# The Effect of Tumor Bulk on the Metabolic Response to Cancer

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**The derangements in energy/substrate metabolism seen in oncology patients are similar regardless of the tumor's site of origin, and in advanced disease these metabolic derangements can be manifested as cancer cachexia. The relationship between tumor size and the degree of metabolic abnormality, however, remains unclear. Using primed constant infusions of stable and radiolabeled isotopes and indirect calorimetry, the authors have determined the rates of net protein catabolism (NPC), glucose oxidation, Cori cycling of glucose, and oxygen consumption in 85 patients with cancer. They have assessed the association between bulk of tumor and metabolic abnormality using regression analysis. A positive correlation was found between tumor bulk and the rates of NPC ($r^2$ = 0.8), plasma glucose appearance ($r^2$ = 0.72), plasma glucose clearance ($r^2$ = 0.70), the percentage of tissue glucose uptake recycled to lactate ($r^2$ = 0.62), and oxygen consumption ($r^2$ = 0.79). The percentage of tissue glucose uptake oxidized was negatively correlated with tumor bulk ($r^2$ = 0.75). The data indicate that the degree of metabolic abnormality seen in cancer patients is closely related to the quantity of malignant tissue present. Progressive increase in tumor size is associated with an increase in peripheral substrate mobilization, an increase in the rate of hepatic glucose production, an increase in tissue glucose uptake, an increase in energy-expensive glucose cycling to lactate, and an increase in protein loss.**

IT IS NOW clear that tumor burden is associated with abnormal energy substrate metabolism in the host.[1-3] In spite of this, the relationship between the stage of disease or bulk of tumor present and the development of abnormal energy/substrate metabolism is unclear. Cancer cachexia is more common in advanced tumors, and weight loss is a sign of heavy tumor burden.[4] There are, however, a number of reports in the oncology literature of significant weight loss in association with relatively small tumor burdens.[5,6]

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We have previously shown that patients with small or early tumors are metabolically similar to postabsorptive cancer-free volunteers,[1] whereas patients with more advanced or aggressive tumors exhibit a number of metabolic abnormalities that eventually may present as cancer cachexia.[1,7,8] In addition, we and others have previously shown a remarkable similarity in the metabolic derangements that accompany cancer regardless of the primary site or tissue of origin,[1-3,7,8] and it has been postulated that the elaboration of endocrine mediators by rapidly growing malignant tissue alters host metabolism in a way that is more advantageous to tumor growth.[3,9,10]

This study of metabolic profiles in cancer patients was undertaken to define the relationship between the bulk of tumor and the common metabolic abnormalities associated with tumor burden.

## Methods

### *Patients*

All patients in this investigation were recruited from the general surgical wards at Auckland Hospital. This investigation was approved by the Ethical Committee at Auckland Hospital, and the use of radioisotopes was approved by the National Radiation Laboratory of New Zealand. Many of the metabolic data from these patients have been published previously in a number of investigations concerning the metabolic profile of individual malignancies.[1,7,8] We have not previously investigated the association between the bulk of tumor and the metabolic response to tumor burden, however. We therefore reviewed the results of 5 years of isotopic studies in cancer patients and selected all oncology patients who were studied preoperatively. No oncology patient was included in this analysis if they had significant sepsis, concurrent en-

docrine disease (including diabetes mellitus), or if they were receiving total parenteral nutrition. The majority of patients studied were suffering from solid tumors of the gastrointestinal tract, retroperitoneum, or limbs. The patients with myeloproliferative cancers who were studied all had disseminated disease and were referred to the surgical service for staging laparotomy or splenectomy.

The clinical details of the 85 patients are presented in Table 1.

### *Measurement of Tumor Bulk*

The pathologic records of the patients who had solid tumors removed after metabolic study were reviewed, and the dimensions of tumor in the resected specimen made by an independent pathologist were noted. It was assumed that solid tumors were uniformly spherical in shape, and the volume of tumor present was calculated using these dimensions. It also was assumed that 1 $cm^3$ of tumor tissue weighed 1 g. No attempt was made to subtract the dimensions of any necrotic tumor segments from this value. The volumes and weights of any hepatic or pulmonary metastases were calculated in the same manner using the dimensions obtained with ultrasound or computed tomographic (CT) scanning.

