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METABOLIC APPROACHES TO CANCER CACHEXIA

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CONTENTS

I. OVERVIEW OF CANCER CACHEXIA

A. Introduction

Progressive wasting, weakness, anorexia, and anemia are frequent complications of neoplastic disease. As the tumor enlarges, the host's muscle mass and adipose mass are depleted; in contrast, the liver, kidney, adrenal glands, and spleen tend to be spared and may actually enlarge. In the early stages, total body protein may be unchanged, although nitrogen is redistributed from muscle to tumor. Later, when anorexia is pronounced, total body protein declines, and other essential nutrients may also be depleted. This syndrome has been extensively studied in both man and rodent (9, 26, 37, 47, 113) but remains poorly understood.

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B. Prevalence of Clinical Cancer Cachexia

Cachectic cancer patients frequently have not only protein-calorie undernutrition (PCU) but also depletion of vitamins and minerals. Nevertheless, most surveys have concentrated on weight loss, contraction of lean body mass, depletion of fat mass, and hypoproteinemia as indicators of cancer cachexia. This necessity to rely on convenient indicators probably causes a significant underestimation of the problem, in that the metabolic abnormalities presumably responsible for the undernutrition precede appreciable changes in body weight (16). At the time of presentation, 54% of untreated patients with disseminated cancer had lost some weight and 32% had lost greater than 5% of their usual weight in the preceding six months. The frequency of weight loss ranged from 31% for patients with non-Hodgkin's lymphomas of favorable histological pattern to 87% in patients with gastric carcinomas. Whereas only 14% of patients with carcinoma of the breast had lost more than 5% of their usual weight during the preceding six months, 67% of patients with gastric cancer had suffered this degree of weight loss (33). Nixon and co-workers (95) reported that 42% of their patients with widespread cancer had subnormal adipose stores as determined by triceps skin-fold measurements less than 80% of standard (as compared to only 3% of controls), and 19% were less than 60% of standard. None of the healthy control subjects fell below 60% of standard. Fully 88% of these patients had creatinine : height indexes of less than 80% of standard (compared to 28% of controls), and 53% were less than 60% of standard. No controls fell below this level. Serum albumin concentration was subnormal in 31% of these patients. Furthermore, 45% of patients who had lost at least 6% of their premorbid weight also had subnormal serum concentrations of vitamins A and C, and 20% had decreased levels of serum folate.

These studies demonstrate a high frequency of nutritional abnormalities in cancer patients, confirming the widely held clinical impression. However, it must be emphasized that protein-calorie undernutrition (PCU) is not unique to cancer. On the contrary, 30–50% of hospitalized patients presently have some degree of PCU (51), and most chronic, fatal, nonneoplastic diseases terminate in a cachectic state (e.g. chronic disseminated infections, or prolonged insufficiency of heart, lungs, liver, kidneys, or the small intestines).

C. Relationship of Protein-Calorie Undernutrition to Survival in Cancer Patients

Recent studies have documented the association between undernutrition and decreased survival. DeWys and co-workers (33) found that median survival was significantly shorter in patients who had lost weight with most

tumor types examined. Further examination revealed that weight loss was also associated with a worse performance status (activity level) in all tumor types except pancreatic and gastric carcinoma. Since performance status has a known relationship to length of survival, the correlation of weight loss with longevity was evaluated within performance-status categories. The adverse effect of weight loss persisted as an independent variable in most patients with a favorable performance-status rating. In the unfavorable performance status group, however, weight loss had a significantly adverse relationship to survival only in patients with nonsmall-cell lung cancer.

Visceral protein and lean body mass depletion (as assessed by serum albumin concentration and creatinine:height index) have a worse prognostic import than adipose depletion (as measured by triceps skin-fold thickness) (95). Twelve of 27 patients (44%) with triceps skin-fold measurements less than 60% of standard died within 70 days of nutritional evaluation compared to 7 of 31 (23%) patients with higher measurements; this difference was not significant. Fifty-three percent (16/30) of patients with serum albumin concentration less than 3.5 gm/dl died within this time period, compared to only 18% (7/39) of patients with higher serum albumin concentrations. Similarly, 56% (18/32) of patients with a creatinine:height index less than 60% of standard died within 70 days of study, compared to only 4% (1/26) of patients with higher values ($p<0.05$).

In 1932, Warren (126) attempted to determine the cause of death in 500 autopsied cancer patients. In 114 cases, the charts documented progressive weakness, wasting and anemia, and at autopsy no other clear cause of death could be discerned. Warren concluded that these 22% of his patients had died of cancer cachexia. He commented that cachexia was also present in many, but certainly not all, of the other patients, and thus could have contributed to death from other causes, such as infection. Other investigators (58) fail to mention undernutrition as a cause of death, while still others list cachexia as the cause of death in about two thirds of cancer patients (45). Thus although there is a general *association* between PCU and survival in cancer patients, a cause and effect relation is not clearly established. Primary PCU is known to affect adversely resistance to some infections, wound healing, and cardiorespiratory, hepatic, and renal functions; these factors probably contribute to cancer mortality. The precise mechanisms by which the cancer cachexia syndrome may cause death in some patients and perhaps contribute to it in others, however, are not completely understood. Consequently, the features of the syndrome that must be reversed to prolong survival are unknown.

D. Postulated Mechanisms for the Development of Cancer Cachexia

In general, people lose weight because of reduced food intake, because of gastrointestinal malabsorption, or because of endogenous metabolic abnormalitites leading to various combinations of impaired protein synthesis, accelerated protein breakdown, or hypermetabolism. An additional mechanism, unique to cancer, for the erosion of lean body mass and adipose tissue even in the absence of weight loss, is the redistribution of protoplasmic elements from host to tumor.

Hypophagia is prominent in rodents and patients with advanced cancer. Although mechanical factors (dysphagia, GI obstruction, ascites) and anorexigenic chemotherapeutic drugs are major contributors, many cancer patients and laboratory animals show pronounced food aversion in the absence of such factors. In the rat, the degree of hypophagia is not regularly correlated with tumor size (40). If the food's nutrient density is reduced by unabsorbable bulk, the hypophagia often becomes demonstrable at an earlier stage. In some cases, feeding activity commences at normal intervals, but is terminated abnormally rapidly. This suggests that responsiveness to preabsorptive signals is intact but satiety signals are hyperactive (90). Abnormalities of taste are also often demonstrable in both rats and patients with cancer (32). The metabolic mechanisms by which tumors depress appetite are unknown (32, 40), but leading possibilities include: (*a*) abnormal amino acid metabolism, (*b*) effect on hepatic glucoreceptors believed to influence food intake, and (*c*) anorexigenic effect of lactic acid or circulating free fatty acids, or bioactive factors released from tumors, including products of necrosis, inflammation and infection.

Gastrointestinal malabsorption occurs frequently in clinical cancer and contributes significantly to the wasting (74). The malabsorption is usually caused either by treatment (resection of a portion of the GI tract, or enteropathic effects of chemotherapeutic drugs or irradiation) or by the metabolic infiltration of mesenteric lymphatics, or by the nonspecific intestinal atrophy caused by semistarvation.

In both rat and man, erosion of muscle and adipose tissue frequently precedes a detectable fall in food intake (26). In undernourished cancer patients, moreover, measured food intake fails to correlate with degree of PCU (14, 28). Finally, when control rats are pair fed with tumorous rats, the atrophy of muscle and adipose mass in the latter exceeds that in the former (40). These observations show that anorexia is only a partial cause of the wasting process. Evidently there are metabolic disturbances within the tumor or within the host tissues, or both, that also contribute. The nature of these metabolic disorders is the focus of the remainder of this

review. First, metabolic characteristics of cancer cells themselves are discussed. Then tumor-associated changes in host tissues are mentioned, followed by an overview of metabolic abnormalities at the whole-organism level. Finally, some of the possible mediators of these effects are listed.

II. METABOLIC ABNORMALITIES IN CANCER SUBJECTS

A. Metabolic Characteristics of Cancer Cells

1. "REGULATORY" NUTRIENTS VERSUS "BUILDING BLOCK" NUTRIENTS The progressive wasting of host tissue contrasts with the often vigorous growth of tumor tissue. Evidently tumor cells can divide (and thus cause tumors to grow) under conditions where host cells atrophy. This growth advantage is responsible for both the atrophy of muscle and adipose tissue during the early phase of some rat cancers, when food intake is not yet depressed, and for the "N trapping" action of tumors. Therefore a discussion of the characteristics of cancer cells that account for or contribute to this growth advantage is in order.

