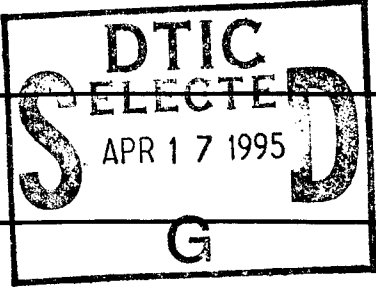


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Chapter 15

NUTRITIONAL SUPPORT OF IRRADIATED INTESTINE

Venkataraman Srinivasan and Andre Dubois

I. NUTRITION AND GASTROINTESTINAL MUCOSA

Eating, digestion, and the presence of food within the intestinal lumen produce a series of complex physiological responses that result in the growth of gastrointestinal (GI) mucosa and the maintenance of gut mass.¹ Pancreaticobiliary secretion and hormones such as insulin and thyroxine as well as trophic hormones are known to substantially influence the GI tract morphology and function. The presence of food in the GI tract directly affects mucosal growth by contributing to villus exfoliation and by providing local nutrition (Figure 1). The indirect effects of the food in the GI tract include neuronal stimulation, increased motility, and release of several gastrointestinal peptides.²

- **Direct effects**
 - Local nutrition
 - Villus desquamation
- **Indirect effects**
 - Secretion ▲
 - Motility ▲
 - Nerve stimulation
 - Release of stimulatory peptides
 - Gastrin
 - Cholecystokinin
 - Secretin
 - Neurotensin
 - Epidermal growth factor
 - Enteroglucagon

Figure 1. Influence of nutrition on GI structure.¹ (Redrawn with permission.)

During starvation the intestinal mass is significantly reduced with a concomitant decrease in the count of proliferating enterocytes, a prolongation of cell cycle and a delay in cell migration.² Similar changes have also been noted during gastrointestinal injury due to stress or surgery. The route of administration and the composition of the nutrients are also important in mucosal morphology.³ Thompson et al. demonstrated that rats given total parenteral nutrition developed significant intestinal hypoplasia.⁴ The activity of diamine oxidase, an intestinal mucosal enzyme which serves as a marker of cellular maturity and integrity, was also significantly reduced in these

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intravenously-fed rats.⁴ Similarly, it has been well documented in humans that long-term parenteral nutrition results in loss of integrity of the GI tract. In contrast, increased food intake during cold acclimatization results in increased food intake and adaptive hyperplastic growth of mucosa in experimental animals.³ Therefore, there appears to be a correlation between the nutrient distribution in the GI tract and its normal structural profile.⁵ Despite the recognition of a role for oral nutrient intake on the maintenance of gastrointestinal mucosa, the precise relationship between individual dietary components and the mucosal integrity has not been clearly established. Studies in jejunectomized rats indicate that intragastric administration of carbohydrates or proteins do not effectively prevent hypoplasia associated with total parenteral nutrition.⁶ However, recent clinical and experimental studies show that administration or feeding of the amino acid glutamine is effective in preventing gastrointestinal injury. Furthermore, patients undergoing postoperative care as well as patients exposed to total body irradiation for bone marrow transplantation exhibit characteristic gastrointestinal injury that is significantly reduced by oral or parenteral administration of glutamine.⁷ Therefore, glutamine is emerging as the single potential nutrient for the prevention of gastrointestinal injury under various experimental conditions. The role of glutamine in radiation-induced gastrointestinal injury will be described later.

The gut is a metabolically active tissue with enormous cellular surface accounted for by mucosal villi and microvilli. The specific nutritional needs of this organ to sustain normal structure and adequate function have been recognized.⁸ The enterocytes and colonocytes covering this surface are in a constant state of rapid proliferation, and their increased demand for nutrients is met by the unique ability of the intestine to draw nutrients from both the blood and the intestinal lumen. Animal studies have shown that the amino acid glutamine acts as the preferred respiratory fuel for the GI tract.⁹ The other major fuels of the GI tract are the ketone bodies β -hydroxybutyrate and acetoacetate. However, use of these fuels appears to be species specific.⁹ The ketone bodies are utilized by the rat enterocytes while the dog enterocytes do not utilize them. Colonocytes on the other hand utilize short chain fatty acids (SCFA), produced by bacterial fermentation of polysaccharides from the dietary fiber as well as from *n*-butyrate, glutamine, and ketone bodies as primary fuels. Structural and functional changes may occur in the colon by depletion of these nutrients.¹⁰

The relationship between functional aspects of the GI tract and nutrition have also been studied extensively. Starvation and malnutrition alter mucosal permeability, resulting in bacterial translocation and generalized bacteremia and death.¹¹ The immunological system of the GI tract, consisting of intestinal lymphocytes, macrophages, secretory IgA, and mesenteric lymph nodes, is critical in the prevention of bacterial translocation. Alverdy et al.¹² have shown that decreased secretion of intestinal IgA is inversely

related to increased bacterial translocation of cecal anaerobes. Furthermore, Ardawi and Newsholme¹³ and Newsholme et al.¹⁴ have demonstrated that lymphocytes and macrophages possess high glutaminase activity and utilize significant amount of glutamine. Finally, it was suggested that glutamine is essential for lymphocyte proliferation in response to antigenic challenge both as a precursor of nucleotide and as a major energy source (Figure 2).