In those patients with myeloproliferative cancers, it was assumed that all hemopoietic tissue (excluding the spleen) was uniformly malignant and the volume of this was cal-

TABLE 1. *Clinical Details of Oncology Patients*

| Patient | Sex | Age | Diagnosis | Patient | Sex | Age | Diagnosis |
|---|---|---|---|---|---|---|---|
| 1 | M | 64 | Ca esophagus | 44 | M | 67 | Ca colon |
| 2 | F | 80 | Ca pancreas | 45 | F | 72 | Ca rectum |
| 3 | M | 64 | Ca stomach | 46 | F | 69 | Melanoma |
| 4 | M | 87 | Ca esophagus | 47 | F | 58 | Melanoma |
| 5 | M | 57 | Ca esophagus | 48 | F | 33 | Melanoma |
| 6 | M | 58 | Ca pancreas | 49 | F | 72 | Melanoma |
| 7 | M | 71 | Ca esophagus | 50 | M | 43 | Ca salivary gland |
| 8 | F | 73 | Ca stomach | 51 | F | 58 | Ca tongue |
| 9 | F | 60 | Ca esophagus | 52 | F | 75 | Ca lip |
| 10 | M | 80 | Ca stomach | 53 | M | 59 | Ca salivary gland |
| 11 | M | 56 | Ca stomach | 54 | M | 68 | Ca tongue |
| 12 | M | 58 | Ca esophagus | 55 | F | 64 | Ca tongue |
| 13 | M | 63 | Ca stomach | 56 | F | 57 | Ca thyroid |
| 14 | F | 63 | Ca pancreas | 57 | F | 28 | Ca thyroid |
| 15 | M | 63 | Ca esophagus | 58 | M | 63 | Ca thyroid |
| 16 | M | 88 | Ca stomach | 59 | F | 48 | Ca salivary gland |
| 17 | M | 59 | Ca esophagus | 60 | F | 67 | Ca tongue |
| 18 | M | 79 | Ca esophagus | 61 | F | 79 | CML |
| 19 | F | 81 | Ca stomach | 62 | M | 68 | CML |
| 20 | M | 80 | Ca stomach | 63 | M | 47 | AML |
| 21 | F | 68 | Ca esophagus | 64 | M | 41 | HKL |
| 22 | F | 76 | Ca esophagus | 65 | M | 79 | CLL |
| 23 | M | 60 | Ca stomach | 66 | M | 66 | CLL |
| 24 | M | 70 | Ca bile duct | 67 | M | 68 | CLL |
| 25 | M | 73 | Ca colon | 68 | M | 54 | CLL |
| 26 | F | 79 | Ca colon | 69 | F | 70 | CLL |
| 27 | M | 77 | Ca rectum | 70 | M | 37 | HKL |
| 28 | F | 75 | Ca rectum | 71 | M | 72 | CLL |
| 29 | M | 69 | Ca colon | 72 | M | 88 | ALL |
| 30 | F | 56 | Ca rectum | 73 | F | 51 | NHL |
| 31 | F | 73 | Ca colon | 74 | F | 80 | NHL |
| 32 | M | 79 | Ca colon | 75 | F | 28 | NHL |
| 33 | M | 77 | Ca colon | 76 | M | 60 | HKL |
| 34 | F | 60 | Ca colon | 77 | M | 47 | SARC |
| 35 | M | 57 | Ca colon | 78 | M | 21 | SARC |
| 36 | M | 77 | Ca rectum | 79 | M | 67 | SARC |
| 37 | F | 55 | Ca colon | 80 | M | 48 | SARC |
| 38 | F | 83 | Ca colon | 81 | M | 76 | SARC |
| 39 | F | 61 | Ca colon | 82 | M | 17 | SARC |
| 40 | M | 75 | Ca colon | 83 | F | 86 | SARC |
| 41 | M | 81 | Ca colon | 84 | F | 71 | SARC |
| 42 | M | 59 | Ca colon | 85 | F | 32 | SARC |
| 43 | F | 66 | Ca colon | | | | |

