. There is a specific zinc requirement for lymphocyte response (86). It is an intriguing and paradoxical observation that our current methodology of hyperalimentation can produce zinc deficiency because of inadequate supplementation (49). Our own unpublished experience suggests that in young children the dose of zinc must be ten times the adult requirement on a proportional body weight basis.

Not only is there a clear relationship between nutrition and immunity, but the claim is frequently made that nutritional deprivation depresses in vivo skin testing activity and that nutritional restoration results in weight gain and the return of skin test reactivity to normal. This claim has been translated that delayed cutaneous hypersensitivity skin testing is useful in nutritional assessment of hospitalized patients. We found that this was not valid in children but originally this was attributed to the unchallenged immune system of the child (147). However, a recent exhaustive review of the utility of skin testing in nutritional assessment concluded that there were usually problems in experimental design, frequent lack of appropriate controls, and low specificity of

abnormal delayed cutaneous hypersensitivity responses. The reviewers concluded that the utility of skin testing in nutritional assessment remains unproved (153).

In addition to the humoral and cellular immune system, there is often a claim of decreased opsonic activity. Dillon et al (43) demonstrated that fibronectin is diminished in starvation in rats and man (76). Fibronectin is a useful measure of nutritional state. The subject has been reviewed by the Dillon group (129).

The role of nutritional defenses in tumor destruction is far from clear. If it occurs at all it is likely to be early in the course of the disease before malnutrition sets in. However, infections continue to claim more patients than do the tumors themselves. This is especially true in patients subjected to extensive surgery, radiotherapy, and chemotherapy. Yet, a recent extensive review of infections in hematology fails to mention nutrition as a significant weapon in the defense against such infections (122). Our own experience shows that in a prospective randomized trial of hyperalimentation in children with metastatic malignancies, the infectious incidence in the well nourished group was significantly lower than in the malnourished group, though the outcome of the tumor was not changed (161). Other specific nutrients frequently mentioned in immune status are protein, vitamin A, and iron (146).

Synthesis of Information

There are significant differences in the metabolism of the "average" cancer cell and the normal host. These differences can be in themselves responsible for the metabolic aberrations seen in the cancer-bearing host. These differences may result in a selective advantage of the tumor cell whether the host is starved or fed. The effect of nutrition on the host with cancer is further complicated by the effect of nutrition on the immune system. Because of that latter effect, it seems prudent to consider a well-fed host to be more advantageous than a malnourished host, independent of the growth of cancer. However, the question then arises whether selective dietary manipulation might be useful in the treatment of cancer.

EFFECT OF NUTRITIONAL MANIPULATION ON TUMOR GROWTH

Introduction

Ultimately, nutritional requirements are determined by the composite needs of individual cells. The organism's capacity to absorb the proffered foods and to transform individual metabolites into a mixture optimal for cellular homeostasis does contribute. A person who has cancer, but has not yet been treated with radiation therapy or chemotherapy, and who does not have as yet a large tumor burden, may exhibit no fundamental difference in the ability to absorb and

transform foodstuffs. Yet, there are some fundamental differences between the metabolism of the cancer and the normal host cell. Therefore, it is potentially feasible to use nutritional manipulations to affect the cancer growth. In fact, much of cancer chemotherapy is the use of analogues against cellular nutrients. This is an important way of viewing chemotherapy (155), and was carefully reviewed by Demetrakopoulos & Brennan (38). The effect of nutritional manipulation is most often seen at the micronutrient level, such as vitamins and purine and pyrimidines. However, the exploitation of differences in protein calorie requirements is ultimately even more intriguing, especially in view of the differences in gross carbohydrate and fat metabolism between the tumor and the normal cell.

Selective Starvation of Tumor Cells—Protein Calorie Sources

FAT There is an overwhelming demand for carbohydrate as calorie source by the tumor. Certain tumors cannot utilize fat as the primary energy source. Buzby and associates (23) attempted to use this differential metabolism between tumor and host cells by utilizing a model of a transplantable mammary adenocarcinoma in the rat. They studied the relative effects of different exogenous intravenous nutrients on tumor growth and maintenance. Fat-based parenteral hyperalimentation showed a lower final tumor volume, a lengthened doubling time, and a lower protein synthesis rate. Starvation slowed down the tumor growth even more, but the tumor had a positive nitrogen balance while the host did not on starvation. The tumor showed a significantly lower nitrogen balance on fat-based total parenteral nutrition than the carbohydrate based for controls. Others have shown similar effects (48). Unfortunately, such a nutrient formula is very poorly tolerated by the experimental animals (23, 48, 79).

