Cachexia, the Metabolic Component of Neoplastic Diseases

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Summary

The growth of cancer leads to profound alterations of host organs and functions. The overall result is cachexia, a syndrome characterized primarily by weakness, anorexia, and the depletion and redistribution of host components. Cachexia is the consequence of anatomical alterations, decreased food intake or absorption, and altered metabolism. Anatomical alterations are always present in a cancer patient. It has been repeatedly observed, however, that the degree of cachexia bears no simple correlation to tumor burden, tumor cell type, or anatomical site of involvement. The consequences of impaired food intake or food absorption are a major contributor to the overall morbidity of the cancer patient. Depletion of protein and/or fat stores, hypovitaminoses, and decrease in the concentration of trace elements, variously combined, lead to states nearly identical to kwashiorkor or marasmus. Clear guidelines for recognition of these states have been set recently for cancer patients. Awareness of these syndromes is of enormous clinical importance since they are potentially reversible by the modern techniques of hyperalimentation.

It is also important to recognize metabolic effects produced by tumors and independent of either anatomical alterations or insufficient delivery of nutrients. Such effects, exemplified by the endocrine syndromes produced by nonendocrine tumors, are of substantial conceptual importance inasmuch as they imply secretion by the tumor of biochemical toxins. The growth of cancer leads to profound alterations of organs and functions, a consequence of multiple interactions between destruction, attempted repair, homeostasis, and production by the tumor of biochemical toxins. The overall result is the widely recognized although poorly understood syndrome known as cachexia (24, 25, 29, 33, 37, 47, 50, 93, 94, 101). Cachexia occurs in man and animals. Its more apparent manifestations are weakness, anorexia, depletion and redistribution of host components, hormonal aberrations and, finally, a progressive alteration of vital functions. The patients affected appear chronically ill and often emaciated. Their skin is pale and atrophic. Edema, ulcerations, tumor masses, fractures, and abnormal drainages (when present) completely subvert familiar shapes, habits, and frames of reference. The progressive fading of physical wholeness is eventually associated with a flatness of the affects and a longing for annihilation.

Cachexia is at least in part due to anatomical alterations that are always present in a cancer patient, the extent and distribution of which can span pathological anatomy. It has been repeatedly observed, however, that the degree of cachexia bears no simple correlation to caloric intake, tumor burden, tumor cell type, or anatomical site of involvement. Individual patients might have obvious widespread tumors and no recognizable cachexia. In accounting for this fact, the attention of investigators has been focused on distant metabolic effects produced by cancers. Such effects are well documented in both cancer patients and experimental models and are known collectively as "systemic effects of tumors" or "paraneoplastic syndromes" (Chart 1; Refs. 24, 25, 29, 33, 37, 47, 50, 93, 94, and 101). Because such effects occur at sites remote from the site of anatomic involvement, the postulation of chemical mediators appears inescapable. It has been well established that tumors can indeed elaborate pharmacologically active substances; this is shown convincingly by the various hormonal syndromes associated with lung cancer (71) and by the endocrine effects of cancers originating from nonendocrine organs (59). Besides hormones, other substances can be postulated, and the literature overflows with claims (often poorly documented) of their isolation (25, 69, 80, 81, 91, 96).

Study of the systemic effects of tumors is of fundamental importance. They affect significantly the ability of the host to tolerate cancer intervention (21, 39, 70) or to respond immunologically (12). Their impact on the overall morbidity is such that they are credited with the death of a significant number of patients (94). They are potentially reversible (at least in part) by nutritional means. They are useful models for the study of the mechanisms of cancer aggression. It is reasonable to infer that the devastations produced by cancers, rather than being due to the juxtaposition of a neoplastic cell to a normal cell, are due to the destruction of the latter by the former via the production of chemically definable toxic mediators active in the immediate vicinity of the tumor cell or on more distant targets.

The subject has been reviewed extensively in the past 5 years (22, 25, 47, 83, 93). In this paper the author will attempt to discuss only events characterized by all of the following properties. (a) They are clinically well documented. Nonclinical material will be discussed only if it contributes to clarification of clinical events. (b) They are examples of depletion of important host compartments and

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are mediated through either inadequate nutrition or humoral factors. (c) They either contribute significantly to the overall morbidity of the patient or exemplify important mechanisms.

With this paper it is hoped that the substantial morbidity accrued to patients by inadequate nutrition (a condition potentially reversible at present) will be brought to the attention of the clinician. At the same time those manifestations of cachexia in which neither direct invasion by the tumor nor nutritional inadequacy play a detectable role will be pointed out.