Ca, cancer; Ca thyroid, papillary carcinoma of the thyroid gland; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; HKL, Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia, ALL, acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; SARC, sarcoma.

culated by assuming it occupied 5.9% of the patient's body weight.[11]

*Experimental Protocol*

All experiments involved the infusion of isotopes and the collection of blood samples. Multiple tracers were infused with each study, and each patient was studied once. Multiple tracers using the same isotopic label were not infused simultaneously; for example, $^{14}$C-urea and $^{14}$C-glucose. The rates of plasma glucose appearance and plasma glucose clearance were determined in all 85 patients using a primed constant infusion of 6–$^{3}$H glucose. The rate of net protein catabolism (NPC) was determined using a primed constant infusion of $^{14}$C-urea in 33 patients, and the rates of plasma glucose oxidation and glucose recycling were not determined in these studies. The rates of plasma glucose oxidation and glucose cycling to lactate were determined in the remaining 52 patients. Because this required the infusion of both 6–$^{3}$H glucose and $^{14}$C-labeled glucose, the rate of net protein catabolism in these patients was determined using a primed constant infusion of di-$^{15}$N urea.

At the start of each study, a primed constant infusion of isotopes was commenced through a forearm vein and maintained for a minimum of 3 hours. Blood samples were taken over a 60-minute period after 120 minutes of isotope infusion. The blood then was immediately centrifuged and the plasma was frozen.

*Isotopes*

Glucose kinetics were assessed using primed constant infusions of $^{14}$C glucose and 6–$^{3}$H glucose.[1,12,13] The rate of net protein catabolism was obtained using primed constant infusions of $^{14}$C-urea or di-$^{15}$N urea as we have described previously.[1,12,13] Plasma glucose and urea specific activity was determined as described elsewhere,[1,12,13] as was the plasma enrichment of di-$^{15}$N urea.[13,14]

*Calorimetry*

Indirect calorimetry was performed using an ADC CO2 Analyser (Hoddesdon, United Kingdom), and the rate of oxygen consumption in the postabsorptive state measured directly using a Sybron Taylor Oxygen Analyser (Hertsfordshire, United Kingdom).

*Statistical Analysis*

The degree of correlation between the estimated weight of tumor tissue present and the metabolic indices was determined using a regression analysis.[15]

## Results

*Protein Metabolism*

A positive correlation ($r^2$ = 0.80) was found between the rate of plasma urea appearance and the rate of net protein catabolism and the bulk of tumor present (Fig. 1).

*Glucose Metabolism*

The bulk of tumor present was positively correlated both with the rate of plasma glucose appearance ($r^2$ = 0.72; Fig. 2) and the rate of plasma glucose clearance ($r^2$ = 0.70; Fig. 3). A negative correlation ($r^2$ = 0.72; Fig. 4) existed, however, between the percentage of glucose uptake oxidized by tissue and tumor bulk, and this was associated