When serum or any one of a large number of nutrients is provided to cultured cells in less than a certain minimum amount, the cells "growth arrest" and enter a stable G1 phase (72). When serum or the limiting nutrient is supplied, growth resumes in a few hours. One of the earliest changes induced by the addition of serum factors to growth-arrested cells is an increase in nutrient uptake. Apparently, a serum factor–nutrient interaction is involved in the control of proliferation of mammalian cells. Holley (53) has proposed that the critical factor is the intracellular concentration of certain key nutrients, and that extracellular nutrients and serum factors exert their effects by altering this intracellular concentration. Since intact organisms maintain the extracellular concentrations of nutrients at a fairly constant level, changes in the levels of the serum factors appear to be the most likely mechanism for growth regulation.

Based on these observations, Holley (53) has further proposed that transformation to the malignant state may result from an alteration in membrane transport such that nutrient uptake is increased. This would result in a decrease in the requirement for serum factors and consequent escape from control by normal growth restraints. Viewed differently, serum factors may act by allowing a cell to divide while exposed to an extracellular concentration of nutrients that is ordinarily unable to support division; transformation may represent alterations in the cell such that this extracellular nutrient concentration is virtually always adequate, and proliferation continues unchecked.

To investigate this hypothesis further, McKeehan and co-workers have developed a system for studying proliferation control in which they hold serum factor concentration constant and vary the extracellular concentration of various nutrients, or hold nutrient concentration stable and vary the extracellular concentration of serum factors, and measure the rate of proliferation (86). Using this system and a normal human lung fibroblast cell line, these investigators have tried to answer this question: "If serum factors act by transiently decreasing the extracellular concentration of nutrients required for proliferation, which specific nutrients are affected?" The extracellular concentrations of sugars, amino acids, purines, and pyrimidines required to support growth were not affected by serum factors. On the other hand, serum factors did affect the required concentration of five nutrients: Ca^{2+}, Mg^{2+}, K^+, P_i, and oxocarboxylic acids (e.g. pyruvate). These "regulatory" nutrients could thus be distinguished from "building block" nutrients (amino acids, choline, glucose, inositol, polyamines, purines, pyrimidines), which, in this system at least, did not appear to be of regulatory significance. Transformation with the SV40 virus resulted in nutrient requirements for proliferation that resembled those of growth factor–stimulated normal cells; thus the transformed cell in this sense resembled the chronically growth factor–stimulated cell. This work suggests that the behavior of the "building block" nutrients is controlled by the interaction between serum factors and "regulatory" nutrients. Nitrogen accumulation by a tumor, then, would reflect the results of this interaction; that is, the cancer cell, with a decreased requirement for "regulatory nutrients," would have a growth advantage over the host tissues and thus would win in the competition for "building block" nutrients.

Another view of the relationship of "building block" nutrients to cell growth comes from the work of Baserga and co-workers (39). By microinjection of fragments of SV40 virus DNA into NIH 3T3 cells, these investigators showed that when some fragments were injected DNA synthesis occurred without the synthesis or accumulation of ribosomal RNA, whereas injection of other fragments induced RNA synthesis but not DNA synthesis. This work suggests that it may be possible to regulate DNA replication and growth in cell size separately, or that a cell could be stimulated to increase in size (hypertrophy), with increased utilization of "building block" nutrients, without dividing. This is in some ways analogous to the finding that the metabolic effects of some insulin-like peptides are separable from their effects on cell division (44). This separation between classical metabolic and "building block" nutrient effects and features of transformation, including proliferation, is also evident in the studies of cancer cells discussed below. The possibility of dissociating these two effects offers some hope that, if these mechanisms are more completely understood,

restoration of normal nondividing host cells (e.g. muscle) can be accomplished without stimulating growth in cancer cells.

In the next section, certain aspects of carbohydrate, lipid, and amino acid metabolism of cancer cells are reviewed, with an emphasis on those features that may contribute to the growth advantage of malignant cells or to the overall picture of cancer cachexia.

2. CARBOHYDRATE METABOLISM IN CANCER CELLS An increase in hexose uptake is frequently associated with the transition from quiescence to the proliferating state (59); therefore, it is not surprising that most transformed cell lines examined have also shown elevated hexose uptake. Although in some systems there is a transformation-specific augmentation of hexose uptake (131), in others there is a clear dissociation between increased hexose uptake and proliferation (6) and transformation (100). Thus enhanced hexose uptake is not a universal feature of malignancy and is neither necessary nor sufficient by itself for the initiation of proliferation.

There are several possible fates of a hexose taken up by a malignant cell, the most prominent of which is utilization for energy production. Weber (129) has demonstrated that many chemically and virally induced neoplasms are characterized by marked increases in the specific activities of the key enzymes of glycolysis (hexokinase, 6-phospho-fructokinase, and pyruvate kinase). Furthermore, in a series of Morris hepatomas, the rate of glycolysis was proportional to the rate of tumor growth. The increased glycolytic activity reflects in part the fact that many tumors express fetal glycolytic (and other) enzymes normally repressed during adult life (61, 132). These fetal isozymes often demonstrate increased glucose avidity and freedom from host control (61, 132). This high rate of glycolysis is not completely abolished by oxygen, as it is in normal cells (Pasteur effect); however, the hypothesis of Warburg (124) that this represents a universal and fundamental defect in respiration in all cancer cells is no longer accepted (132). Increased glycolysis is neither an universal nor a necessary finding in malignancy (59, 100, 132).

Some idea of the complexity of the area of carbohydrate metabolism in cancer cells may be gained from a brief consideration of the enzyme pyruvate kinase. This enzyme catalyzes the formation of pyruvate from phosphoenol pyruvate, with the concurrent generation of ATP from ADP. There are three distinct isozymes of pyruvate kinase (K, L, and M) (60). The normal adult liver primarily expresses the L-type, whereas the K-type is the predominant isozyme of fetal life. The activity of the L-type isozyme was found to be decreased and the activity of the K-type isozyme increased in hepatomas of progressively less differentiation. The K-type isozyme is apparently better able to compete with the mitochondrial respiratory sys-

tem for available ADP than is the adult L-form, and is not subject to known host control mechanisms. Weinhouse has suggested (132) that this may account for the fact that glycolysis does not stop when the cells are exposed to oxygen, and thus may help explain some of Warburg's observations. Furthermore, pyruvate may play a role in the regulation of cell proliferation beyond its participation in glycolysis (86). The McKeehans' work, mentioned above, suggests that the extracellular concentration of pyruvate and its interaction with serum factors may be important in the regulation of cell division in normal human lung fibroblasts. It is not clear why a cell should have a requirement for a nutrient that is synthesized intracellularly; however, it has been hypothesized that the increased ratio of oxidized to reduced pyridine nucleotide (NAD+/NADH) that results when 2-oxocarboxylic acids are reduced is the link between the extracellular requirement for pyruvate and cellular proliferation (87). It is conceivable that increased glycolysis resulting in increased intracellular pyruvate might lower the extracellular requirement of this nutrient for multiplication and thus, in some systems, facilitate the escape from normal growth controls that is characteristic of malignant cells. On the other hand, Rous sarcoma virus transformation of chick embryo fibroblasts is associated with decreased affinity of pyruvate kinase for the substrate phosphoenol pyruvate and a more rapid inactivation of the enzyme by Mg ATP (41). Thus abnormalities in this enzyme may contribute to two of the observed characteristics of malignant cells, but its behavior in intact cells may vary from cell line to cell line.

The hexoses taken up by a malignant cell may, in addition to participation in the glycolytic pathway, be shunted to the pentose phosphate pathway for the synthesis of both DNA and RNA. Weber has demonstrated increased activity of the primary enzymes of this pathway in Morris hepatomas (129). Still another use of hexoses in malignant cells is glycosylation of membrane proteins and lipids. This area has not been completely evaluated, but there are studies suggesting that hexose uptake does affect membrane glycoproteins (71) and alter cell behavior.

Thus the cancer cell is frequently a high consumer of glucose and a producer of lactate; both functions clearly affect the host. Furthermore, the hexoses utilized by many malignant cells may support proliferation in ways other than the production of energy, ultimately contributing to the growth advantage of these cells. Much work remains to be done in this area.

3. LIPID METABOLISM IN CANCER CELLS The ability of tumors to synthesize fatty acids varies widely, but in many cases the synthetic rate is felt to be inadequate for replication (115). From such studies has come the belief that tumor cells derive most of their constituent fatty acids from host

tissues. However, tumor cells implanted intraperitoneally in mice maintained on a lipid-free diet for 26 weeks, and clearly showing signs of essential fatty acid deficiency, grow just as well as similar tumor cells injected into adequately nourished animals (2). Furthermore, over 20 cell lines of various types have been successfully adapted to growth in de-lipidized medium, though other cell lines are reported to exhibit a lipid requirement. Thus the fatty acid requirements of tumors and the contribution of host lipids to these requirements are not completely understood, but malignant cells have some ability to adapt to decreased fatty acid availability (102, 115).