**Weight Loss and Anorexia**

Weight loss or, more precisely, the loss of biomass occurs commonly in both man and animals that succumb to cancer. In principle it can occur as a consequence of anorexia (i.e., a decrease in the spontaneous consumption of food) or of decreased absorption of food from the alimentary canal. It can also occur in the absence of the above factors as a consequence of altered metabolism.

Weight loss is listed in the older literature as one of the initial and common manifestations of cancer (53), a warning signal. The documentation is largely anecdotal. Equally anecdotal clinical impressions by contemporary observers imply that weight loss occurs only or predominantly later in the natural history of cancer. This discrepancy is at least in part due to the recent refinement in diagnostic techniques that allows earlier detection. Yet even today unexplained weight loss in a patient requires a search for a possible occult neoplasm.

In considering weight loss on the part of the host, one must keep in mind that severe depletion can be masked by the abnormal expansion of one body compartment (most often water) at the expense of another. One must also remember that a given compartment might be depleted selectively.

Among the very few well-documented data describing the incidence of weight loss in patients with cancer are those by Lanzotti (V. Lanzotti, personal communication) who has noted a loss of at least 6% of body weight in ~40% of 129 patients with limited bronchogenic carcinoma. In 187 patients with extensive disease, weight loss was of the same magnitude. The biological consequences of weight loss were clearly recognized. Median survival times of the depleted patients were less than one-half those observed in their better nourished counterparts. More extensive data on a variety of tumor types are critically needed.

It is not difficult to understand how weight loss might occur in patients with extensive disease and destructions when loss of appetite and/or decreased absorption of food are such general and possibly nonspecific phenomena. On the other hand the weight loss that occurs in patients with limited disease is of particular significance inasmuch as it is more likely to be cancer specific and mediated humorally through either the induction of anorexia or some other mechanism.

Anorexia is unquestionably one of the possible causes of weight loss. A clinical impression, which is probably well founded, suggests that anorexia is a common phenomenon in most cancer patients at some time during their illness. It might reach such a degree of severity that spontaneous nutrition is almost completely suppressed. It is not uncommon to observe patients in whom a meager breakfast represents the only form of intake p.o. One must remember that many of these patients may be bedridden, febrile, nauseated, plagued by intractable pain, and devastated by the thought of impending death. One does not have to look far to understand their loss of appetite although the precise mechanism may not be obvious. In these circumstances anorexia is certainly a nonspecific symptom experienced by the majority of acutely or severely ill patients.

It would be of great interest to determine whether anorexia, like weight loss, might occur in patients with limited disease and therefore might be truly a paraneoplastic syndrome. Unfortunately, reliable data on the incidence and timing of anorexia are practically nonexistent. This is not surprising. In determining changes in food consumption, one must either prospectively follow patients or compare appropriate groups. The difficulties of obtaining reliable
nutritional data on free-living populations are known (1). Existing surveys have centered primarily on low-income groups and are therefore of limited value even as historical controls (16, 20, 55, 61). Simultaneous studies by a single set of investigators of groups of patients with various cancer types and of appropriate control groups have not yet been performed and are urgently needed.

Within these limitations the available data suggest that anorexia is a widespread phenomenon. Thus, DeWys (36) has studied (by the 5-day food diary technique) 50 patients with a variety of tumors; he noted that the severity of anorexia was related to the extension of the tumor. Theologides (95) has compared the food consumption of 39 patients who bear a variety of tumor types and tumor burdens with their recalled "normal" food intake. Marked anorexia was suggested. In our laboratory (31) we have studied by the nutrition interview technique the food consumption of 17 female and 13 male patients with a variety of neoplastic diseases. In each patient, food consumption was then compared with the recalled normal intake. The female patients had decreased their average food intake from 1718 kcal/day (protein, 256 kcal/day; fat, 883 kcal/day; carbohydrates, 579 kcal/day) to an average 1444 kcal/day (protein, 200 kcal/day; fat, 630 kcal/day; carbohydrates, 614 kcal/day). The weight of the females prior to diagnosis exceeded ideal weight by an average of 31 lb. The average weight loss of the females was 23 lb. Male patients had changed their intake from an average 2827 kcal/day (protein, 424 kcal/day; fat, 1371 kcal/day; carbohydrates, 1032 kcal/day) to an average 1772 kcal/day (protein, 257 kcal/day; fat, 810 kcal/day; carbohydrates, 705 kcal/day). The weight of the males prior to diagnosis exceeded ideal weight by an average 21 lb. The average weight loss in the male was 38 lb. In further studies (M. Aragon and G. Costa, unpublished observations) we have noted that the average daily caloric intake of 50 adult ambulatory women who were receiving active chemotherapy was 1463 kcal/day compared to 1706 kcal/day consumed by 50 healthy women matched for age and socioeconomic characteristics.