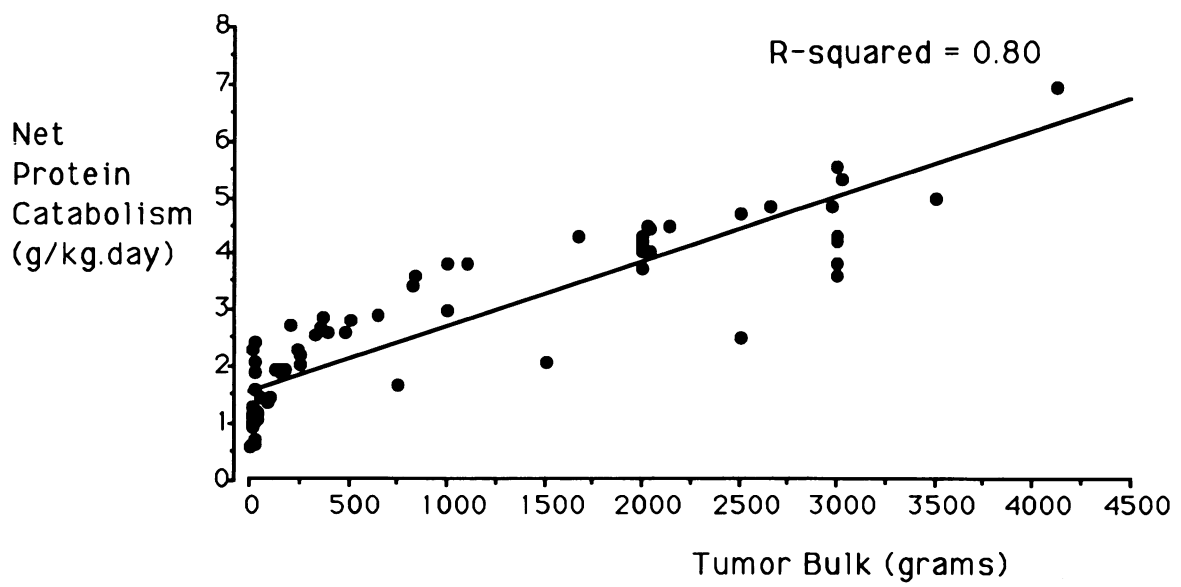


FIG. 1. Tumor bulk *versus* the rate of net protein catabolism in 85 patients with cancer.

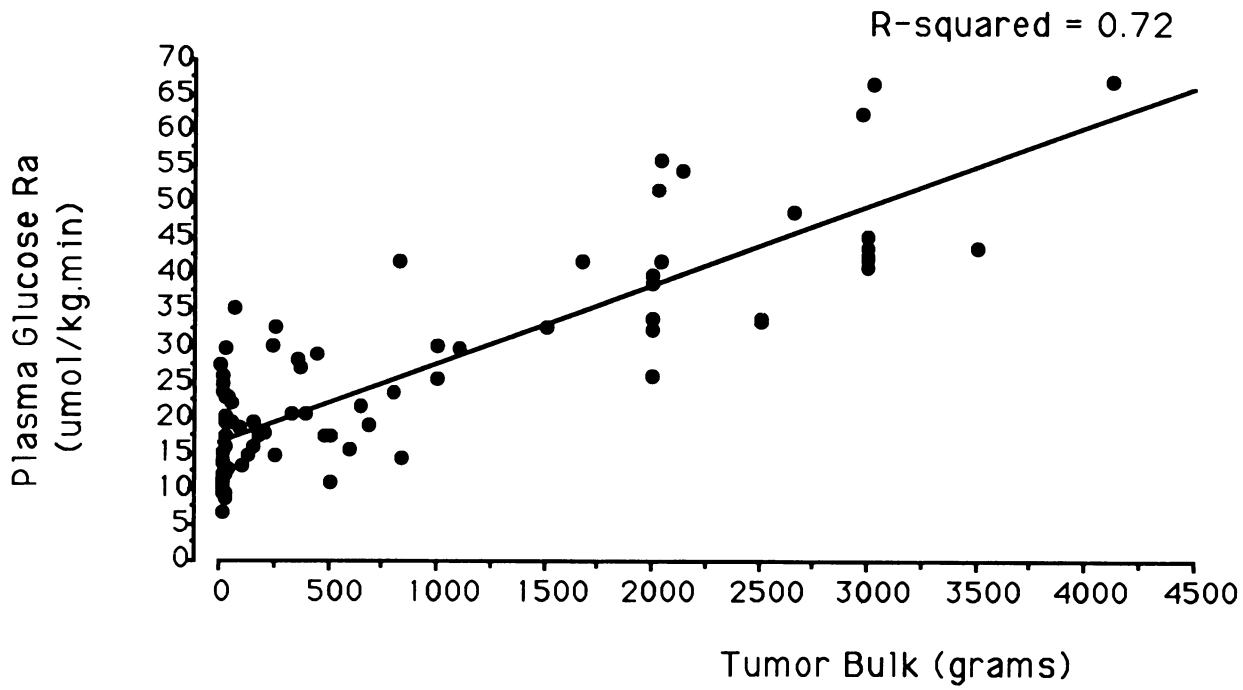


FIG. 2. Tumor bulk *versus* the rate of plasma glucose appearance. Ra, rate of appearance.

with a proportional increase in the percentage of tissue glucose uptake recycled to lactate ($r^2$ = 0.62; Fig. 5).