Three of the many aspects of lipid metabolism that may impinge on the ability of cancer cells to grow effectively are energy production, cell membrane composition, and abnormalities of cholesterol synthesis. Although many tumors can oxidize fatty acids rapidly, other less well differentiated ones have essentially lost the ability to use them as fuel (19, 31, 132) and have increased requirements for carbohydrate or amino acids as energy sources.

Some of the differences in lipid composition between normal and transformed cells may be related to the stage of differentiation of the cells or to the proliferative state rather than to transformation per se. For example, the lipid composition of blast cells from patients with acute myeloblastic leukemia differs from that of normal neutrophils, but is similar to that of normal immature myeloid cells isolated from the bone marrow (69). Membrane phospholipids of quiescent cells differ from those of proliferating normal or transformed cells in degree of saturation. An increased proportion of unsaturated fatty acids increases the fluidity of the membrane (15, 106), alters the transport of drugs (15) and some nutrients (62) and the exposure of some cell membrane proteins (114), increases the activation of certain membrane enzymes (25), and alters the mobility of cell surface receptors (57), all of which may affect growth. Interestingly, unsaturated fatty acids (linoleic acid) may act directly on both normal and neoplastic mammary epithelium in vitro to promote growth (68), whereas saturated fatty acids are inhibitory. Linoleic acid cannot initiate proliferation in the absence of hormones in this system; rather it augments growth in cells stimulated by the appropriate hormonal factors. The growth-promoting effect of the unsaturated fatty acids may result from their incorporation into cell membranes, perhaps with resultant increased availability of hormone receptors. The extent to which dietary unsaturated fatty acids contribute to this is unclear.

There is increasing interest in the cholesterol metabolism of malignant cells (20). Loss of feedback control of cholesterol is a frequent occurrence in the malignant cell lines examined to date (73, 101). Such abnormalities may account for many of the other anomalies of malignant cell proliferation

(73). Although much interest in the past has centered on the role of cholesterol in the cell membrane, recent evidence (101) suggests that increased hydroxymethylglutaryl (HMG) CoA reductase activity in transformed cells may promote cell division by providing mevalonate, a cholesterol precursor, rather than through an effect of cholesterol per se. HMG CoA reductase activity consistently rises just before increased DNA synthesis in BHK-21 transformed fibroblasts in the S phase. Blockage of the increased HMG CoA reductase activity prevents the entry of the cells into S phase, an effect that is reversible by the provision of exogenous mevalonate.

4. AMINO ACID METABOLISM IN CANCER CELLS There are interesting differences in the uptake of amino acids by transformed cells, proliferating normal cells, and quiescent normal cells (99). Growth and transformation are associated with increased uptake of some amino acids due to an increase in V_{max}, with no change in apparent K_m. These characteristics usually indicate that the carrier protein(s) for the molecule under study are normal, but that there is increased availability, either through synthesis of new transport proteins or through increased exposure of existing ones. Alternatively, there may be enhanced carrier mobility through the membrane because an unchanged number of carriers have increased transport capability (99).

Growth and transformation do not affect the uptake of all amino acids. However, as a generalization, amino acids transported primarily by the Na^+ dependent A system (e.g. alanine, glycine, serine, proline, α-amino isobutyric acid) are more subject to growth control than those transported primarily by other systems (21, 99). For example, a pure preparation of the insulin-like growth factor Multiplication-Stimulating Activity (MSA) added to quiescent cultures of chick embryo fibroblasts caused enhanced transport of A system amino acids that preceded the onset of DNA synthesis by several hours, but did not affect the uptake of amino acids transported by the L (Na^+-independent; leucine, isoleucine, phenylalanine) system, or by the ASC (alanine, serine, cysteine-preferring) or Ly^+ (lysine-preferring) systems. A similar effect on A system transport was observed when cells infected with a temperature-sensitive transforming virus moved from a nonpermissive to a permissive temperature. MSA was unable to stimulate transport above that associated with transformation (31). Clearly, however, there is no one transport system alteration unique to malignant cells (8, 99).

The fate of amino acids, once transported into the cell, may also differ in quiescent, proliferating and transformed cells. For example, when the enzymes of the metabolic pathways for the utilization of L-ornithine were examined in hepatomas of varying growth rates and compared to those of

normal liver, it was found that the activities of L-ornithine carbamyl transferase (130), the enzyme that channels ornithine into the urea cycle, and ornithine transaminase (123), which directs ornithine into the synthesis of glutamic-γ-semialdehyde and L-glutamate, were decreased, with the amount of the decrease showing a rough inverse correlation with the growth rate of the tumor. In contrast, the activity of ornithine decarboxylase, which directs ornithine into polyamine biosynthesis, is increased in these neoplasms, with the activity of the enzyme roughly paralleling the growth rate of the tumor (133). The requirement of many malignant cell lines for glutamine has been theoretically explained (73) as secondary to the abnormal synthesis of cholesterol and fatty acids, with shunting of substrate away from the Krebs cycle and resultant entry of increased amounts of glutamine distal to the shunt. Abnormally high requirements of the Walker 256 carcinoma cell line for methionine have been suggested (120).

Thus malignant cells may use disproportionately large amounts of certain amino acids; this could impact on the metabolism of the host. A possible regulatory role for some amino acids in cell division remains a possibility.

B. Altered Metabolism of Host Cells: The Divergent Behavior of Liver and Muscle

1. ALTERATIONS IN THE LIVER Either protein deprivation or starvation produces a marked loss in weight and content of protein (1) and glycogen (46) in the liver. This represents an actual decrease in size of the liver cells due to actual loss of cytoplasm (46). In contrast, liver dry weight frequently increases in rodents bearing either spontaneous or transplanted tumors (88, 119). There is also evidence that transplanted tumors induce proliferation of both the hepatocytes and reticuloendothelial cells of the liver (7, 89), with the majority of mitoses occurring in the reticuloendothelial cells.

Hepatic protein synthesis in tumor-bearing animals has been evaluated both in vivo and in vitro by uptake of labeled amino acid into protein. In both mice and men, the rate of uptake is consistently increased (78, 79, 97, 98) when compared to that found in ad lib fed controls. This was not due to an alteration in the precursor pool (79). Quantitatively, the increased label is found primarily in high molecular weight proteins. The low molecular weight peptides and proteins, however, show the greatest relative increase in incorporation when compared to controls. Some molecular weight regions actually show a decrease in incorporation (79). Lysosomal enzyme activity is also increased in the livers of tumor-bearing animals, suggesting that the rate of protein breakdown may also be increased (80). Similar

increases in activity are seen in starved mice; however, the V_{max} and K_m of the cathepsin D activity differ in these two groups, suggesting that undernutrition is not the sole cause of the change in the cancer subjects.

There are also marked changes in the activities of many liver enzymes, with prominent reexpression of fetal isozymes (48, 49, 50). In some respects the hepatic enzyme composition resembles that of the fetal liver, and in other respects the composition resembles that of the tumor itself. Certainly this is not unique to cancer (61). Nevertheless, it is important to note that the liver now resembles, to some extent, the tumor itself, in that enzymes important in carbohydrate and amino acid metabolism are altered such that increased glycolysis and disproportionate metabolism of amino acids may occur here, too. Thus the liver, and possibly other organs, may contribute to the disordered metabolism of cancer patients in some of the same ways as the tumor cells.

2. ALTERED METABOLISM OF HOST CELLS: SKELETAL MUSCLE The mass of skeletal muscle tends to decline during the course of progressive tumor growth. White or phasic muscle tends to atrophy more rapidly than red or tonic muscle, and contractile proteins are more extensively depleted than the sarcoplasmic proteins (22).

Intraperitoneal injection of either radioactive leucine (78) or valine (22) prior to sacrifice results in decreased incorporation of label into muscle protein in tumor-bearing animals compared to either pair-fed (22) or ad lib fed (78) controls. This depression is more marked in the phasic gastrocneimus than in the tonic soleus, and more severe for contractile than for sarcoplasmic proteins (22). A similarly decreased uptake of labeled amino acid has been recorded for skeletal (rectus abdominis) muscle of undernourished cancer patients with well-nourished noncancer cases as controls (78).

The cause of the decreased incorporation of amino acids into muscle protein and its specificity to neoplasia are in dispute. Clark & Goodlad have proposed, on the basis of in vitro studies, that there is a defect in the 40S ribosomal subunit that causes defective translation at a post-initiation stage (23). Since the decrease in skeletal muscle protein synthesis associated with starvation is believed to occur at the level of peptide-chain initiation (103), this suggests a tumor- (or stress-) specific defect in protein synthesis. However, this has been questioned by Lundholm and co-workers (82), who have found many of the changes in amino acid incorporation into skeletal muscle protein to be similar in starvation and the tumor-bearing state. Thus the relative contributions of hypophagia and some tumor- (or stress-) specific anomalies to muscle wasting remain unclear.

