



In defense of the surgical cancer patient: Nutrition may be key

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Currently, over 80 percent of cancer patients undergo surgery as the sole or major component of their therapy, and relative to non-cancer patients, appear to be at increased risk for postoperative morbidity and mortality. It has long been held that the act of abdominal surgery, “letting the air inside,” increases the risk for metastatic disease and morbidity through some unknown immunosuppressive event. Thus, it has been proposed that surgical injury in the presence of cancer and in association with malnutrition adversely affects the immune system, increasing the risk of sepsis and progression of metastatic disease.¹

The metabolic response to a major operation is characterized by neuroendocrine stimulation, which is driven by the magnitude of the operative procedure, the host’s physiologic and nutritional state, and the degree of bacterial contamination. Net-negative nitrogen balance of some duration

is the ultimate result. The immunologic impairment affects both specific and nonspecific host defense systems including cell-mediated and humoral immunity. T-cell functions, nonspecific neutrophil functions, and natural killer cell activity, as well as antigen presentation and immunoglobulin synthesis, are all adversely affected. Complement activation and prostanoid production by monocytes are increased following injury. The etiology of perioperative immunosuppression is multifactorial and may be due to the type and degree of operative injury, anesthesia, blood transfusion, the type of malignancy, and the patient’s age and nutritional status. In terms of T-cell mitogenesis, the duration of an operation is the most significant factor adversely affecting T-cell function. The mediators of immune dysfunction relate to a variety of substances such as wound factors, bacterial products, prostanoids, neuroendocrine hormones, and medications.

The macrophage is one component of many different host defense mechanisms. Its functions include phagocytosis and killing of microbes, the presentation of antigen to lymphocytes, and the release of cytokines which serve both autocrine and paracrine functions. Macrophage functions include both effector and immunoregulatory roles. Effector functions may be antibacterial, antitumoral, or part of the tissue modeling process that occurs with wound healing and repair. In the immunoregulatory system, they act in processing antigen and presenting it to T cells, as well as contributing to natural killer cell interactions and other T-cell functions. They produce a variety of products from enzymes to cytokines and to reactive oxygen intermediates, which may cause organ dysfunction when released in large quantities. Experimentally, the magnitude of injury affects the degree and duration of macrophage dysfunction as measured by the cell's ability to kill microorganisms.

In the process of antigen presentation, the macrophage produces a variety of cytokines, which act to stimulate or to suppress certain T-cell functions. Prostaglandin E₂, interleukin (IL)-10, reactive nitrogen intermediates, and transforming growth factor (TGF)-beta for example can direct the type of immunologic response that will occur. Following injury, the T-helper-1 response appears to be diminished, with decreased production of interferon-gamma. In contrast, the T-helper-2 response after injury is markedly increased with greater production of IL-4 and IL-10. In traumatized animals who are infected with *Candida albicans* one week after injury, survival is significantly impaired compared with animals who have not been injured but have been infected with *Candida albicans*.

Another co-existing problem in many cancer patients is that of severe malnutrition, which is the most common form of secondary immunosuppression. Preoperative weight loss is known to correlate with postoperative mortality. In 1988, Windsor and Hill evaluated the relationship of body composition to physiologic function.^{2,3} They noted that body compositional changes in malnutrition included a decrease in lean body mass and a relative increase of extracellular water. Grip strength was decreased. Respiratory function and the ability to cough and clear tracheobronchial secretions were also impaired. In individuals who

underwent GI surgery, the incidence of atelectasis between well-nourished and malnourished patients was approximately the same, 20/41 (well-nourished) and 16/39 (malnourished) patients. Of those patients who developed atelectasis postoperatively, 15 percent of well-nourished patients developed pneumonia, whereas 50 percent of those who were malnourished and had atelectasis developed pneumonia and, as a consequence, had an extended length of hospital stay. Thus, body compositional and physiologic studies correlate with postoperative clinical outcome.

Immunologic impairment in malnutrition includes a decrease in a variety of cellular functions: T-cell mitogenesis, cytotoxic T-cell activity, natural killer (NK) activity, and lysozyme production.⁴ In addition, there is a diminution of delayed cutaneous hypersensitivity, complement production, and immunoglobulin synthesis. These effects are quite similar to the effects of injury. In chronic malnutrition in a murine model, the ability of peritoneal macrophages to produce superoxide and tumor necrosis factor (TNF)-alpha decreases over a period of time.⁵ When animals are placed back on a normal diet, it requires 10 days before there is return to normal function. If this was caused by a simple nutrient deficiency or an enzyme deficiency, one would assume that within 24 hours of ingesting a normal diet, these cellular functions would be improved. Why does it take 10 days to return to normal, and what is the relationship of this time requirement to that which we see in the clinical situation in hospitalized patients receiving nutritional support? Multiple studies suggest that there is a neuroendocrine response to malnutrition that is similar to the neuroendocrine response to injury with increasing catecholamines and cortisol. This neuroendocrine reaction is responsible partly for macrophage or monocyte dysfunction. These results suggest a reason whereby early replenishment with nutrients fails to rapidly return immune function to normal. In summary, biologic cell studies such as macrophage cell functions correlate with body compositional studies, which correlate with clinical outcome.