*Oxygen Consumption*

The volume of oxygen consumed per minute was positively correlated with tumor bulk ($r^2$ = 0.79; Fig. 6).

## Discussion

This investigation has shown that the abnormalities in energy/substrate metabolism seen in the oncology patient are closely related to the quantity of malignant tissue present. Patients with a small tumor bulk are metabolically similar to normal volunteers,[1] and the alterations in intermediary metabolism characteristic of the oncology pa-

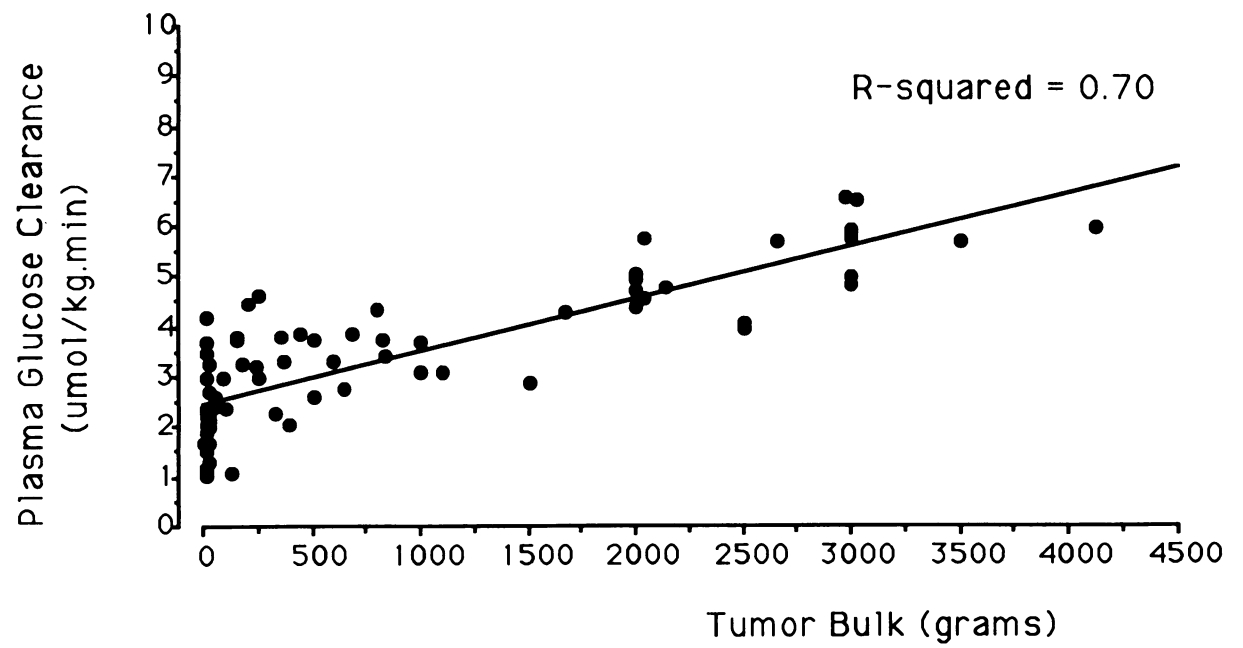


FIG. 3. Tumor bulk *versus* the rate of plasma glucose clearance.