The pathogenesis of anorexia is unclear (Table 1). A change in taste perception has been described by DeWys (36) and is discussed more extensively elsewhere (37). The postulation that lactate, known to be produced abundantly by tumors, could serve as an anorexogenic agent is attractive (2) but requires further documentation in man. The data obtained by Morrison (67) that show that, with the general reduction in energy available to the host, energy for seeking and processing food has almost vanished might provide an explanation for the anorexia of terminal patients only. It is probable that pain, fever, and anxiety (49) might well contribute to the lessening of food consumption. The effects of cancer intervention on appetite are well known and are discussed elsewhere (39, 57, 70, 84). A more specific pathogenesis can be postulated in the rare subjects with small tumors of the 4th ventricle (97). One could think here in terms of a direct effect on the appetite center.

In addition to anorexia, interference with the patency and function of the alimentary canal or losses through abnormal drainages are unquestionably the leading causes of weight loss (84) and possibly of anorexia itself.

Poor intake and poor absorption of food are not the only determinants of weight loss. This point is of fundamental importance. It is exemplified quite convincingly by children with the diencephalic syndrome (see below), in whom loss of fat (but not loss of lean body mass) occurs in the presence of normal or even supranormal intake. The fact that anemia can occur in cancer patients without overt hemolysis, bleeding, marrow replacement, or recognizable nutritional deficiencies (5, 56) reinforces the concept that additional explanations of host depletion are required, besides decreased delivery of nutrients into the blood stream, and that newer forms of intervention, in addition to increased nutrition, should be devised.

Loss of Specific Body Compartments

Tumor and host are metabolically separated but not totally independent districts. In certain circumstances the tumor can parasitize the host and thus add to the depletion produced by insufficient intake. This is well illustrated by tumor growth in totally starved animals. It is therefore easy to understand how specific needs of the tumor might result in specific depletions of the host. To what extent these processes occur if food supply is adequate is not known. One must remember that, in the great majority of patients who have been studied at autopsy and who have therefore played out the ultimate act of the metabolic drama, the tumor mass seldom exceeds 500 g (J. W. Pickren, personal communication) and thus remains a small fraction of the host biomass. Parasitization per se therefore is not likely to be an important mechanism except possibly in the case of trace nutrients. By whatever mechanism, specific depletions do occur in cancer patients and are discussed below.

Fat Depletion

Profound alterations of host lipid metabolism occur during the growth of a variety of tumors in both experimental animals and man (4, 22, 23, 25). Often the changes observed are clearly related to anorexia and involve other body compartments. There are nevertheless models in which neither anorexia nor parasitization of the host by the tumor play a significant role. These models are of very special interest because they are prima facie examples of distant, humorally mediated metabolic effects of neoplasms.

In man the best known example is represented by the diencephalic syndrome, (3, 81, 82, 87), described first by Russell. The diencephalic syndrome, which is not generally known, affects children under 10 years of age and is characterized by an almost complete arrest or even reversal of the normal weight growth. Height, however, is not affected. The

Table 1

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<th>Possible causes of anorexia</th>
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<td>1. Nonspecific manifestation of diseases</td>
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<td>2. Alterations of taste and/or smell perception</td>
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<td>3. Production of lactate</td>
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<td>4. Production of ketones</td>
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<td>5. Hypothetical tumor toxins</td>
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<tr>
<td>6. Direct effect on appetite center</td>
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<td>7. Psychological factors</td>
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children appear extremely emaciated with a loss of most of their adipose tissue, as gauged by clinical criteria (Fig. 1). Preservation of lean body mass in the face of fat loss has been implied. Associated with the fat loss, there is frequently motor hyperactivity and a change of mood toward joviality. Nystagmus is common, but the neurological examination of these patients is otherwise within normal limits. Body temperature is usually normal. Laboratory examinations including serum protein levels are by and large normal. Nonesterified serum fatty acids have been measured in only 1 case and found to be markedly elevated. Other serum lipids are usually normal. Hormonal studies have shown no abnormalities.

