Working Conference on Anorexia and Cachexia of Neoplastic Disease

Report of a Conference

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A conference was sponsored by the American Cancer Society in Philadelphia in the fall of 1969 to bring together investigators from a variety of disciplines for formal and informal discussions on the problem of anorexia and cachexia of neoplastic disease.

Definition of the Problem. Definitions of the terms anorexia and cachexia presented by various participants ranged from dictionary definitions through operational definitions of reduced food intake or nonregulatory eating (anorexia) or reduced carcass weight (cachexia). A definition of anorexia presented by Dr. Seoras D. Morrison was that of food intake which was inadequate to meet the combined needs of the host and the tumor: thus even if food intake remained constant, this could result in a loss of carcass weight in a tumor-bearing host. In addition, in man the concept of anorexia might also include nausea and other discomforts related to eating. Thus, for each patient, it may be of value to distinguish between lack of hunger on the one hand and nausea or an aversion to food on the other.

Cachexia could be defined to include not only the effects of anorexia but also many as yet poorly understood metabolic derangements which occur in the cancer-bearing host. These derangements may in turn lead to a decline in motor activity which might lead to reduced feeding (a
motor activity), thus accentuating the cachexia. The clinical spectrum of the cachexia of cancer ranges from the patient with an undiagnosed neoplasm who consults the physician because of slight weight loss to the patient with end stage disease with marked weakness and muscle wasting.

Normal Mechanisms of Control of Appetite and Body Composition. Neuroanatomic and neurophysiological research on appetite control has emphasized the role of hypothalamic areas in appetite control. Dr. Eliot Stellar emphasized that one must consider hypothalamic areas interacting with the cerebral cortex, sensory stimuli, and internal chemical and physical factors. As a possible example of cortical factors, Dr. John Garcia and Dr. Albert J. Stunkard presented examples of conditioned aversion to the smell and taste of food induced by drugs, toxins and X-rays administered hours after eating. Study of sensory stimuli may elucidate the clinical observation of aversion for protein by the cancer patients. As an example of an internal chemical factor influencing appetite, the onset of loss of appetite within a few days of fasting coincides with the appearance of ketosis, and experimental infusion of β-hydroxybutyrate is known to produce decreased eating in experimental animals.

The neuroanatomy of the hypothalamic areas involved in hunger and satiety was reviewed by Dr. Robert A. Liebelt and Dr. Philip Teitelbaum. Dr. Liebelt discussed the ventromedical area of the hypothalamus which is considered to be the satiety center. Dr. Teitelbaum discussed lesions of the lateral hypothalamus which caused loss of the drive for eating and drinking and described the sequence of recovery after lesions in this area. During the later stages of the recovery sequence, the animal is observed to be “finicky”: the animal will eat certain foods but will avoid others, and Dr. Teitelbaum suggested that this may in some way parallel the eating behavior of the anorectic patient.

In discussion, it was noted that the relationship between anorexia and hypothalamic centers is not completely understood. An experimental system was described in which anorexia was observed in an animal in which hyperphagia had previously been produced by ventromedial hypothalamic lesion.

Appetite control in humans was reviewed by Dr. George Cahill. Patients given a totally synthetic diet, without instructions as to amount to be eaten, consumed an amount necessary to maintain their weight at a steady level.

Metabolic Abnormalities Which May Relate to the Anorexia and Cachexia of Cancer. Alterations in lipid metabolism induced by cancer were suggested by Dr.
Liebelt who described an animal tumor system (CBA No. 2336 stomach tumor) in which increased serum steroid esters were observed. He stated that these steroid esters may be used for the metabolic requirements of the tumor but that they had the consequences of depressing the appetite of the animal. He advanced the hypothesis that the tumor produced a lipid-mobilizing substance which caused mobilization of fat from the depots of the tumor-bearing animal, which would then cause cachexia. This hypothesis was supported by Dr. Giovanni Costa who has studied the Krebs-2 carcinoma system and reported that body fat was lost very early in the tumor growth. However, using modern analytical procedures for lipid analysis, Dr. Christopher Carruthers reported that the Krebs-2 carcinoma had very little influence upon the carcass lipids of mice until the tumors were very large (premortal) and that the transplantable Walker carcinoma increased the neutral lipid content in liver and decreased the neutral lipid level and skeletal muscle; other methylcholanthrene-induced rat transplantable mammary tumors, however, produced no effect on the neutral lipid content of either muscle or liver. Apparently, the host lipid depletion property is restricted to some transplantable animal tumors.

