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Letter to the Editor

Correspondence re: R. I. Inculet *et al.* Altered Leucine Metabolism in Noncachectic Sarcoma Patients. Cancer Res., *47:* 4746–4749, 1987.

R. I. Inculet *et al.* in their recent paper (1) assess various proposals for the pathogenesis of cancer cachexia yet omit what is perhaps the most significant, namely, the establishment of a systemic energy-losing cycle in the interplay of tumor glycolysis and host gluconeogenesis, first proposed by me in 1968 (2) and subsequently set forth in clinical and experimental studies (3–6). In regard to this mechanism one of the authors of this paper previously wrote: "One consequence [of increased Cori cycle activity] is an energy-wasting cycle between host and tumor [reference to Gold (3)]. In this situation, the host supplies glucose to the tumor, which it avidly consumes and anaerobically produces lactate. This lactate is released, carried back to the host's liver, and used to resynthesize glucose. The host not only expends the energy needed to resynthesize glucose from lactate, but also 'loses' the energy released by glycolysis of the glucose which the tumor has parasitized" (7).

The recently published prospective, double-blind studies of Harbor-UCLA Medical Center demonstrating normalization of carbohydrate and amino acid components of this mechanism (8–11) by the antigluconeogenic agent hydrazine sulfate, the metabolic investigations of Holroyde and coworkers (12, 13) implicating a high rate of gluconeogenesis to be a "little recognized" factor in the progressive weight loss of some cancer patients, and the large-scale clinical investigations in the Soviet Union (14, 15) demonstrating the beneficial effect of antigluconeogenic therapy have made clear the fundamental position of this mechanism in the production of cancer cachexia.

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Reply

On August 18, 1984, Dr. Gold wrote a letter (1) to the editor of *Lancet* in response to an article by Jeevanandam *et al.* (2). The previous letter was very similar to the letter published above, and the studies that provoked the two letters were again very similar. Both studies (2, 3) investigated protein metabolism in cancer patients using stable isotopes. Neither study quantitated carbohydrate metabolism so neither study referenced Gold's work in the discussion.

In our recent work (3) we formulated a hypothesis for cachexia in sarcoma patients based on observations from our current (3) and prior studies (4). Sarcoma patients demonstrated three changes which were consistent with cachexia: increased whole-body protein turnover; increased resting energy expenditure; and decreased body cell mass (3, 4). We and others have measured carbohydrate changes in rats bearing sarcomas, including increased gluconeogenesis and avid uptake of glucose analogues by tumors (5–7). We agree that abnormal carbohydrate metabolism may occur, but we have not, nor have others, measured it in noncachectic sarcoma patients. Because little information is available about carbohydrate metabolism in sarcoma patients, we did not include it in our hypothesis.

Abnormal carbohydrate metabolism (1), abnormal protein metabolism (2, 3), and abnormal fat metabolism (8, 9) probably all contribute to cancer cachexia in humans. We do not agree that the interplay of tumor glycolysis and host gluconeogenesis is the single most significant cause of human cachexia. It may be part of the syndrome in some patients. In our study (3), we focused on leucine metabolism and found it to be abnormal. We believe that the importance of our study is not the exact pathogenesis of cachexia, but the observation that abnormal protein metabolism occurs prior to any clinical evidence of cachexia (abnormal food intake or weight loss). The closer we and others investigate cancer cachexia, the more it appears that host changes (including abnormal carbohydrate, protein, and fat metabolism) occur early at the beginning of tumor growth. Cancer cachexia includes all these metabolic changes.

Treatment of cachexia should focus on methods to reverse metabolic changes associated with it. Examples are hydrazine sulfate, which blocks gluconeogenesis (10), and insulin, which blocks gluconeogenesis, increases host protein and lipid synthe-

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