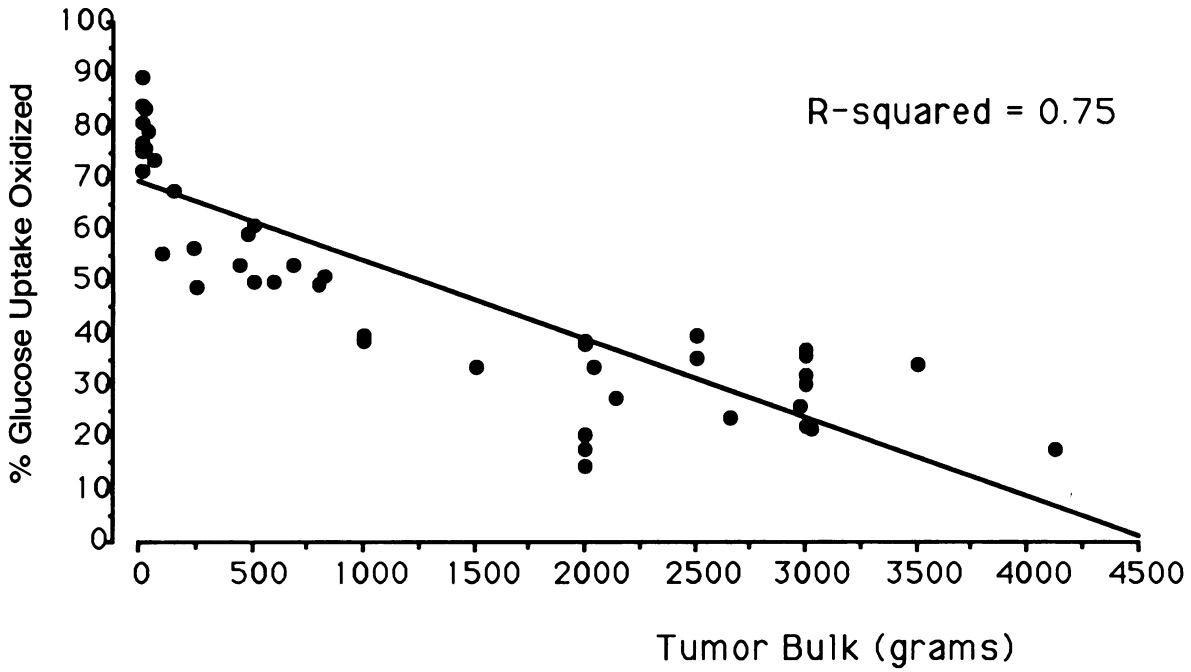


FIG. 4. Tumor bulk *versus* the percentage of tissue glucose uptake oxidized to carbon dioxide.

tient become increasingly marked as the tumor increases in size.

Although this investigation was not conducted in a prospective manner, we believe it is useful because a large standardized group of cancer patients have been studied; all of whom had histologically proven and accurately staged cancers with no concomitant sepsis or endocrine disease. In this way, we have been able to eliminate a number of potentially confounding variables. In addition, this methodology enabled independent measurements of tumor weight by histopathologists assessing the resected specimen and radiologists reviewing diagnostic CT and