An increased fractional rate of degradation may also contribute to the loss of muscle protein. Proteases in muscle of tumor-bearing rats and cancer patients are more active than those in ad lib fed controls (78, 80). The possible quantitative importance of this may be estimated from the fact that in one study the dry weight of tumor-influenced muscle decreased by 48 ± 11% (S.E., $p<0.025$), while the dry weight of muscle from pair-fed controls decreased only 4 ± 7% (not significant) despite similar protein synthetic rates (82).

Glucose metabolism is also impeded in muscle of tumor-bearing patients in that rates of uptake and subsequent conversion of glucose to CO_2, glycogen, or lactate are slowed (76), and the levels of several enzymes involved in the oxidative and glycolytic degradation of glucose are reduced (78). Again, the contribution of semi-starvation to these findings is unclear.

C. Altered Metabolism of Host at the Whole Organism Level

1. ALTERED METABOLISM OF HOST AT THE WHOLE ORGANISM LEVEL: CARBOHYDRATE The rate of endogenous glucose production and turnover is accelerated in undernourished as compared to normally nourished cancer patients by an average of 80%, although the range is wide (55). In uncomplicated starvation, the rate of glucose production declines; however, it increases in calorie deprivation complicated by sepsis or trauma (43, 83). Endogenous gluconeogenesis arises by two main pathways: the recycling of lactate-pyruvate (Cori cycle), and de novo production from glucogenic amino acids, largely mobilized from skeletal muscle proteins.

In normally nourished cancer patients, the Cori cycle accounts for about 20% of glucose turnover. In the undernourished cancer patients of Holroyde, whose glucose turnover averaged 180% of normal, the Cori cycle activity averaged 90 mg/kg/hr (range, 22–193), compared to 18 mg/kg/hr (range, 13–24) in non–weight losing cancer patients (55), and accounted for about 50% of total glucose turnover. Mean lactate production is increased in patients with metastatic cancer, although again the range of values is wide (54). Although there was only a modest increase in the rate of lactate oxidation in these patients, this mechanism still accounted for the disposal of about 60% of the lactate produced. The excessive lactate recycling in cancer patients cannot be attributed to starvation, because it rises even further during the parenteral hyperalimentation of these subjects (56). The extent to which the excess lactate production occurs in tumor tissue, as opposed to host tissues, is unknown.

The rate of gluconeogenesis from plasma ^{14}C alanine in cachectic cancer and noncancer patients was found to be similar (127), and alanine contributed only 4–5% of total glucose production. Furthermore, the alanine

→ glucose conversion was promptly suppressed by exogenous glucose, as it is in normals. Thus glucose production from lactate probably accounts for most of the increase in glucose turnover in cancer patients.

2. ALTERED METABOLISM OF HOST AT THE WHOLE-ORGANISM LEVEL: FAT In the progressive weight loss of cancer, loss of adipose mass constitutes the major proportion and exceeds that seen in simple starvation (9, 37). Cancer patients oxidize normal amounts of fatty acid to CO_2 after an overnight fast (128). Entry of free fatty acids into the circulation is also similar in fasting cancer patients and normals. However, free fatty acid oxidation showed a much less than normal decrease in response to a glucose load in cancer patients than in controls, suggesting a continued drain on fat stores for oxidative purposes even in the presence of exogenous glucose. Lipogenesis is decreased in tumor-bearing animals, with decreased food intake (102), but the rate of lipogenesis in animals with normal food intake has been reported in different series to be decreased (27) or normal (102).

The marked hyperlipidemia observed in some animal systems has prompted several studies of plasma lipids in man. Fasting levels of free fatty acids tend to be normal (112, 128) or even low (81), and they show a normal decrease after a glucose load (112). More detailed analyses in humans with breast cancer (4, 5) and in rodents (12) suggest that α-lipoprotein levels may be depressed and at least some fraction of the very low density lipoproteins may be elevated, although no consistent abnormalities have been identified.

3. ALTERED METABOLISM OF HOST AT THE WHOLE-ORGANISM LEVEL: PROTEIN Protein deficiency may result in inequality of the specific activity of the plasma and intracellular pools of protein. This severely limits the reliability of estimates of protein synthesis rate based on infusion or injection of labeled amino acids (117). Using these techniques, measured whole body protein synthesis rates in undernourished cancer subjects are significantly elevated compared to healthy controls (116, 117), with much of the increase in whole body protein turnover apparently in host tissue (116).

Many studies of the concentration of individual amino acids in the plasma and urine have revealed differences between cancer patients and various controls. To date, however, these measurements have not revealed a consistent profile of abnormalities in any neoplastic disease. In patients with acute leukemia, elevated plasma levels of glutamine, phenylalanine, tyrosine, and leucine plus isoleucine, with decreased levels of asparagine

and threonine were reported (67). In contrast, Rudman et al found that 60% of their leukemic patients had subnormal fasting plasma levels of total α-amino nitrogen at some point during their disease, with decreases in alanine, glutamine, histidine, proline, threonine, and methionine (108). In solid tumors, no abnormalities in plasma aminograms were noted in some studies (109), while others have reported that plasma aminograms did not become abnormal until the tumors were 30% of host weight (134). In one study (135) of patients with advanced malignant melanoma, although no abnormalities were noted in the plasma aminograms, urinary aminograms revealed decreased excretion of phosphoserine, alanine, isoleucine, ornithine, ethanolamine, and histidine. Others have confirmed the decreased excretion of histidine and also noted decreased glycine excretion (35). Clarke and co-workers (24) compared plasma aminograms in well-nourished cancer patients with normals; they noted increased plasma alanine, isoleucine, and lysine concentrations in the cancer group. When cancer patients who had anorexia and weight loss were compared wih undernourished controls, several differences were noted. Of the gluconeogenic amino acids, glycine concentrations were elevated in the malnourished noncancer patients compared to the malnourished cancer patients, and proline and aspartate/asparagine values were decreased. Of the branched-chain amino acids, both valine and leucine were lower in the malnourished noncancer patients than in the undernourished cancer patients. In addition, methionine levels were lower in the noncancer malnourished patients. All these discrepancies represent instances in which the malnourished patients' values have changed, but the cancer patients' values have failed to show adaptation to semistarvation.

4. BASAL METABOLIC RATE Several clinical studies have found generally higher metabolic rate in cancer patients than in subjects with primary undernutrition (who are hypometabolic in comparison to normal subjects) (11, 125). Nevertheless, in none of these studies is it possible to eliminate the possible influence of fever, anemia, recent surgery, infection, or the presence of necrotic tissue, all of which are common in cancer patients. Thus the effect of tumor-bearing per se on basal metabolic rate is unclear.

5. MEDIATORS Although some of the metabolic abnormalities of the tumor-bearing host are due to characteristics of the cancer cells themselves, others are clearly secondary to alterations in host tissues. These effects are almost certainly mediated by circulating factors, as originally demonstrated by Lucké et al (75) in parabiotic rats, one tumor-bearing and one free of tumor. These factors may be altered levels of normal hormones, either

produced in response to the tumor or by the tumor cells themselves, or other products of either host or tumor cells.

Insulin resistance and increased cortisol secretion are the two most frequently discussed hormonal changes in malignant disease. Other hormones (especially catecholamines and growth hormone/somatomedin) deserve further study. Glucose tolerance tests have revealed "diabetic" responses in both cachectic (112) and noncachectic (84) cancer patients. Baseline plasma glucose concentrations were not significantly different in two studies (81, 112) but were increased in another (77). The amount of insulin released in response to a glucose challenge has been reported to be normal (112) and decreased (77, 81); the disappearance rate of this hormone is normal (81). The disappearance rate of plasma glucose has been reported to be normal (77, 81) and decreased (10). The steady-state concentration of glucose during infusion of a known amount of glucose plus insulin was higher in cancer patients than in controls (112).

Although most of the results above are compatible with a degree of insulin resistance, the finding of a normal disappearance rate of glucose in association with lower than normal plasma insulin concentrations is more compatible with insulin sensitivity (77, 81), a discrepancy that has not been explained. The possible contribution of enhanced gluconeogenesis to this picture has not been completely evaluated (81, 84).