The syndrome has been associated with tumors of the 3rd ventricle and of the anterior hypothalamus, which are demonstrable by standard neuroradiological techniques. Astrocytomas have been the most common tumors although glioblastomas, oligodendrogliomas, and ependymomas have been described. Interestingly, the syndrome develops in the great majority of cases in the absence of anorexia. In a few cases increased appetite and increased food intake have been described.

The syndrome finds a parallel in the experimental tumors described by Liebelt et al. (60) and in those studied in our laboratory (28), in which severe fat loss was documented in animals with noninvasive tumors, without changes of carefully measured food intake and body temperature. The metabolic effects could be reproduced with a frozen and thawed tumor extract. More recently, Cox and Gocken (34) have described changes in a variety of serum lipid fractions, changes that occurred as early as 4 days after the injection of SV40 cells into golden hamsters. In further experiments in our laboratory (31), we have demonstrated that the rate of excretion of $^14$CO$_2$ by mice that were bearing 24-hr-old s.c. tumors and were given i.p. injections of $[^{14}C]$tripalmitin was reduced to 15 to 20% of that of controls. The rapidity of the effect (already present 24 hr after implantation of the tumor) militates against tumor parasitization as the explanation.

Studies on the composition of human muscle conducted in our laboratory tend to support the hypothesis that early fat loss is a common event in patients with cancer (32). Muscle samples were obtained at primary surgery from patients with various tumors (primarily breast and colon) and from patients with a variety of acute and chronic surgical conditions. In cancer patients, on the average, muscle fat content was approximately one-half that of controls (Table 2).

The mechanism underlying the fat loss in these patients and in the experimental animals is unknown. It is well known, at least in certain animals bearing transplanted tumors (67) and sporadically in cancer patients (25, 102, 103, 106), that the energy expenditures of the host are increased. It is unlikely that this is due solely to the thermodynamic cost of synthesizing tumor protoplasm. The hypothesis that the tumor can produce an uncoupler of oxidative phosphorylation, however attractive, has not been substantiated (35).

Energy loss associated with a high rate of glyconeogenesis from lactate has been suggested as an explanation for increased energy expenditures in some cancer patients, which thus contributes to mechanisms that promote fat loss (45, 52). Such losses appear inadequate quantitatively as an explanation of the fat loss described above. Other potential biochemical pathways through which energy might be lost are known and are discussed more extensively elsewhere (107).

Since the determinants of the amount of total body fat and of its major compartments are poorly understood at present, explanations for the fat loss described in this section remain speculative (14, 54). Critical well-designed experiments are needed to elucidate this area.

The contribution of host fat depletion to the total morbidity of the patient is difficult to assess. One could speculate that, in the more severe cases, loss of structural lipids occurs with irreversible consequences for cell function. Lipid metabolites could produce systemic effects and be

Table 2

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<th>Group</th>
<th>Surgery</th>
<th>n</th>
<th>Fat (g/kg)*</th>
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<tr>
<td>I</td>
<td>Noncancer</td>
<td>35</td>
<td>106 ± 20*</td>
</tr>
<tr>
<td>II</td>
<td>Cancer</td>
<td>30</td>
<td>51 ± 11</td>
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*a I versus II, p < 0.001.

*Mean ± S.E.
responsible for anorexia, apathy, and some of the less palpable manifestations of the neoplastic cachexia. Experimental documentation of such considerations is not yet available.

Protein Depletion and Hypoalbuminemia

It is a common observation that many cancer patients lose a significant fraction of their stable proteins. The mechanism subtending the loss is unknown.

In the recent past it was common to think of tumors as 1-way nitrogen traps and to infer that the nutritional consequences of tumor growth on the host were dominated by this irreversible step. Thus, selective depletion of the protein compartment or parasitization of strategic enzymes was considered the key issue (25). Recently, generalization of this concept to other animal models was proven to be unjustified (28, 51). Its applicability to cancer patients is at best questionable. This was foreseen, and Mider et al. (66) had warned against extension of the concept of the nitrogen trap beyond its original experimental conditions.

Nitrogen balance studies have been a common starting point for the investigation of the effects of cancer on protein metabolism. Balance experiments in rats bearing Walker 256 carcinoma have shown that growing hosts fed ad libitum can continue to store the same amount of nitrogen as do pair-fed controls, until the tumor has reached about 30% of the weight of the animal (65, 66). At this point protein storage in the tumor compartment is greater than the overall positive nitrogen balance of the animal, and the host loses protein to the tumor (65). Such loss had been confirmed by carcass analysis (66). Attempts made to increase caloric and protein intake by force feeding were successful only in delaying the depletion of host protein (4, 90), which eventually occurred even at very high intakes. The relevance of these studies to man is questionable. It is very exceptional that the tumor compartment exceeds 10% of the weight of the cancer patient.