There appear to be two major etiologies of malnutrition in cancer patients. The first type is that which occurs due to therapy such as radiation treatment or to upper gastrointestinal partial obstruction secondary to the malignancy itself. There

is a second type, which parallels the stage or type of malignancy. The second type produces cancer cachexia in which anorexia, weight loss, and abnormal protein, carbohydrate, and fat metabolic responses occur. Indeed, the host response in cancer cachexia is similar to that which occurs in infection, oxygen toxicity, or after injury.

In terms of protein metabolism, there is an increase in whole body and liver protein synthesis, an increase in skeletal muscle breakdown, and a decrease in skeletal muscle synthesis and nitrogen balance.^{6,7} This leads to a decrease in skeletal muscle strength. In terms of carbohydrate metabolism, there is an increase in glucose production as well as consumption, and there are increases in Cori cycle activity.⁸ There is a decrease in glycogen synthesis and storage and a decrease in the peripheral insulin effect. In terms of lipid metabolism, there is an increase in serum lipid and triglyceride levels, with a decrease in total body fat stores due to an increase in fat breakdown.

These metabolic responses appear to be due not specifically to the tumor itself, but to the reaction of the host to that tumor and the production of a variety of circulating factors such as TNF-alpha, IL-1, IL-6, or interferon gamma, a neuropeptide, leukocyte inhibitory factor, or a newly identified 24 kilodalton proteoglycan. Blocking these products using monoclonal antibodies to these cytokines experimentally in animal models has improved the metabolic pattern that occurs in the tumor-bearing host.^{9,10}

A variety of studies have also demonstrated monocyte or macrophage dysfunction in the tumor-bearing host. These cells show decreased ability to kill microorganisms intercellularly and to migrate and chemotax properly. These effects relate to the autocrine production of prostanoids, IL-10, TGF-beta, and other substances. If one looks histologically at solid tumors, while there may be an infiltration of macrophages within the tumor itself, those macrophages do not seem to work very well. The question is, why?

In experimental studies, we implanted either a B-16 melanoma or a K-1735 melanoma subcutaneously and, after a period of time, harvested peritoneal macrophages. Macrophage-mediated cytotoxicity was dramatically reduced in the tumor-bearing host, in the absence of cachexia, weight loss, injury, or malnutrition. We then went on to

investigate the etiology of this macrophage dysfunction. In Transwell studies, there was a marked decrease in cellular function as measured by macrophage nitrite production. Using melanoma-conditioned media, the ability of macrophages to produce nitrate was similarly decreased. A substance less than 100 kilodaltons appears to be secreted by tumor cells and is at least partially responsible for macrophage dysfunction.

If malnutrition, cancer, and injury often occur together, what is the role of nutritional support in trying to alter biologic or clinical outcome in cancer patients undergoing major operations? In the mid-1960s, Dudrick and others demonstrated that one could promote growth and positive nitrogen balance by providing nutritional support entirely by vein.¹¹ This landmark study changed the way that we would care for patients. Copeland and others demonstrated that there was a very low complication rate with central venous catheterization, particularly when a team approach was used in providing parenteral nutritional support.¹² Early trials demonstrated a variety of efficacious biological outcomes that could be measured in these patients receiving parenteral nutrition. Weight gain, positive nitrogen balance, the ability to increase serum protein levels or improve muscle strength, and substrate kinetics were documented. Early studies also indicated that postoperative outcome was improved in high-risk patients. These retrospective studies translated into a whole series of prospective randomized trials involving patients receiving surgical, medical oncology, and radiation treatment, which looked at the efficacy of parenteral nutritional support.¹³⁻¹⁶ Only a few of these prospective trials demonstrated efficacy in terms of mortality and tumor response to treatment.

We could summarize studies in the 1970s and 1980s by noting that in cancer patients, total parenteral nutrition (TPN) had positive effects on body composition, with gains in body nitrogen and glycogen and a dramatic gain in body fat. Clearly, there was biologic value, but there was not clinical or tumor response improvement in those who received routine intravenous nutritional support. This paradox led to a whole series of trials, which investigated specific nutrients that might alter the host immune response.

Arginine is a nonessential amino acid that has metabolic, hormonal, immunologic, and cytotoxic

effects. Arginine is part of the urea cycle which produces ornithine, citrulline, and reactive nitrogen intermediates.^{17,18} Arginine appears to be an important amino acid, and, under certain conditions, cells require it to adequately function. It has specific cellular immune effects that appear to counteract those effects due to trauma, malnutrition, and the presence of cancer. Thymic size and cellularity are improved and lymphocyte mitogenic responses are increased. There is a substantial increase in macrophage tumor cytotoxicity, NK cell cytotoxicity, and the ability of lymphocytes to produce IL-2 when arginine is administered in controlled laboratory studies. Results from the animal laboratory led to a series of human studies in which enteral diets containing a variety of different substrates were given to patients in controlled trials.¹⁹