The mechanism of "insulin resistance" is also unclear. Binding of ^{125}I-labeled insulin to insulin receptors on circulating monocytes is normal (112). The incorporation rate of glucose carbon into glycogen and CO_2 and the ability of insulin to stimulate this effect were both less than control in isolated skeletal muscle fibers of cancer patients; however, the incorporation of palmitic acid and leucine into CO_2 was not different from control (81). These results are compatible with a cellular defect in carbohydrate metabolism beyond the receptor level (i.e. abnormal enzyme activity, as previously discussed), but clearly more work is needed in this area. There are also changes in cortisol metabolism associated with cancer. In animals with transplanted tumors there is marked adrenal hypertrophy that is not prevented by force-feeding (9). Hypophysectomy does prevent the hypertrophy (3), indicating at least a permissive role for pituitary-derived or pituitary-dependent factors. The mean fasting plasma cortisol is elevated in patients and animals with various cancers when compared to normal controls (110, 111), but this is not a universal finding (105). Some of the apparent discrepancies in these studies may be due to the inclusion of patients at different points in their natural histories. In the early stages of tumor growth the adrenals have been shown to be hyporesponsive to ACTH (66). As tumor growth progresses, the cortex becomes hyperresponsive for a time; however,

as the animal or patient enters the final stages of his disease, the adrenals become markedly hyporesponsive again.

There is increasing evidence that tumor cells, often specifically the neoplastic cell rather than a host cell, produce a host of hormones and hormone-like products that exert powerful effects on host metabolism. Humorally mediated paraneoplastic "syndromes" range from identification of a product without detectable clinical manifestations to well-defined clinical findings without a known causative humoral factor (e.g. neuropathies, myopathies, hypercalcemia without detectable bone disease). Odell and co-workers have demonstrated that most cancer patients have increased plasma levels of materials that cross-react immunologically with a variety of hormones (96), and have hypothesized that virtually all cancers synthesize ectopic proteins. Many of these are biologically inactive as determined by lack of binding in radioreceptor assays (e.g. high molecular weight ACTH), but others produce clinically recognizable syndromes. The extent to which these peptide hormones or hormone-associated tumor products exert subclinical, but deleterious, effects, is unknown.

Recently, a new group of growth-promoting substances called growth factors have been extracted from a variety of malignant and nonmalignant cell lines (42). Elevated levels of nonsuppressible insulin-like activity have been detected in the serum of patients with tumor-associated hypoglycemia (63), and elevated levels of immunoreactive nerve growth factor have been detected in patients with neurofibromatosis (36); thus these peptides may represent a new class of mediators of paraneoplastic syndromes. In addition, tumor cells have been shown to release mitogenic peptides related to several of these growth factors into culture medium (70, 121, 122); similar activities are extractable from tumor cells (104). Several features of these tumor-derived growth factors suggest that they may account for some of the systemic effects of tumors. First, they are mitogenic for some normal cells (70, 121, 122); although not yet directly tested, this ability could account for some of the increased mitoses seen in liver cells of tumor-bearing hosts and for tumor-associated fibrosis. Second, some of them have the ability to confer transformed characteristics (ability to grow in soft agar) on nontransformed cells (121, 122). This capacity could account for the reexpression of fetal isozymes in host livers in patterns somewhat similar to those seen in tumors. Third, growth factors in general are metabolically active, with the ability to stimulate uptake of some, but not all, amino acids (31, 52) and to stimulate glycolysis, apparently by a direct effect on phosphofructokinase (34). Such effects could contribute to the abnormal plasma aminograms and increased lactate production seen in cancer patients. Finally, some of these tumor-derived growth factors have been shown to bind

to receptors for normal growth factors (121, 122). Thus a tumor-derived growth factor could conceivably compete with normal growth factors and hormones, induce down-regulation of receptors, and, by inducing an incomplete or abnormal metabolic response in the target cell, have the effect of altering the pattern of nutrient utilization in some host cells.

Several other tumor-associated factors with possible significance in the cancer cachexia syndrome have been reported. Nakahara & Fukuoka described an activity (called toxohormone) extractable from all the tumors they studied which, when injected into normal animals, caused many of the host changes associated with neoplastic disease (91, 93). The possibility that this activity actually reflects bacterial contamination has been raised (64) and denied (92). It is likely that several components are responsible for all the effects attributed to toxohormone (38). Lipid-mobilizing substances in tumor extracts and body fluids of patients and animals with tumors have been reported. One of the better characterized is a 75,000 dalton protein isolated from cell-free ascitic fluid of mice inoculated intraperitoneally with sarcoma 180 cells (85) and from ascitic fluid of humans with hepatoma and carcinoma of the kidney, but not from ascites caused by peritonitis or cirrhosis. Tumor production of prostaglandins is well documented; there is some evidence that these factors may be mediators of tumor-associated hypercalcemia (65). Many tumor cells secrete active proteinases (29, 107) that may have systemic effects we well as contribute to tissue destruction. Finally, Theologides (118) has postulated that tumors produce a host of small, metabolically active peptides and other factors that interfere nonspecifically with the metabolism of the host.

In addition to metabolically active factors produced by tumor cells themselves, the presence of a cancer in the body elicits a host response, with prominent involvement of macrophages and other cells. These cells have been shown to release proteinases, complement components, plasmin inhibitors, reactive metabolites of oxygen, prostaglandins, factors capable of affecting protein synthesis in hepatocytes and other cells, and other products with potentially significant effects upon the host (94).

Clearly, then, there are many possible humoral mediators of the cancer cachexia syndrome. What remains is to determine the biological significance of these factors.

III. CONCLUSIONS

1. Wasting of skeletal muscle and adipose tissue is a general feature of advanced cancer; however, the liver, spleen, and adrenals tend to enlarge. Protein synthesis and carbohydrate utilization are suppressed in skeletal

muscle. In the liver, enzymes of glucose metabolism and amino acid catabolism are altered, with increased activity and reexpression of isozymes normally suppressed during adult life.

2. Cancer cachexia is usually associated with decreased food intake, which results from mechanical effects of the tumor, treatment effects, associated infection, and incompletely understood biochemical disturbances in the tumor-bearing subject.

3. Like patients with cachexia caused by prolonged infections or inflammatory diseases, the cancer subject manifests both semi-starvation and stress. Undernutrition, with associated abnormalities in insulin metabolism, probably accounts for most of the wasting of muscle and fat, while hepatic enlargement and enzymatic alterations may be the liver's response to the release of bioactive products from the tumor. Hypercorticoidism further contributes to the changes in both organs.

4. The truly unique feature of cancer is the cancer cells themselves. In addition to the mechanical effects of tumors, these cells affect host metabolism in two ways: (*a*) their own uptake and metabolism of nutrients; and (*b*) hormones and hormone-like factors they secrete. Accelerated glucose utilization and lactate production are the most widely discussed of these; the possibility of a "disordered" pattern of amino acid utilization also deserves consideration. The possible effects of tumor-secreted metabolically active products on host metabolism are also potentially fruitful areas of investigation. The presence of large amounts of growing tissue is not sufficient to account for cachexia, as is demonstrated by uncomplicated pregnancy.

5. Tumors are composed of not only neoplastic cells but also host cells (macrophages, lymphocytes, neutrophils); the host cells are also capable of releasing biologically active factors. In addition, the tumors are often superinfected, and low grade infection may be present in other organs (e.g. GI tract, bronchial tree). Furthermore, there are zones of necrosis in most, but not all, tumors. Each of these features may contribute to the cachexia associated with malignant disease and may account for some of the similarities between cancer cachexia and the wasting associated with infectious diseases.

6. Almost all studies comparing tumor growth rates with and without nutritional supplementation show an acceleration in tumor growth rate when nutrient intake is increased in anorexic animals (17, 18, 30). While this may make little difference in the rat with a nonmetastasizing tumor implanted on the hip, even a slight stimulation of tumor growth may hasten death or debility in the patient with brain or spinal cord metastases, tumor threatening to obstruct bronchi or bowel, or tumors infiltrating vital organs

such as lung or liver. Clearly these patients represent a majority of individuals with advanced cancer. This may account for the failure of vigorous nutritional support to prolong the life of patients with advanced cancer (13).

7. The challenge of cancer cachexia is thus two-fold. First of all, the characteristics of cancer cells that give them an advantage in the competition for "building block" nutrients must be elucidated and circumvented. Second, the tumor-related causes of anorexia, hypermetabolism, and hepatopathy must be determined and ways found to reverse their effects. Both tasks are formidable, but it is unlikely that truly effective approaches to cancer cachexia will be found that do not deal with these basic questions.

