

Dietary protein, growth factors, and cancer

Dear Sir:

Fontana et al (1) have shown a strong effect of a low-protein, low-calorie diet and endurance running on circulating concentrations of several growth-promoting hormones and other clinical biomarkers. Their study was well done, and the dietary associations with the clinical biomarkers are internally consistent. Of particular interest is the finding of a substantial depressing effect of a persistently used diet on circulating total and free insulin-like growth factor (IGF). Primarily on this basis, the authors hypothesize that low dietary protein ($\approx 9\%$ of dietary calories) may decrease cancer risk, citing evidence from other studies showing a correlation between circulating IGF-1 and risk of certain cancers.

Although the authors' speculation about a long-term linkage of dietary protein with cancer is most welcome, I wish to note that my research group worked for many years on the hypothesis that dietary protein in excess of $\approx 10\%$ of calories is a risk factor for cancer. Our work began after an observation of an association between primary liver cancer and animal protein consumption in Filipino children (2), which coincided with the findings of a highly supportive experimental animal study in India (3). This led to a series of experimental research investigations and publications over the next 30 y concerning the association of animal protein consumption with primary liver cancer, its mechanisms, and its implications for human cancer at many sites.

We showed that tumor growth in rats was greatly enhanced by diets containing $>10\%$ animal protein (casein) and was completely repressed with either 5% animal protein or $>20\%$ plant protein (4, 5). This protein effect depressed the activity of the major enzyme complex responsible for carcinogen activation (6–10) and for the subsequent and dominant promotion of preneoplastic clones and their sequelae (5), the life-long development of full-blown tumors (4, 11). This effect also existed both for chemically and virally induced cancers and was explained, in 1972 (8), by accelerated cell replication as well as by a variety of cellular and enzymatic mechanisms. We could turn on and off tumor development, both in its early (12) and late (5, 13) stages of development. Shortly after the identification of the IGFs, we observed in hepatitis B virus–transfected mice that the tumor-enhancing effects of dietary protein were closely associated with a greater hepatic synthetic synthesis of IGF-2 but not of IGF-1 (14, 15).

Although we extensively pursued, for many years, the hypothesis that dietary protein enhances tumor development, it was my opinion that the implications of these findings for a broad array of human health and disease conditions were of even more significance. The most important of these implications was the idea that nutrition is an extraordinarily comprehensive phenomenon, involving countless food chemicals and nutrients operating through countless but highly integrated mechanisms affecting countless physiologic and pathological outcomes. For example, it is not only the adverse effects of animal protein, per se, but the combined biologically integrated and consistent effects of animal protein with its dietary covariates that are far more significant, as extensively summarized in a recent trade

book (2). The findings of Fontana et al (1) on dietary protein and IGF-1 production is only one of these countless and highly interdependent cause and effect relations, albeit highly symbolic.

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