Nitrogen balance studies in patients have been generally unrewarding. Nitrogen equilibrium, nitrogen loss, and nitrogen retention have all been reported (mostly in short-term studies) without a clear correlation with intake and overall behavior of the weight of the patient (43, 64, 73, 92, 102, 103, 105, 106). Positive nitrogen balances in patients who were actively losing weight have been explained with the quantitatively inaccurate concept of synthesis of tumor protoplasm.

The validity of the nitrogen balance technique is at this time controversial (Footnote 3; Refs. 23, 26, 44, and 48). The criticisms have been based on 2 sets of considerations. The 1st set has to do with the length of the observations and apparent nitrogen balance data indicated a "retention" of over 6 g nitrogen per day. Suspecting that the patient might be producing N₂ at an exceptionally high rate (23, 26, 30), we measured pN₂ in mixed venous (right atrium) and in arterial blood. Venous pN₂ was about 10% higher than arterial. This gradient, which is larger than in healthy controls, supports the thesis that N₂ was being excreted through the lungs at a higher than normal rate. As compensation for this loss, protein intake was increased to 25 g nitrogen per day. The patient began gaining weight. Seven months later he had gained 18 kg, had lost most of his symptoms, and had shown near normalization of nerve conduction and of nerve and muscle biopsies. Even several months after stabilization of his body weight, his nitrogen balance remained strongly positive (Chart 3).

These data show the necessity of careful noninvasive studies of body composition before the fundamental defects of protein metabolism in cancer patients can be elucidated by the balance technique.

Because of the methodological simplicity, studies of the protein metabolism of the host have often centered on serum albumin. Hypoalbuminemia occurs frequently in cancer-bearing patients and animals. The degree of hypoalbuminemia has been correlated with the extension of cancer (25).

Theoretically, hypoalbuminemia can be the consequence of appropriate changes in the rate of production or in the rate of destruction and can be the consequence of expanded dilution spaces of abnormal losses. Attempts to measure the various determinants of hypoalbuminemia in can-

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cancer patients have generated an abundant literature. The rate of synthesis of albumin can be measured with precursors labeled with \(^{14}\)C, \(^{15}\)N, \(^{35}\)S, or \(^{75}\)Se. The available data suggest that in cancer patients the rate of albumin synthesis is decreased (27, 51, 63, 75, 89, 99). Such data have been obtained at certain times by indirect considerations and at other times without complete assessment of all the involved pools; thus they should not yet be looked upon as conclusive. The explanation for the hypoalbuminemia remains therefore speculative.

It would seem inescapable that hypoalbuminemia is at least to some extent due to the malnutrition of the host (76–79, 86). Serum albumin levels of cancer patients have been restored to normal by parenteral hyperalimentation, which suggests that any decrease in synthesis may not be irreversible even in the absence of change in the tumor (41).

Consumption of albumin by the tumor is an attractive hypothesis and has found some support in preclinical work (13). Confirmation of such data by other laboratories and by incorporation of the albumin label into chemically purified tumor fractions (an absolute prerequisite in view of the notorious stickiness of albumin) would be especially valuable. Distribution of albumin into abnormal spaces (a reasonable thought in view of the subclinical edema so common in cancer patients) has been suggested by results obtained in my laboratory (27) and by others (99). Definitive proof is not at hand. Nephrotic syndromes and protein-losing enteropathies have been well described in patients with cancer (62, 98, 100), but such abnormal losses are so infrequent compared to hypoalbuminemia that they cannot be taken as a general explanation.

The central point, which still needs to be established, is to what extent is hypoalbuminemia secondary to poor nutrition and to what extent is it due to the specific effects of the tumor per se. That poor intake might not be the only explanation for hypoalbuminemia is supported by the observations on occasion of patients in whom the loss of nearly 50% of body weight and a substantial reduction in midarm circumference coexist with normal hemoglobin and serum albumin levels.

In this context it is useful to mention the observations by Goodlad and Clark (17, 18, 46) who have shown that, with adult rats bearing Walker 256, there is a marked inhibition of amino acid incorporation by muscle polyribosomes. The results are interpreted as suggesting some translation defect possibly mediated through the serum factor described by Toporek (96). A defect in the postinitiation stage of translation was also described in a more recent paper by Clark and Goodlad (19). These studies therefore illustrate alterations in the synthesis of host protein, which are independent from nutritional intake. Whether or not these are relevant to albumin metabolism remains to be established.