Literature Cited

1. Addis, T., Poo, L. J., Lew, W. 1936. The quantities of protein lost by the various organs and tissues of the body during a fast. *J. Biol. Chem.* 115:111–16
2. Bailey, J. M. 1980. Essential fatty acid requirements and metabolism of cells in tissue culture. *Adv. Prostagl. Thrombox. Res.* 6:549–65
3. Ball, H. A., Samuels, L. T. 1938. Adrenal weights in tumor-bearing rats. *Proc. Soc. Exp. Biol. Med.* 38:441–43
4. Barclay, M., Calathes, D., DiLorenzo, J. C., Helper, A., Kaufman, R. J. 1959. The relation between plasma lipoproteins and breast carcinoma. Effect of degree of breast disease on plasma lipoproteins and the possible role of lipid metabolic aberrations. *Cancer* 12: 1163–70
5. Barclay, M., Cogin, G. E., Escher, G. C., Kaufman, R. G., Kidder, E. D., Petermann, M. L. 1955. Human plasma lipoproteins. I. In normal women and in women with advanced carcinoma of the breast. *Cancer* 8:253–60
6. Barsh, G. S., Cunningham, D. D. 1977. Nutrient uptake and control of animal cell proliferation. *J. Supramol. Struct.* 7:61–77
7. Baserga, R., Ksielski, W. E. 1961. Cell proliferation in tumor-bearing mice. *Arch. Pathol.* 72:24–30
8. Bass, R., Hedegaard, H. B., Dillehay, L., Moffett, J., Englesberg, E. 1981. The A, ASC, and L systems for the transport of amino acids in Chinese hamster ovary cells (CHO-K1). *J. Biol. Chem.* 256:10259–66
9. Begg, R. W. 1958. Tumor-host relations. *Adv. Cancer Res.* 5:1–54
10. Bishop, J. S., Marks, P. A. 1959. Studies on carbohydrate metabolism in patients with neoplastic disease. II. Response to insulin administrations. *J. Clin. Invest.* 38:668–72
11. Bozzetti, F., Pagnoni, A., Del Vecchio, M. 1980. Excessive caloric expenditure as a cause of malnutrition in patients with cancer. *Surg. Gynecol. Obstet.* 150:229–34
12. Brennan, D. E., Mathur, S. N., Spector, A. A. 1975. Characterization of the hyperlipidemia in mice bearing the Ehrlich ascites tumor. *Eur. J. Cancer* 11:225–30
13. Brennan, M. F. 1981. Total parenteral nutrition in the management of the cancer patient. *Ann. Rev. Med.* 32:233–43
14. Burke, M., Bryson, E. I., Kark, A. E. 1980. Dietary intakes, resting metabolic rates, and body composition in benign and malignant gastrointestinal disease. *Br. Med. J.* 280:211–15
15. Burns, C. P., Luttenegger, D. G., Dudley, D. T., Buettner, G. R., Spector, A. A. 1979. Effect of modification of plasma membrane fatty acid composition on fluidity and methotrexate transport in L1210 murine leukemia cells. *Cancer Res.* 39:1726–32
16. Burt, M. E., Lowry, S. F., Gorschboth, C., Brennan, M. F. 1981. Metabolic alterations in a noncachectic animal tumor system. *Cancer* 47:2138–46
17. Buzby, G. P., Mullen, J. L., Stein, T. P., Miller, E. E., Hobbs, C. L., Rosato, E. F. 1980. Host-tumor interaction and nutrient supply. *Cancer* 45:2940–48
18. Cameron, I. L., Rogers, W. 1977. Total intravenous hyperalimentation and hydroxyurea chemotherapy in hepatoma-bearing rats. *J. Surg. Res.* 23:279–88
19. Cederbaum, A. I., Rubin, E. 1976. Fatty acid oxidation, substrate shuttles, and activity of the citric acid cycle in hepatocellular carcinomas of varying differentiation. *Cancer Res.* 36:2980–87
20. Chen, H. W., Kandutsch, A. A., Heiniger, H. J. 1978. The role of cholesterol

in malignancy. *Prog. Exp. Tumor Res.* 22:275–316
21. Christensen, H. N. 1975. Recognition sites for material transport and information transfer. *Curr. Top. Membr. Transp.* 6:227–58
22. Clark, C. M., Goodlad, G. A. J. 1971. Depletion of proteins of phasic and tonic muscles in tumor-bearing rats. *Eur. J. Cancer* 7:3–9
23. Clark, C. M., Goodlad, G. A. J. 1975. Muscle protein biosynthesis in the tumor-bearing rat: A defect in a post-initiation stage of translation. *Biochim. Biophys. Acta* 373:230–40
24. Clarke, E. F., Lewis, A. M., Waterhouse, C. 1978. Peripheral amino acid levels in patients with cancer. *Cancer* 42:2909–13
25. Coleman, R. 1973. Membrane bound enzymes and membrane ultrastructure. *Biochim. Biophys. Acta* 300:1–30
26. Costa, G. 1963. Cachexia, the metabolic component of neoplastic diseases. *Prog. Exp. Tumor Res.* 3:321–69
27. Costa, G., Holland, J. F. 1962. Effects of Krebs-2 carcinoma on the lipide metabolism of male Swiss mice. *Cancer Res.* 22:1081–83
28. Costa, G., Lane, W. W., Vincent, R. G., Siebold, J. A., Aragon, M., Bewley, P. T. 1980. Weight loss and cachexia in lung cancer. *Nutr. Cancer* 2:98–103
29. Dabbous, M. K., Roberts, A. N., Brinkley, B. 1977. Collagenase and neutral protease activities in cultures of rabbit VX-2 carcinoma. *Cancer Res.* 37: 3537–44
30. Daly, J. M., Reynolds, H. M., Rowlands, B. J., Dudrick, S. J., Copeland, E. M. 1980. Tumor growth in experimental animals. Nutritional manipulation and chemotherapeutic response in the rat. *Ann. Surg.* 191:316–22
31. Derr, J. T., Smith, G. L. 1980. Regulation of amino acid transport in chicken embryo fibroblasts by purified multiplication-stimulating activity (MSA). *J. Cell. Physiol.* 102:55–62
32. DeWys, W. D. 1979. Anorexia as a general effect of cancer. *Cancer* 43: 2013–19
33. DeWys, W. D., Begg, C., Lavin, P. T., Band, P. R., Bennett, J. M., Bertino, J. R., Cohen, M. H., Douglass, H. D. Jr., Engstrom, P. F., Ezdinli, E. Z., Horton, J., Johnson, G. J., Moertel, C. G., Oken, M. M., Perlia, C., Rosenbaum, C., Silverstein, M. N., Skeel, R. T., Sponzo, R. W., Tormey, D. C. 1980. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am. J. Med.* 69:491–97
34. Diamond, I., Legg, A., Schneider, J. A., Rozengurt, E. 1978. Glycolysis in quiescent 3T3 cells. Stimulation by serum, epidermal growth factor and insulin in intact cells and persistence of the stimulation after cell homogenization. *J. Biol. Chem.* 253:866–71
35. Eades, C. H. Jr., Pollack, R. L. 1954. Urinary excretion of fourteen amino acids by normal and cancer subjects. *J. Natl. Cancer Inst.* 15:421–27
36. Fabricant, R. N., Todaro, G. J., Eldridge, R. 1979. Increased levels of a nerve-growth-factor cross-reacting protein in "central" neurofibromatosis. *Lancet* 1:4–7
37. Fenninger, L. D., Mider, G. B. 1954. Energy and nitrogen metabolism in cancer. *Adv. Cancer Res.* 2:229–53
38. Fujii, S., Yuasa, A., Kawachi, T., Okamura, Y., Wakasugi, H., Yamamura, Y. 1964. Purification of toxohormone by carboxymethylcellulose column chromatography. *Gann* 55:67–71
39. Galanti, N., Tsutsui, Y., Jonak, G., Kawasaki, S., Soprano, K., Baserga, R. 1982. Nuclear events in normal and malignant cells and the control of cell proliferation. *Proc. 34th Ann. M. D. Anderson Hosp. Tumor Inst. Symp. on Fund. Cancer Res.* Houston, 1982. In press
40. Garattini, S., Bizzi, A., Donelli, M. G., Guaitani, A., Samanin, R., Spreafico, F. 1980. Anorexia and cancer in animals and man. *Cancer Treat. Rev.* 7:115–40
41. Glossmann, H., Presek, P., Eigenbrodt, E. 1981. Association of the src-gene product of Rous Sarcoma Virus with a pyruvate-kinase inactivating factor. *Mol. Cell. Endocrinol.* 23:49–63
42. Gospodarowicz, D., Moran, J. S. 1976. Growth factors in mammalian cell culture. *Ann. Biochem.* 45:531–57
43. Gump, F. E., Long, C. L., Geiger, J. W., Kinney, J. M. 1975. The significance of altered gluconeogenesis in surgical catabolism. *J. Trauma* 15:704–13
44. Harley, C. B., Goldstein, S., Posner, B. I., Guyda, H. J. 1980. Insulin-like peptides stimulate metabolism but not proliferation of human fibroblasts. *Am. J. Physiol.* 239:E125–31
45. Harnett, W. L. 1952. *British Empire Cancer Campaign: A Survey of Cancer in London,* p. 26 London: British Empire Cancer Campaign
46. Harrison, M. F. 1953. Effect of starvation on the composition of the liver cell. *Biochem. J.* 55:204–11
47. Haven, F. L., Bloor, W. R. 1956. Lipids in cancer. *Adv. Cancer Res.* 4:237–314

