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Letter to the Editor

High Plasma Free Tryptophan Levels as a Possible Promoter of Cancer Growth

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In a recent issue of this journal, Rossi-Fanelli *et al.* [1] reported elevated plasma levels of free tryptophan in cancer patients. The elevated levels of free (non-albumin bound) TRP were proposed as being involved in the mechanism for the development of anorexia. While we find this proposed relationship of interest, we question this interpretation and believe that they have overlooked a much more important proposed role for elevated free TRP in cancer, namely, that of a promoter in the neoplastic process itself.

Rossi-Fanelli *et al.* [1] proposed that the elevated plasma free TRP levels result in altered serotoninergic activity in the central nervous system which, in turn, results in anorexia. There are several reasons for questioning this interpretation. First, plasma free TRP levels were significantly higher in both non-anorectic and anorectic patients as compared with controls. Second, it is difficult to predict whether brain TRP and, therefore, brain serotonin levels, would actually be raised or lowered in the anorectic patients. It is debatable as to whether the ratio of plasma *free* TRP or *total* TRP to other large neutral amino acids is the important variable in controlling brain serotonin levels [2]. Whereas plasma free TRP levels were significantly higher, plasma total TRP levels were significantly lower in the anorectic cancer patients as compared with the control subjects.

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Third, in humans, the amount of TRP intake does not seem to influence dietary pattern [2]. Fourth, it is not clear that the plasma free TRP levels have predictive value in terms of cachexia since none of the patients in either the anorectic or non-anorectic groups in Rossi-Fanelli *et al.*'s study had a weight loss of more than 20% of their usual body weight.

While we have reservations about the interpretation placed on the data of Rossi-Fanelli *et al.*, the data themselves are very exciting to us for they suggest an alternative hypothesis which pertains to the propagation of cancerous tissue.

In order for cancerous tissues to maintain their unrestrained rate of growth, rates of protein synthesis must be elevated above normal. Elevated plasma free TRP may be an integral part of the oncogenic process by stimulating protein synthesis. In normal cells, it has been shown that TRP, uniquely among the amino acids, stimulated protein synthesis by altering both transcriptional and translational control of protein synthesis [3]. Evidence for an effect of TRP on the transcriptional control of protein synthesis includes observations of increased DNA-dependent RNA polymerase activity and increased amounts of radiolabelled nuclear RNA in starved rats administered a TRP containing supplement [3]. TRP is thought to alter the translational control of protein synthesis by enhancing the transfer of mRNA from the nucleus to the cytoplasm by binding to receptor sites on the nuclear membrane [3].

We propose as a working hypothesis that in the early stages of cancer, a gene product is synthesized by the cancer cell and transported to the blood-

stream where it alters the binding of TRP to the albumin molecule. The resulting abnormally high level of free TRP causes the entry of TRP into the cancer cell under normal physiological processes, stimulating protein synthesis.

The data of Rossi-Fanelli *et al.* [1] are confirmed by other evidence which indicates that free TRP levels are abnormal in humans and animals with cancer. For example, Krause *et al.* [4] found higher levels of free TRP in patients preoperatively than following tumor resection. We have obtained evidence on a single subject who had elevated plasma levels of free TRP 4 months prior to the diagnosis of cancer. The free TRP in this subject responded abnormally to insulin administration declining towards normal values (unpublished results).

Similar results have been obtained with animals with tumors. Krause *et al.* [5] found higher plasma levels of free TRP in rats with Walker carcinosarcoma as compared with controls. Chance *et al.* [6] obtained similar results in rats with methylcholanthrene-induced sarcoma.

The available evidence, while sparse, suggests that free TRP levels are elevated in organisms with cancer. It is our hypothesis that this is part of a general mechanism of self-stimulation of protein synthesis by the cancerous tissue. Thus, the results of Rossi-Fanelli *et al.* [1] demonstrating high free TRP levels in cancer patients are significant because they reveal a mechanism whereby the cancer cell usurps a normal physiological mechanism to stimulate its own unrestrained growth.

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