In a series of sequential studies at the University of Pennsylvania, 160 patients who were undergoing surgery for upper gastrointestinal malignancies were entered into prospective, randomized trials (see table, this page).^{20,21} The randomization was to study the effects of standard enteral diet versus diets supplemented with arginine, omega-3 fatty acids, and ribonucleic acid (RNA). Those that received supplemented enteral feeding postoperatively had a decrease in infectious and wound complications and a decrease in hospital length of stay compared with the non-supplemented patients. In addition, lymphocyte proliferation diminished at day one after an operation, but returned to normal at day seven in the argin-

ine-supplemented group, whereas lymphocyte proliferation remained decreased in those that received the standard diet. Subsequently, a number of other randomized prospective trials were carried out.²²⁻²⁵ In several of the trials, there was a decrease in infectious and wound complications in supplemented versus control patients, although other trials revealed no clinical outcome benefit to supplemented feedings.

Gianotti and others randomized patients in a blinded placebo-controlled trial to either receive standard nutritional support or a diet supplemented with arginine, omega-3 fatty acids, and glutamine preoperatively and postoperatively.^{26,27} The supplemented patients had a marked decrease in total complications related to infection compared with controls. These studies suggest that patients who are severely malnourished and who are to undergo elective major gastrointestinal (GI) operations should receive some form of enteral support prior to and subsequent to surgical procedures.

Institution of parenteral nutritional support in cancer patients, while adding fat and adding glycogen, does not necessarily increase lean body mass as it should. Thus, the use of hormones has been proposed to combine with nutritional support and improve metabolic and clinical outcome. Growth hormone is a single-chain polypeptide of 191 amino acids that appears to have dose-dependency as to its effects. It requires that nutritional support be provided, particularly carbohydrates, to meet metabolic needs in order to maximize effects. In

Postoperative enteral nutrition after GI surgery

Author	Year	N	Exp.	Control	Infectious complications	
					Exp.	Control
Daly, et al	1992	80	Ent*	Ent	11%	37%
Daly, et al	1995	60	Ent*	Ent	10	43
Kemen, et al	1997	154	Ent*	Ent	22	31
Giannotti, et al	1997	260	Ent*	Ent/TPN	15	23/28
Reynolds, et al	1997	67	Ent	TPN	27	47
Heslin, et al	1997	195	Ent*	IVF	17	19

*Ent: arginine, omega-3 fatty acids ± glutamine

1996, Thoreback and others noted a significant increase in lean body mass when growth hormone and TPN were used in patients after injury.²⁸ The immune effects included an improvement in delayed cutaneous hypersensitivity, a preservation of circulating immunoglobulins, a reduction in wound infections, a decrease in hospital length of stay, and a decrease in postoperative fatigue syndrome. In a subsequent study, growth hormone was used in 10 patients, seven of which were deemed to be normally nourished and three of which were less than 90 percent of their ideal body weight.²⁹ In the former category, there was an increase in nitrogen balance using growth hormone plus TPN compared with controls; but in the malnourished cancer patient, there was no improvement in nitrogen balance.

One of the questions often asked about the use of nutrition in cancer patients relates to the effect on the tumor itself. Animal studies have shown that increased nutrition increases the growth of the tumor. When one utilizes specific nutrients such as glutamine, arginine, or others in animal studies, there are variable results.³⁰ In humans, it is much more difficult to discern the effects of nutrition on tumor growth because patients tend to have tumors that last a much longer period of time. Patients are treated with multiple other therapies in addition to nutritional support. In almost all clinical trials in cancer patients, there has not been a long-term survival difference in those that have received or have not received nutritional support.

In summary, surgical intervention often is required in malnourished cancer patients. Major operation and cancer both independently and together have metabolic and immunosuppressive effects. Parenteral nutrition as a technique is clearly safe. It does have positive biologic effects and it is required for many therapeutic complications that occur following major operation. Enteral nutrition is also safe and has beneficial biologic effects, which are similar to that of parenteral nutrition. It can be used both short-term and long-term and is less costly. In terms of immunonutrition, there are clear-cut biologic effects, but there are disparate results in clinical outcome trials evaluating elective surgery patients; so, further studies will need to be done before we are certain as to their role in the elective surgery patient. Immunosuppressive cellular effects in the

malnourished cancer patient arise from a variety of causes. Even though a patient who undergoes major operation, has malnutrition, or suffers from cancer may have similar immune cellular effects, the causes are different. Cellular responses may be due to nutrient deficiencies, systemic neuroendocrine responses, and circulating immunosuppressive peptides produced either by the tumor or by the host in response to the tumor. Thus, the simple application of nutrition alone will not be sufficient to return all host defense mechanisms to normal. The paradigm in the past has been that if we fill the tank with nutrients and with calories, whatever is left over after fulfilling energy needs can be used for protein synthesis. The newer paradigm suggests that utilization of specific nutrients, utilization of the gastrointestinal tract, utilization of hormones or other substances may be required not only to improve metabolic effects but improve host defense mechanisms as well. □

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