48. Herzfeld, A., Greengard, O. 1972. The dedifferentiated pattern of enzymes in livers of tumor-bearing rats. *Cancer Res.* 32:1826–32
49. Herzfeld, A., Greengard, O. 1977. The effect of lymphoma and other neoplasms on hepatic and plasma enzymes of the host rat. *Cancer Res.* 37:231–38
50. Herzfeld, A., Greengard, O., McDermott, W. V. 1980. Enzyme pathology of the liver in patients with and without nonhepatic cancer. *Cancer* 45:2383–88
51. Heymsfield, S. B., Horowitz, J., Lawson, D. H. Enteral hyperalimentation. In *Developments in Digestive Diseases,* ed. J. E. Berk, 3:59–83. Philadelphia: Lea and Febiger. 258 pp.
52. Hochstadt, J., Quinlan, D. C., Owen, A. J., Cooper, K. O. 1970. Regulation of transport upon interaction of fibroblast growth factor and epidermal growth factor with quiescent (Go) 3T3 cells and plasma-membrane vesicles isolated from them. In *Hormones and Cell Culture,* ed. G. H. Sato, R. Ross, *Cold Spring Harbor Conf. Cell Prolif.* 6:752–72
53. Holley, R. W. 1972. A unifying hypothesis concerning the nature of malignant growth. *Proc. Natl. Acad. Sci. USA* 69:2840–41
54. Holroyde, C. P., Axelrod, R. S., Skutches, C. L., Haff, A. C., Paul, P., Reichard, G. A. 1979. Lactate metabolism in patients with metastatic colorectal cancer. *Cancer Res.* 39:4900–4
55. Holroyde, C. P., Gabuzda, T. G., Putnam, R. C., Paul, P., Reichard, G. A. 1975. Altered glucose metabolism in metastatic carcinoma. *Cancer Res.* 35:3710–14
56. Holroyde, C. P., Meyers, R. N., Smink, R. D., Putnam, R. C., Reichard, G. A. 1977. Metabolic response to total parenteral nutrition in cancer patients. *Cancer Res.* 37:3109–14
57. Horwitz, A. F., Hatten, M. E., Burger, M. M. 1974. Membrane fatty acid requirements and their effect on growth and lectin-induced agglutinability. *Proc. Natl. Acad. Sci. USA* 71:3115–19
58. Houten, L., Reilley, A. A. 1980. An investigation of the cause of death from cancer. *J. Surg. Oncol.* 13:111–16
59. Hume, D. A., Weidemann, M. J. 1979. Role and regulation of glucose metabolism in proliferating cells. *J. Natl. Cancer Inst.* 62:3–8
60. Ibsen, K. H. 1977. Interrelationships and functions of the pyruvate kinase isozymes and their variant forms: A review. *Cancer Res.* 37:341–53
61. Ibsen, K. H., Fishman, W. H. 1979. Developmental gene expression in cancer. *Biochim. Biophys. Acta* 560:243–80
62. Im, W. B., Deutchler, J. T., Spector, A. A. 1979. Effects of membrane fatty acid composition on sodium-independent phenylalanine transport in Ehrlich cells. *Lipids* 14:1003–8
63. Kahn, C. R. 1980. The riddle of tumour hypoglycaemia revisited. *Clin. Endocrinol. Metab.* 9:335–61
64. Kampschmidt, R. F., Schultz, G. A. 1963. Absence of toxohormone in rat tumors free of bacterial contamination. *Cancer Res.* 23:751–61
65. Karmali, R. A. 1980. Review: Prostaglandins and cancer. *Prostagl. Med.* 5:11–28
66. Kavetsky, R. E., Samundgean, E. M., Butenko, Z. A. 1962. Changes in the functional state of the adrenal cortex during development of tumours. *Acta Unio. Int. Contra Cancrum* 18:115–17
67. Kelley, J. J., Waisman, H. A. 1957. Quantitative plasma amino acid values in leukemic blood. *Blood* 12:635–43
68. Kidwell, W. R., Knazek, R. A., Vonderhaar, B. K., Losonczy, I. 1982. Effects of unsaturated fatty acids on the development and proliferation of normal and neoplastic breast epithelium. See Ref. 39. In press
69. Klock, J. C., Pieprzyk, J. K. 1979. Cholesterol, phospholipids, and fatty acids of normal immature neutrophils: comparison with acute myeloblastic leukemia cells and normal neutrophils. *J. Lipid Res.* 20:908–11
70. Knauer, D. J., Iyer, A. P., Banerjee, M. R., Smith, G. L. 1980. Identification of somatomedin-like polypeptides produced by mammary tumors of BALB/c mice. *Cancer Res.* 40:4368–72
71. Lage-Davila, A., Hofmann-Clerc, F., Torpier, G., Montagnier, L. 1979. Glucose-regulated membrane properties of untransformed and virus-transformed BHK21 cells. *Exp. Cell Res.* 120: 181–89
72. Lanks, K. W., Kasambalides, E. J. 1980. Factors that regulate proliferation of normal and transformed cells in culture. *Pathobiol. Annu.* 10:35–50
73. Lavietes, B. B., Coleman, P. S. 1980. The role of lipid metabolism in neoplastic differentiation. *J. Theor. Biol.* 85: 523–42
74. Lawrence, W. Jr. 1979. Effects of cancer on nutrition: Impaired organ system effects. *Cancer* 43:2020–29
75. Lucke, B., Berwick, M., Zeckwer, I. 1952/53. Liver catalase activity in

parabiotic rats with one partner tumor-bearing. *J. Natl. Cancer Inst.* 13:681–86
76. Lundholm, K., Bylund, A-C., Holm, J., Schersten, T. 1976. Skeletal muscle metabolism in patients with malignant tumour. *Eur. J. Cancer* 12:465–73
77. Lundholm, K., Bylund, A-C., Schersten, T. 1977. Glucose tolerance in relation to skeletal muscle enzyme activities in cancer patients. *Scand. J. Clin. Lab. Invest.* 37:267–72
78. Lundholm, K., Edström, S., Ekman, L., Karlberg, I., Bylund, A-C., Schersten, T. 1978. A comparative study of the influence of malignant tumor on host metabolism in mice and man: evaluation of an experimental model. *Cancer* 42:453–61
79. Lundholm, K., Ekman, L., Edström, S., Karlberg, I., Jagenburg, R., Schersten, T. 1979. Protein synthesis in liver tissue under the influence of a methylcholanthrene-induced sarcoma in mice. *Cancer Res.* 39:4657–61
80. Lundholm, K., Ekman, L., Karlberg, I., Edström, S., Schersten, T. 1980. Comparison of hepatic cathepsin D activity in response to tumor growth and to caloric restriction in mice. *Cancer Res.* 40:1680–85
81. Lundholm, K., Holm, G., Schersten, T. 1978. Insulin resistance in patients with cancer. *Cancer Res.* 38:4665–70
82. Lundholm, K., Karlberg, I., Ekman, L., Edström, S., Schersten, T. 1981. Evaluation of anorexia as the cause of altered protein synthesis in skeletal muscles from non-growing mice with sarcoma. *Cancer Res.* 41:1989–96
83. Long, C. L., Kinney, J. M., Geiger, J. W. 1976. Nonsuppressibility of gluconeogenesis by glucose in septic patients. *Metabolism* 25:193–201
84. Marks, P. A., Bishop, J. S. 1957. The glucose metabolism of patients with malignant disease and of normal subjects as studied by means of an intravenous glucose tolerance test. *J. Clin. Invest.* 36:254–64
85. Masuno, H., Yamasaki, N., Okuda, H. 1981. Purification and characterization of a lipolytic factor (toxohormone-L) from cell-free fluid of ascites sarcoma 180. *Cancer Res.* 41:284–88
86. McKeehan, W. L., McKeehan, K. A. 1981. Extracellular regulation of fibroblast multiplication: A direct kinetic approach to analysis of role of low molecular weight nutrients and serum growth factors. *J. Supramol. Struct. Cell. Biochem.* 15:83–110
87. McKeehan, W. L., McKeehan, K. A. 1979. Oxocarboxylic acids, pyridine nucleotide-linked oxidoreductases and serum factors in regulation of cell proliferation. *J. Cell. Physiol.* 101:9–16
88. Medigreceanu, F. 1910. On the relative sizes of the organs of rats and mice bearing malignant new growths. *Proc. R. Soc. London, Ser. B* 82:286–92
89. Morgan, W. W., Cameron, I. L. 1973. Effect of fast-growing transplantable hepatoma on cell proliferation in host tissue of the mouse. *Cancer Res.* 33:441–48
90. Morrison, S. D. 1982. Control of food intake in the experimental cancerous host. See Ref. 39. In press
91. Nakahara, W. 1960. A chemical basis for tumor-host relations. *J. Natl. Cancer Inst.* 24:77–86
92. Nakahara, W. 1974. A pilgrim's progress in cancer research, 1918–1974: autobiographical essay. *Cancer Res.* 34:1767–74
93. Nakahara, W., Fukuoka, F. 1958. The newer concept of cancer toxin. *Adv. Cancer Res.* 5:157–77
94. Nathan, C. F., Murray, H. W., Cohn, Z. A. 1980. The macrophage as an effector cell. *N. Engl. J. Med.* 303:622–26
95. Nixon, D. W., Heymsfield, S. B., Cohen, A. E., Kutner, M. H., Ansley, J., Lawson, D. H., Rudman, D. 1980. Protein-calorie undernutrition in hospitalized cancer patients. *Am. J. Med.* 68:683–90
96. Odell, W. D., Wolfsen, A. R. 1980. Hormones from tumors: are they ubiquitous? *Am. J. Med.* 68:317–18
97. Oram-Smith, J. C., Stein, T. P., Wallace, H. W., Mullen, J. L. 1977. Intravenous nutrition and tumor host protein metabolism. *J. Surg. Res.* 22:499–503
98. Pain, V. M., Garlick, P. J. 1980. The effect of an Ehrlich ascites tumour on the rate of protein synthesis in muscle and liver of the host. *Biochem. Soc. Trans.* 8:334
99. Parnes, J. R., Isselbacher, K. J. 1978. Transport alterations in virus-transformed cells. *Prog. Exp. Tumor Res.* 22:79–122
100. Pouyssegur, J., Franchi, A., Salomon, J.-C., Silvestre, P. 1980. Isolation of a Chinese hamster fibroblast mutant defective in hexose transport and aerobic glycolysis: Its use to dissect the malignant phenotype. *Proc. Natl. Acad. Sci. USA* 77:2698–701
101. Quesney-Huneeus, V., Wiley, M. H., Siperstein, M. D. 1979. Essential role for mevalonate synthesis in DNA repli-