The interpretation of these observations is further complicated because a diet high in corn oil makes low inocula of Walker carcinosarcoma regress after initial development (91). Kwong et al (91) found that the nonsaponifiable fraction of corn oil appeared to promote this tumor regression. On the other hand, feeding 20% corn oil increased 7,12-dimethylbenzanthracene-induced mammary tumorogenesis when compared to 5% fat diet (127). The subject of lipid-induced carcinogenesis has been repeatedly and extensively reviewed and is specifically not the topic of this review. However, the original experiments by Buzby (23) and by Kwong (91) dealt with the tumorocidal potential of nutritional manipulation rather than the induction or promotion of tumorogenesis.

CARBOHYDRATES The greatest interest lies in the manipulation of carbohydrate metabolism because of the enormous dependence on glucose in tumor cells. It is impossible to utilize an oral diet deprived of carbohydrates, because this does not necessarily change the plasma level of glucose. An experiment

attempting to evaluate the effect of low-carbohydrate diet in lymphoma-bearing mice showed no significant effect on survival (38).

An alternative is utilization of carbohydrate derivatives or analogues. Dietetic supplementation with 2% or 5% of 2-deoxyglucose to a meat-based diet did cause tumor regression without host impairment when compared to pair-fed tumor-bearing controls (139). Administration of 2-deoxyglucose intraperitoneally in Walker 256 carcinoma-bearing rats showed similarly a tumor growth retardation effect (4). However, the use of 2-deoxyglucose in humans showed significant side effects and only small amounts of antitumor effects (92). Other glucose analogues have been used, but these have never been translated to the clinical situation.

A more interesting possibility is the use of alternate calorie sources, less efficiently utilized by the tumor than by the host. Early experiments utilized dietetic supplementation with different sugars, in quantities of 1 to 10 mg/ml of drinking water. Some antitumor effects were seen, but in the quantities used, these substances could not have supplanted glucose as an energy source (57).

One of the interesting possibilities is the use of the carbohydrate xylitol. When animals were given ^{14}C-xylitol or glucose the tumor metabolized the glucose actively but accumulated the xylitol essentially unchanged (130). There are many studies utilizing xylitol as a major carbohydrate source in total parenteral alimentation (93, 165); therefore, such an approach might be explored as a mode of manipulating tumor energy supply. There are no studies specifically directed to patients with cancer. Bozzetti et al (15) did compare the effect of glucose versus xylitol as major carbohydrate on postoperative metabolism of patients with cancer. However, the therapeutic effect on the cancer was not evaluated. Another study from China gave the same resuls (163). Xylitol is not used in the United States in parenteral solutions though it is still advocated as a source of carbohydrate in postsurgical patients in Europe (53, 165). Xylitol has a major effect on insulin secretion and protein metabolism. The previously mentioned insulin resistance in patients with cancer suggests further that xylitol should be explored in a cancer setting.

PROTEINS—AMINO ACIDS Tumor cells may have a high requirement for specific amino acids. This requirement may be quantitatively or qualitatively different from that of normal cells. Therefore, many people have considered the possibility for biochemically rational chemotherapy with depleting enzymes and antimetabolites of specific amino acids. Hanka (66) reviewed very briefly the state of the art up to 1979 (1). The best-described antimetabolites are those of L-glutamine, and the drugs best described are azaserine, 6-diazo-5-oxo-L-norleucine (DON), and azotomycin, a polymer of two molecules of DON and an L-glutamic acid residue (29). Recently, DON has become of interest again to the National Cancer Institute in Bethesda, Maryland. Phase I

trials in children and phase II trials in adults have been reinstituted. We ourselves have confirmed the effectiveness of DON in childhood malignancies (M. P. Sullivan, unpublished observations). However, DON is not primarily an antagonist to protein synthesis but more an antagonist to glutamine in its role in de novo purine biosynthesis.

Different tumor cells do have different requirements for amino acids. The best described is the use of asparagine deprivation in lymphoid malignancies. This is usually accomplished by the infusion of exogenous L-asparaginase. It is clear that T cells have a different sensitivity to asparagine deprivation than do B cells (116). This therapy was highly effective in many leukemias, though the results are somewhat disappointing compared to other chemotherapeutic approaches (125). Analogues of L-aspartic acid have not been very effective to date (78). Again, it is highly likely that the effect on asparagine is not on protein biosynthesis, but on the role of asparagine in pyrimidine biosynthesis.