Dr. Cahill discussed experimental evidence for a circulating lipostat hormone in normal animals. Tumor-bearing animals have not been studied.

Altered amino acid metabolism in cancer was discussed by Dr. Cahill. He reported increased alanine in the blood of patients with advanced cancer and presented evidence that alanine enters the blood at the expense of breakdown of muscle protein. The alanine circulates to the liver where it is converted into glucose which then enters the circulation and supplies the glucose requirements of the central nervous system. Cahill stated that this catabolic loss of amino acid from muscle may be responsible for much of the weakness and cachexia of advanced cancer. Additional evidence for abnormalities of amino acid metabolism was presented by Dr. J. F. Holland who discussed the hypoalbuminemia of advanced cancer. Using labeled methionine, he was able to demonstrate a decreased rate of biosynthesis of albumin in cancer patients and suggested that this may be related to a limitation of critical amino acids.

Abnormalities of glucose metabolism were discussed by Dr. Christine Waterhouse. She presented evidence of a decreased rate of glucose utilization and a decreased production of labeled CO2 following administration of labeled glucose in advanced cancer patients compared with normal subjects. Patients with metastatic malignant disease utilized more free fatty acid for CO2 production than did normal subjects, and glucose in advanced cancer patients produces a marked reduction in free fatty acid oxidation caused very little change in this parameter in diseased subjects. In discussion, Dr. John E. Ullmann pointed out that abnormal glucose tolerance tests are frequently noted in association with cancer; but, he noted, an increased frequency of abnormal glucose tolerance is also observed in other chronic diseases such as uremia, congestive heart failure and chronic granulomatous diseases. Starvation also can alter metabolism, and the role of decreased eating in the metabolic abnormalities observed in patients with advanced cancer is not clear.

Tumor growth may influence host metabolism by way of tumor by-products. The spectrum of ectopic production of hormones or hormone-like substance was reviewed by Dr. W. P. L. Myers. Ectopic production by tumors of most of the known polypeptide hormones has been described. These hormones may have marked metabolic effects which may
contribute to anorexia and cachexia. Nonhormonal tumor by-products affecting cell metabolism have also been described. Dr. Bengt Sylvén presented studies of a polypeptide with a molecular weight of 1,900 which is not detectable in normal body fluids but is present in the interstitial fluid from tumors or in malignant ascites fluid. Studies with a partially synchronized cell population showed that this peptide damages cells in the S phase of the mitotic cycle. Normal cells were two to four times as sensitive to this damage as were cancer cells under similar bioassay conditions. It is not clear whether this polypeptide is a synthetic product of tumor cells or whether it is a cellular component which leaks from dying cancer cells.

Tumor growth may influence host metabolism by producing nutritional deficiencies in the tumor-bearing host, for example, the depletion of sodium in rats bearing the Walker 256 carcinosarcoma. It was suggested that the Richter method of self-selection of diet might be used to elucidate nutritional deficiencies in the patient with cancer.

Dr. Larry Nathanson reviewed the spectrum of liver abnormalities which may be observed in patients with advanced cancer in the absence of direct involvement of the liver. Abnormalities in enzymes noted in these patients may be due to induction, depression or excretion of enzymes, and a wide spectrum of liver function abnormalities may be observed. Histological abnormalities, which are as yet poorly understood, may also be observed.