cation. *Proc. Natl. Acad. Sci. USA* 76:5056–60
102. Ramaswamy, K., Lyon, I., Baker, N. 1980. Dietary control of lipogenesis in vivo in host tissues and tumours of mice bearing Ehrlich ascites carcinoma. *Cancer Res.* 40:4606–11
103. Rannels, D. E., Pegg, A. E., Rannels, S. R. 1976. Starvation results in descreased initiation factor activity in rat skeletal muscle. *Biochem. Biophys. Res. Commun.* 72:1481–88
104. Roberts, A. B., Lamb, L. C., Newton, D. L., Sporn, M. B., DeLarco, J. E., Todaro, G. J. 1980. Transforming growth factors: Isolation of polypeptides from virally and chemically transformed cells by acid-ethanol extraction. *Proc. Natl. Acad. Sci. USA* 77:3494–98
105. Rose, D. P., Stauber, P., Thiel, A., Crowley, J. J., Milbraths, J. R. 1977. Plasma dehydroepiandrosterone sulfate, androstenedione and cortisol excretion in breast cancer. *Eur. J. Cancer* 13:43–47
106. Rosenfeld, C., Jasmin, C., Mathe, G., Inbar, M. 1979. Dynamic and composition of cellular membranes and serum lipids in malignant disorders. *Rec. Results Cancer Res.* 67:63–77
107. Recklies, A. D., Tiltman, K. J., Stoker, A. M., Poole, A. R. 1980. Secretion of proteinases from malignant and non-malignant human breast tissue. *Cancer Res.* 40:550–56
108. Rudman, D., Vogler, W. R., Howard, C. H., Gerron, G. G. 1971. Observations on the plasma amino acids of patients with acute leukemia. *Cancer Res.* 31:1159–65
109. Sassenrath, E. N., Greenburg, D. M. 1954. Tumor host relationships. I. Effects on free amino acid concentrations of certain tissues. *Cancer Res.* 14:563–69
110. Schaur, R. J., Fellier, H., Gleispach, H., Fink, E., Kronberger, L. 1979. Tumor host relations. I. Increased plasma cortisol in tumor-bearing humans compared with patients with benign surgical diseases. *J. Cancer Res. Clin. Oncol.* 93:281–85
111. Schaur, R. J., Semmelrock, H-J., Schauenstein, E., Kronberger, L. 1979. Tumor host relations II. Influence of tumor extent and tumor site on plasma cortisol of patients with malignant diseases. *J. Cancer Res. Clin. Oncol.* 93:287–92
112. Schein, P. S., Kisner, D., Haller, D., Blecher, M., Hamosh, M. 1979. Cachexia of malignancy: potential role of insulin in nutritional management. *Cancer* 43:2070–76
113. Sherman, C. D. Jr., Morton, J. J., Mider, G. B. 1950. Potential sources of tumor nitrogen. *Cancer Res.* 10:374–78
114. Shinitzky, M., Rivnay, B. 1977. Degree of exposure of membrane proteins determined by fluorescence quenching. *Biochemistry* 16:982–86
115. Spector, A. A. 1975. Fatty acid metabolism in tumors. *Prog. Biochem. Pharmacol.* 10:42–75
116. Stein, T. P. 1982. Tumor-induced changes in the host's protein metabolism. See Ref. 39. In press
117. Stein, T. P., Buzby, G. P., Rosato, E. F., Mullen, J. L. 1981. Effect of parenteral nutrition on protein synthesis in adult cancer patients. *Am. J. Clin. Nutr.* 34:1484–88
118. Theologides, A. 1972. Pathogenesis of cachexia in cancer. *Cancer* 29:484–88
119. Theologides, A., Pegelow, C. H. 1970. Liver weight changes during distant growth of transplanted tumor. *Proc. Exp. Biol. Med.* 134:1104–8
120. Tisdale, M. J. 1980. Methionine metabolism in Walker carcinosarcoma in vitro. *Eur. J. Cancer* 16:407–14
121. Todaro, G. J., DeLarco, J. E. 1978. Growth factors produced by sarcoma virus-transformed cells. *Cancer Res.* 38:4147–54
122. Todaro, G. J., DeLarco, J. E., Fryling, C., Johnson, P. A., Sporn, M. B. 1981. Transforming growth factors (TGFs): Properties and possible mechanisms of action. *J. Supramol. Struct. Cell. Biochem.* 15:287–301
123. Tomino, I., Katunuma, N., Morris, H. P., Weber, G. 1974. Imbalance in ornithine metabolism in hepatomas of different growth rates as expressed in behavior of L-ornithine: 2-oxoacid aminotransferase (ornithine transaminase, EC 2.6.1.13). *Cancer Res.* 34:627–36
124. Warburg, O. 1956. On the origin of cancer cells. *Science* 123:309–14
125. Warnold, I., Lundholm, K., Schersten, T. 1978. Energy balance and body composition in cancer patients. *Cancer Res.* 38:1801–7
126. Warren, S. 1932. The immediate causes of death in cancer. *Am. J. Med. Sci.* 184:610–15
127. Waterhouse, C., Jeanpretre, N., Keilson, J. 1979. Gluconeogenesis from alanine in patients with progressive malignant disease. *Cancer Res.* 39:1968–72
128. Waterhouse, C., Kemperman, J. H. 1971. Carbohydrate metabolism in sub-

jects with cancer. *Cancer Res.* 31: 1273–78
129. Weber, G. 1982. Differential carbohydrate metabolism in tumor and host. See Ref. 39. In press
130. Weber, G., Queener, S. F., Morris, H. P. 1972. Imbalance in ornithine metabolism in hepatomas of different growth rates as expressed in behavior of L-ornithine carbamyl transferase activity. *Cancer Res.* 32:1933–40
131. Weber, M. J., Salter, D. W., McNair, T. E. 1982. Increased glucose transport in malignant cells: Analysis of its molecular basis. See Ref. 39. In press
132. Weinhouse, S. 1982. Changing perceptions of carbohydrate metabolism in tumors. See Ref. 39. In press
133. Williams-Ashman, H. G., Coppoc, G. L., Weber, G. 1972. Imbalance in ornithine metabolism in hepatomas of different growth rates as expressed in formation of putrescine, spermidine, and spermine. *Cancer Res.* 32:1924–32
134. Wu, C., Bauer, J. M. 1960. A study of free amino acids and of glutamine synthesis in tumor-bearing rats. *Cancer Res.* 20:848–57
135. Young, S. E., Griffin, A. C., Milner, A. N., Stehlin, J. S. Jr. 1967. Free amino acids and related compounds in the blood and urine of patients with malignant melanoma. *Cancer Res.* 27:15–17