Ambitious attempts have been made to incubate tumor explants with a variety of synthetic amino acid mixtures and to determine which amino acid is the most essential for that particular tumor growth. Following that, the patient would be treated with a defined diet that would selectively starve the tumor of an essential amino acid. Methionine deprivation has been used most frequently. Transformed fibroblasts require exogenous methionine (72), but when serum growth factors are held constant, the requirements are frequently reduced (101). Nevertheless, the Japanese have attempted intravenous methionine-free hyperalimentation as an adjuvant to the use of anticancer drugs on adenocarcinoma of the intestinal tract. This was recently reviewed in the Japanese literature. The investigators concluded that the effectiveness of the chemotherapy and radiotherapy, as judged by x-ray examination, was enhanced in most cases by the administration of a parenteral alimentation solution that had the sulfur-containing amino acids methionine and cysteine specifically deleted (62). However, attempts in humans to use nutritional therapy for neoplasia usually fail because the diet is totally unpalatable and therefore the prolonged periods required to reduce serum or plasma amino acid levels precluded clinical applications (10, 38).

Selective Starvation of Tumor Cells—Micronutrients

PURINES AND PYRIMIDINES The vast majority of chemotherapeutic agents affect directly or indirectly the purine and pyrimidine pathways. Cancer cells do utilize preformed purines and pyrimidines, and therefore analogues of purines and pyrimidines have been successfully used as antimetabolites for decades. However, the cells are capable of de novo biosynthesis of purines and pyrimidines. Therefore, selective starvation through nutrition manipulation is not possible except at the very early stages in the biosynthetic pathways. This is the rationale for asparagine, glutamine, and methionine deprivation effects.

VITAMINS This is again an area where an enormous amount of quackery information is extant. Claims of antineoplastic effects of the manipulation of a wide variety of vitamins have been reported. These include folic acid, pyridoxine, pantothenic acid, riboflavin, thiamin, nicotinamide, vitamin C, cyanocobalamine, alpha-tocopherol, vitamin A, and vitamin K. In all cases, the dietary deficiency caused host toxicity to such a degree that any benefits derived from the vitamin deficiency were outweighed by the host toxicity.

However, antagonists to vitamins have found their place in the standard cancer chemotherapeutic armamentarium. The best described is methotrexate, which binds to the enzyme dihydrofolic reductase, and thereby blocks the conversion of dihydrofolate to a tetrahydrofolate. This conversion is required to maintain the effectiveness of the folic acid derivatives as coenzymes from one-carbon transfer reactions in metabolism. There are other enzymes that are inhibited by methotrexate, specifically the enzyme that synthesizes thymidilate. Finally, folate transport proteins bind methotrexate. The level of dihydrofolate in the cell does determine, to some degree, the effectiveness of methotrexate. Tetrahydrofolate derivatives inhibit the action of methotrexate and are used routinely as "rescue" therapy. Most commonly used is leucovorin a formyltetrahydrofolic acid preparation.

The literature on methorexate is vast, and growing daily (12, 164). One may question whether dietary manipulation would help or hinder the effectiveness of methotrexate. There are no good data at this time that folic acid derivatives normally found in the diet affect methotrexate effectiveness in ordinary nutrient quantities. Furthermore, there are data that suggest that the uptake of folic acid by cells and the uptake of methotrexate are by different carriers (182). The amount of folate that is required in parenteral alimentation to maintain normal folic acid levels has only infrequently been studied. Data seem to suggest that 7 mg of folate per day will maintain normal serum vitamin levels in adults (83). Patients who are on protocols that include small doses of methotrexate are not usually on intravenous hyperalimentation. Their ordinary diet does not seem to interfere with the methotrexate effectiveness. Patients who are on high-dose methotrexate, wherein doses of several hundred mg/kg are administered, may be on intravenous hyperalimentation. However, in such instances, the dose of folic acid in the fluid is not likely to counteract that much methotrexate. Our experience has shown no deleterious effect of intravenous hyperalimentation on the effectiveness of high-dose methotrexate (161).

Nicotinic acid antagonists have been investigated as potential chemotherapeutic agents. There was an early flurry of excitement around these drugs in the 1960s when 6-aminonicotinamide and aminothiadiazole were introduced. Recently, drugs that are antagonist to nicotinamide have been reintroduced in the clinical armamentarium: specifically, the drugs tiazofurin and aminothiadiazole. This subject was reviewed extensively recently (178). The role

of nicotinamide and nicotinic acid metabolism is so pivotal and pervasive that very profound metabolic effects are to be expected from these antagonists. In general, the side effects can be extremely severe.