Model Systems Which May Elucidate the Mechanisms of Anorexia and Cachexia. The uremic syndrome which is also characterized by anorexia and cachexia was reviewed by Dr. H. Earl Ginn. The anorexia of uremic patients improves following dialysis, thus focusing attention on dialyzable factors, such as cyanates, amino acids, organic acids, amines, phenols and small polypeptides with a molecular weight of less than 4,000. Both amino acids and polypeptides have been alluded to previously in this report as possible factors in the anorexia of cancer.

Possible mechanisms of anorexia of liver disease was discussed by Dr. Jay Tepperman. A nonspecific alarm reaction to sickness may influence the central nervous system to reduce appetite; secondly, postprandial hyperglycemia associated with liver disease may signal the central nervous system glucostat in such a way as to reduce the appetite; a third mechanism may involve hepatic glucoreceptors, which fire the vagus nerve in response to glucose perfusion in the liver. It is thus possible that liver disease may produce hypersensitivity of these hepatic glucoreceptors, and thus inappropriate messages may reach the central appetite control center and lead to anorexia. Finally, liver disease may result in amino acid imbalance in plasma which may in turn lead to anorexia. The mechanism of this is unclear, but experimental evidence points to cells in the central nervous system which may monitor the amino acid levels of the blood. In patients with cirrhosis and also in patients with chronic active hepatitis, elevated levels of tyrosine have been observed.

A third syndrome characterized by anorexia is the irradiation syndrome. Experimental studies of radiation exposure were reviewed by Dr. Solomon Michaelson. This model has the advantage that discrete areas of the animal can be irradiated, facilitating study of the role of the brain, the liver, etc., in the development of anorexia.

Pharmacological studies of drugs with

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1 Russek, M.: Participation of hepatic glucoreceptors in the control of intake of food. Nature 197: 79-80, 1963.
2 Niijima, A.: Afferent impulse discharges from glucoreceptors in the liver of the guinea pig. Ann. N.Y. Acad. Sci. 157: 690-700, 1969.
anorexigenic and antianorexigenic properties were discussed by Dr. Larry Stein. Anorexigenic drugs such as amphetamines may act by releasing norepinephrine in the brain, and chlorpromazine and closely related drugs may have an antiadrenergic effect and may under certain circumstances have an antianorectic effect.

Model systems in which anorexigenic humoral factors could be studied were described by Dr. John D. Davis and Dr. Barbara Walike. Dr. Davis described a method of cross-transfusion between unanesthetized rats, and Dr. Walike described a method for cross-circulation between unanesthetized monkeys. They have just established methodology and have initiated studies of feeding behavior in the cross-circulated animals; Dr. Davis and his colleagues have been able to demonstrate a circulating factor influencing food intake.

**Theorpeutic Possibilities.** Dr. Stanley J. Dudrick discussed parenteral feeding with infusion of protein hydrolysate and hypertonic glucose into the superior vena cava which was developed by Dr. Dudrick to meet the metabolic requirements of surgical patients and which has recently been studied in patients with cancer. He described several patients in whom this therapy produced reversal of the patient's cachexia with significant weight gain and gain in muscle mass. When queried about the effect of this therapy on the patient's tumor. Dr. Dudrick pointed out that most of his patients were receiving other therapy, so that he could not reach any conclusions as to the effect of the feeding on the course of the tumor.

Dr. Thomas Hall discussed the therapeutic role of exogenous steroids, particularly androgens and androgen derivatives, and possible therapeutic advantages of exogenous insulin were discussed by Dr. Cahill.

A psychophysiological approach to cachexia was discussed. It was suggested that, if anorexia were the result of conditioned aversion, this might be reversed by suitable conditioning experiences. Metabolic factors, however, may limit the value of this approach.

It became clear during these sessions that much too little is known about the anorexia and cachexia of cancer. To understand anorexia, one needs a fuller understanding of the control of normal food intake and one must know what has gone wrong with this control. The techniques for such study of anorexia and cachexia at several levels of organization are now available. It is hoped that the cross-fertilization afforded by this meeting will lead to meaningful studies of the problems raised.