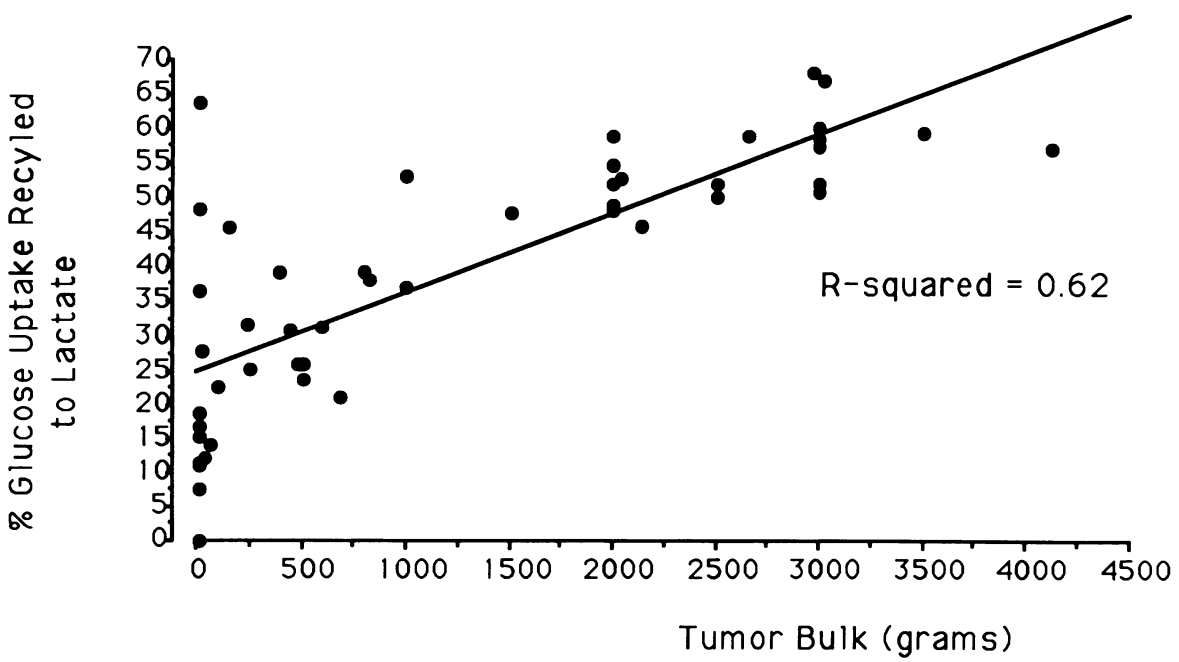


FIG. 5. Tumor bulk *versus* the percentage of tissue glucose uptake recycled to lactate.

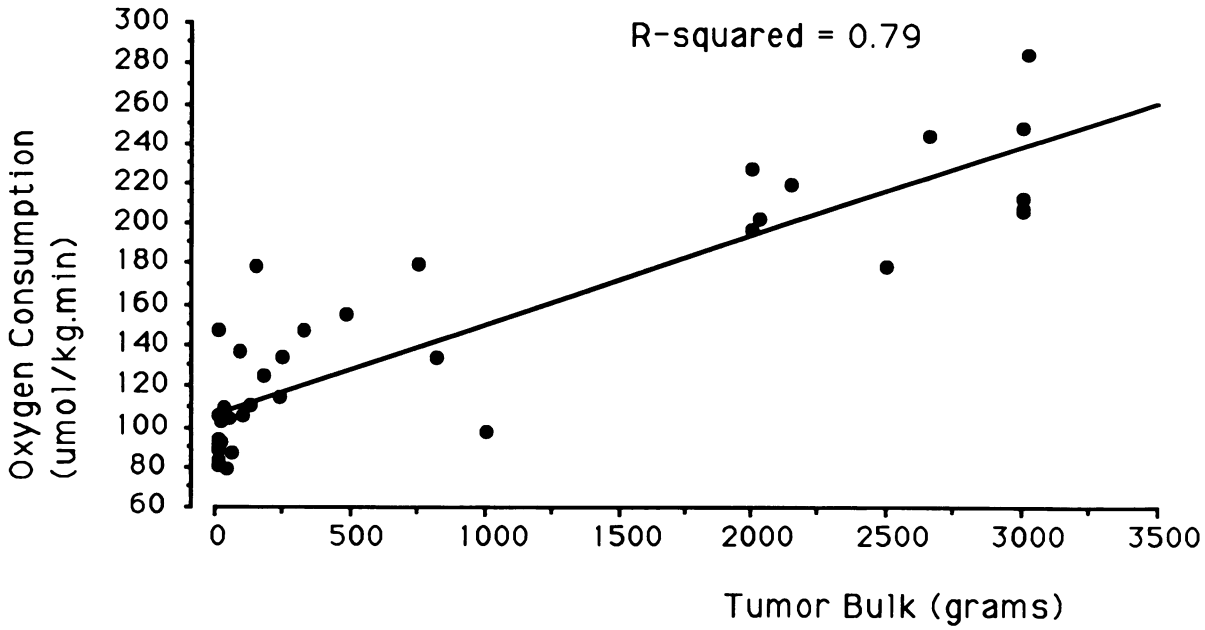


FIG. 6. Tumor bulk *versus* oxygen consumption in patients with cancer.