Recently, protein malnutrition in man has been studied effectively by Bistrian et al. and by Blackburn et al. (7–10) with a combination of anthropometric and biochemical parameters. The simplicity of the methods gives hope that effective guidelines can be developed for quantifying overall protein depletion and for monitoring the effects of hyperalimentation.

The contribution of hypoalbuminemia to the overall morbidity, as long as albumin levels do not decrease below 2 g/100 ml, is hard to assess at the present time. There is no question that protein depletion can contribute significantly to the overall morbidity of the cancer patient. The pathology of protein malnutrition as it occurs within the context of starvation is well known. Shorter survival time; inability to tolerate chemotherapy, radiotherapy, or surgery; loss of immunological competence (24); and altered respiratory homeostasis (38) have all been described in protein-depleted patients. The cumulative effects of protein depletion on the viability of the patient can therefore be overwhelming.

**Glucose Depletion**

The syndrome of hypoglycemia associated with tumors of nonpancreatic origin is a well-documented entity. Since 1929, when the 1st report appeared in the literature, about 150 cases have been described. Nearly 50% of the tumors have been fibrosarcomas and another 30% have been hepatomas. Nearly 90% of the tumors were growing in the retroperitoneal space or in the liver (15, 72, 85). The hypoglycemia induced by the above tumors is at variance with the tendency of most other neoplasms to impair glucose utilization in the host (104).

One of the outstanding characteristics of these tumors is their size. The great majority of those that were weighed exceeded 1 kg. A 9-kg tumor is probably the largest of the series. The age or sex distribution of the syndrome is not substantially different from that of tumors in general.

The pathogenesis of the hypoglycemia is the subject of considerable controversy. The large size of the majority of these tumors has suggested overutilization of glucose by the neoplasm (15). The other potential pathogenetic mecha-
nism proposes secretion by the tumor of a substance or substances capable of producing hypoglycemia. In a number of cases, insulin-like activity has been demonstrated in the tumor, whereas in an approximately equal number of cases this claim could not be substantiated (25, 85).

The hypoglycemic syndrome can add significantly to the morbidity of patients. On occasion a blood glucose level compatible with life can be maintained only with great difficulty. The predominance of 2 types of tumors and substantially 1 general localization makes the syndrome anatomically and clinically a well-defined entity. Its pathogenesis remains to be further elucidated.

Conclusions

We have discussed manifestations of cachexia characterized by depletion of protein, fat, and carbohydrates, and we have attempted in each case to evaluate the relative pathogenetic roles of decreased delivery of nutrients and of altered host metabolism. Until recently the student of cachexia was limited to the description and the interpretation of phenomena. The added dimension of metabolic intervention was not available. In the 1960's the recognition that undernutrition was highly prevalent in patients hospitalized for nonneoplastic diseases (11, 58) stimulated the development by Dudrick et al. (41) of methods of parenteral nutrition, which were shown to be effective in repleting such individuals. These same techniques are now being applied to cancer patients and appear already to be nutritionally effective and synergistic with other modalities of cancer intervention (21, 40). Their application to cancer patients will do more than replete the patient. They will finally allow (having wholly reversed the consequences of poor intake) adequate identification of the nonnutritional effects of cancer, if indeed these effects exist (Chart 4).

The question of parasitization of the host by the tumor will come under proper perspective by observing the growth of cancer in the well-fed host. A number of studies in animal models have implied that cancer grows best in a well-fed host (6, 42, 68, 74, 88). This fear of stimulating tumor growth has in the past been a deterrent (in the minds of some) to the institution of hyperalimentation to cancer patients. It seems unlikely that such fear is justified. In the animal models studied, the tumor biomass exceeds 30% of the host, a condition which makes parasitization an important factor but which is not applicable to man in whom tumor mass rarely exceeds 5% of the host. Moreover, the improved therapeutic effects that can be obtained in well-fed patients (21) will probably prove conclusive in showing the beneficial effects of hyperalimentation.

It is probable (in the mind of this reviewer) that distant effects of tumors will still be observable in well-fed patients. It is hoped that recognition of these effects will finally give impetus to the search and isolation of those chemical mediators of tumor aggression, the existence of which was broadly hinted at in our discussion. The technology for this task can be borrowed initially from the investigations of the chemical mediators of inflammation and of lymphocyte factors. The unambiguous demonstration of the existence of tumor toxins and the definition of their role might well be the significant breakthrough in oncology.

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