The greatest interest recently has been around fat-soluble vitamins, especially vitamin A derivatives. There are many relationships between vitamin A and neoplastic transformation. Retinoids are effective inhibitors of chemical carcinogenesis in epithelial systems, especially the mammary gland and urinary bladder (107). Similar claims have been made for lung cancer, but the data are still be inconclusive (119). From such studies, beta-carotene and vitamin A and its derivatives are being proposed as potential chemopreventative agents (11). Chemoprevention trials are beginning to be executed, but definitive data are not yet available (89).

Within the context of this review, the question asked is whether vitamin A and/or its analogues can be used to treat established malignancies. In a phase I trial of retinol in cancer patients, significant neuropsychiatric and hepatic toxicities were encountered (61). The best-studied system is superficial bladder cancer. 13-*Cis*-retinoic acid is synthetic retinoid analogue undergoing clinical trials because this agent is less toxic than transretinoic acid. It is neither stored in the liver nor transported in the blood by retinol binding protein (141). There are several ongoing studies in the use of this drug and other vitamin A analogues in the treatment and the chemoprevention of superficial bladder cancer. The only reported human study for *cis*-retinoic acid was by Peck & Yoder (120), who found significant activity in keratinizing dermatoses.

No attempt is made here to review the multiple claims around ascorbic acid. Suffice it to say that multiple pharmacological effects are to be expected from a free-radical-generating substance such as ascorbic acid when given in high doses. Therefore, claims of effectiveness might have no relationship to vitamin C, the nutrient.

The use of vitamin K analogues as anticoagulants has been primarily advocated in inhibition of metastatic spread (71).

MINERALS As is the case with vitamins, many minerals have been implicated in tumor growth, and therefore depletion of such minerals has been advocated as a therapeutic or preventative measure. Of all the proposed targets of nutritional modulation, zinc and magnesium are most frequently mentioned. In addition, selenium has been advocated as a chemopreventative. Manipulation of zinc status in experimental models resulted in decreased tumor growth, but the deficiency of zinc is so all-pervasively toxic that it has shown no practical benefit to date. The best animal experiment was reported by Pories et al (121).

The effects of dietary deficiency of magnesium are also reported as beneficial in tumor progression. This was observed in transplanted Yoshida hepatoma

and Walker's sarcoma in rats (183). It was recently reconfirmed for transplanted mammary adenocarcinoma in rats (105). Human experiments have been done. Hypomagnesemia was induced by dialysis (134) and by magnesium-deficient hyperalimentation (20). Beneficial effects have not been substantiated. Hypomagnesemia is a frequent complication of hyperalimentation, especially in patients with malignancies (52). Furthermore, *cis*-platinum is well known to give magnesium wastage. Therefore, hypomagnesemia is a frequent finding in patients with malignancies, and beneficial effects are not readily apparent.

Synthesis of Information

It is clear that the rapid growth of tumor cells makes it possible to exploit the purine and pyrimidine biosynthesis rates as targets of chemotherapy. Because many of the metabolites needed for growth are nutrients at the cellular level, nutritional manipulation is possible, especially through antimetabolites. However, the basic metabolic differences, especially those seen in carbohydrate metabolism, still await further exploration. It is likely that the nicotinic acid analogues exert their effect in part through metabolic pertubations. It is one area that requires further investigations.

SUMMARY

The Case For or Against a Specific Cancer Effect

There are many tumors that have paraneoplastic syndromes. Furthermore, location of certain tumors can result in very specific effects on the host, especially tumors in the hypothalamus, the intestinal tract, or the liver. Finally, tumors of the immune system can have significant distant consequences. However, from direct experimental evidence, from model systems, and from the utilization of nutritional manipulation in the treatment of cancer, the data suggest very strongly that there is no unique cancer malnutrition. Early diagnosed cancer does not show malnutrition as a presenting symptom. Furthermore, all metabolic disturbances can be explained on the basis of the metabolic differences of tumor cells and normal cells and are very frequently proportional to the bulk of the tumor. The cachexia that is associated with malignancies is more likely cachexia in cancer patients than it is a specific cancer cachexia, unless the tumor burden is very large. This point was clearly made in a short review of the causes of cachexia in nearly 1500 cancer patients in Russia (145). Brennan also feels that most cases of malnutrition are uncomplicated starvation, and cancer cachexia has many features seen in major injury or sepsis (16). This distinction has great implications in the management of cancer patients.

Conclusion

Malnutrition can be treated in cancer patients as it can in any other patient. There is no doubt that this will stimulate tumor growth but, if concomitant therapy is given, that may be beneficial rather than detrimental. Furthermore, because of the metabolic changes of the cancer at the cellular level, the manipulation of macronutrients may well be the most promising exploitation of the physiological derangements of human malignancies.

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