ultrasound scans. Measurement of tumor bulk using this methodology, however, may have underestimated the total volume of malignant tissue present in the patient with bulky metastatic disease. For this reason, although we have found a linear correlation between the measured metabolic parameters and tumor bulk, this relationship may become exponential in the large rapidly dividing tumor or in patients with large metastatic burdens. This is more consistent with the known kinetics of tumor growth.[16]

A progressive increase in oxygen consumption was seen with increases in tumor bulk. We have previously shown that patients with small colorectal cancers are normometabolic in comparison with normal volunteers,[1] whereas patients with disseminated cancers and bulky local disease often display increased energy expenditure up to 25% above normal.[7,17] Dempsey et al[18] have emphasized the considerable heterogeneity present in cancers of differing sizes by showing that patients with colorectal cancer may be normometabolic, hypometabolic, or hypermetabolic. Increased tumor bulk, however, tended to be associated with increased oxygen consumption. Because anaerobic glycolysis is characteristic of malignant tissue,[19,20] this increase in oxygen consumption may represent increased aerobic demand of nonmalignant host tissue, possibly for an acute phase response.[21]

One of the key findings of our study revolves around the marked alterations in glucose metabolism associated with increasing tumor bulk. Increasing tumor bulk is accompanied by a progressive decrease in the ability of the cancer patient to oxidize glucose completely to carbon dioxide, and there is a corresponding increase in the rate of glucose recycling to lactate. Other investigators have also documented similar findings in oncology patients.[1,2,12] Glucose recycling to lactate is an energy-expensive process resulting in a deficit of 2 moles of adenosine triphosphate for each mole of glucose recycled,[17] and this results in a net energy imbalance. Anaerobic glycolysis is a characteristic of malignant tissue,[19,20] and it is likely that glucose cycling to lactate occurs in tumor tissue. The manufactured lactate is then cycled back to glucose in the host liver.[22] The changes in the fate of available glucose therefore reflect increased use of available glucose by an increasing volume of tumor, leaving less glucose for oxidation by nonmalignant tissue.

The increased demand for glucose in the cancer patient is met by increased hepatic glucose production. This is associated with an increase in the clearance of glucose from plasma. Kokal et al.[2] have shown that patients with advanced colorectal cancers have a significantly higher rates of glucose turnover when compared with patients with localized colorectal cancers. Similarly, Holroyde et al.[22] found that patients with weight-losing metastatic cancer had increased rates of glucose turnover and glucose cycling to lactate. The association between progressively increasing rates of protein catabolism and elevated hepatic glucose production suggests that the negative nitrogen balance characteristic of cancer cachexia[9,10] results from an increased rate of gluconeogenesis from amino acids. We have previously shown that there is an increased rate of gluconeogenesis from amino acids in advanced upper gastrointestinal cancer,[1] and it is possible that the increased availability of substrate may "drive" hepatic glu-

cose production. In addition, there is evidence that the key hepatic gluconeogenic enzymes are induced in cancer-bearing animals.[23]

The growth of malignant tissue results in progressive alterations in host energy/substrate metabolism that are directly proportional to the quantity of malignant tissue present. Carmichael et al[3] have suggested that growing tumor causes the translocation of host protein from skeletal muscle to areas of accelerated protein synthesis, the most prominent of which is the tumor itself. In addition, cancer bearing is also associated with abnormal energy metabolism, and it is clear that in the cancer patient, as opposed to the starving normal volunteer, there is an increased reliance on amino acids as a metabolic fuel, coupled with increasingly inefficient use of glucose. In contrast to other forms of metabolic stress, the response to cancer bearing is "aggressive and progressive" rather than an "all or nothing response" seen in patients suffering from trauma and sepsis.[24]

In summary, this investigation has shown the following:

1. Patients with small tumors usually have only minimal metabolic derangements.
2. The degree of metabolic abnormality is strongly correlated with the quantity of malignant tissue present.
3. Progressive tumor growth is accompanied by an increased rate of glucose cycling to lactate and a corresponding decrease in the percentage of available glucose completely oxidized to carbon dioxide.
4. The increased demand for glucose seen in patients with bulky tumors is met by an increase in hepatic gluconeogenesis, and this is probably partly fueled by amino acids mobilized from muscle.

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