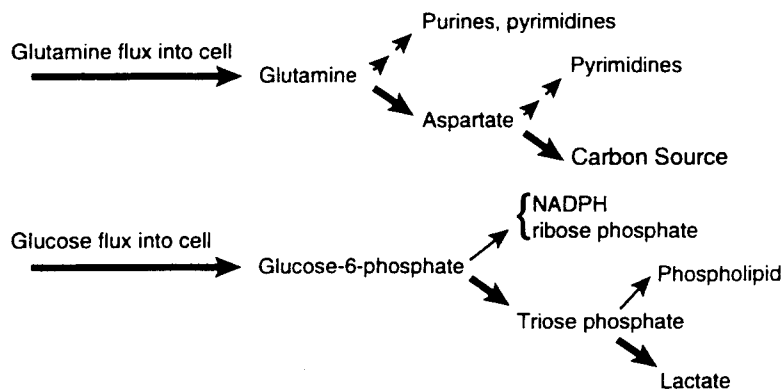


Figure 2. Glutamine utilization as a precursor for nucleotides and as a major energy source.¹⁴ (Redrawn with permission.)

II. RADIATION-INDUCED GI INJURY

The degree of GI injury due to ionizing radiation depends on a variety of conditions. The acute, subacute and chronic effects of ionizing radiation on the digestive tract appear in a manner that is both dose- and time-dependent.^{15,16} The relationship between dose-rate, fractionation, type of radiation with different linear energy transfer (LET) potential, and their influence on GI damage has been described.¹⁷ Thus, neutron radiation is more destructive to intestinal cells than similar quantities of gamma photon irradiation. As discussed by Gunter-Smith elsewhere in this volume (Chapter 11), radiation causes early functional alterations of electrolytes transport¹⁸ as well as subsequent structural damage. The GI injury that may appear one to three weeks after radiation is characterized by diminished replacement of epithelial cells that, when combined with normal sloughing of differentiated cells, leads to the depletion of mature intestinal surface epithelial cells. Such a subacute injury results in the breakdown of the intestinal luminal barrier and may be responsible in part for radiation-induced lethality. The alterations in the crypts and villi have been used as an index to assess GI damage following ionizing radiation. More recently, scanning and transmission electron microscopy have delineated the ultrastructural changes observed in the GI tract of animals exposed to X-radiation, either alone, or in combination with hyperthermia and neutron irradiation (Figure 3).^{19,20}

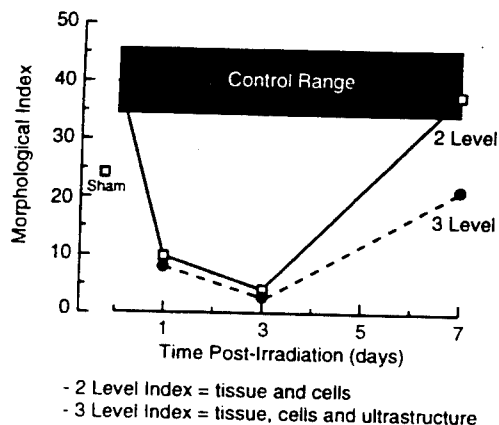


Figure 3. Multiple morphometric index range: summary of tissue, cell and ultrastructural scores.²⁰

Thus, 20, 65, and 90% of all proliferating cells were inhibited after 2.5 Gy, 8 Gy, and 12 Gy of gamma irradiation, respectively.²⁰ In addition, different cell types and tissues of the mouse small intestine were modified by ionizing radiation (Figure 3, Table 1). Tissue indices showed a drop at day 1 and 3 and partial recovery of nerve cells and epithelial cells (not shown) while the muscle score continued to drop up to at least the last time point. Therefore, the electron microscopic studies²⁰ suggest that the conventional crypt/microcolony assay utilized by several investigators to describe changes in GI due to ionizing radiation does not totally describe the fine alterations induced by ionizing radiation in different cell types of the GI tract (Table 1).

Table 1. Comparison of Tissue Scores.²⁰

Type	Day 1	Day 3	Day 7
Villus scores	↓	↓	↓↓
Muscle 3 level	↓	↓↓	↓↓↓
Nerve 3 level	↓*	↓↓*	↓↓↓
Cryptal cell-separation	↓	↓↓	↓↓↓
Connective tissue-vacuoles	↓	↓↓	↓↓↓

III. PROTECTION AGAINST RADIATION-INDUCED GI DAMAGE: ROLE OF NUTRITION

As discussed in Chapters 13 and 14, free radical scavengers such as WR-2721 as well as prostaglandins have been shown to minimize radiation-induced damage to stem cells in the crypts of the GI tract.²¹ In this chapter, we will focus on the role of nutrients in GI radioprotection. Antioxidant nutrients such as vitamin E and selenomethionine have been shown to be effective radioprotectors when given either alone or in combination with phosphorothioate (WR compounds) radioprotectors such as WR-3689 and WR-2721.^{22,23} Radioprotection by other nutrients such as selenium,²³ copper,²⁴ zinc,²⁵ and vitamin A²⁶ have also been demonstrated in experimental animals, whereas vitamin C has been shown to have no radioprotective characteristics *in vivo*.²⁷ Furthermore, injection of ascorbate together with cysteamine (β -mercaptoethylamin or MEA) partially reversed the radioprotective action of MEA and suppressed the action of MEA on RNA synthesis in bone marrow cells in mice.²⁸ The concept of combining different radioprotective compounds in achieving a better protection has been considered by many investigators and has been reviewed by Weiss et al.²⁹ For example, significant radioprotection was achieved in rodents by using a combination of non-nutrient compounds: a low dose of WR-3689 (50 mg/kg), a dose with minimal behavioral toxicity, plus eicosanoids (misoprostol and iloprost) and the immunomodulator 3D-MPL.³⁰

In addition, various lines of evidence indicate that the antioxidant nutrients may exert their radioprotective effect by influencing the immune system in addition to acting as radical scavengers. We have shown, for example, that vitamin E and WR-2721 significantly reversed immunosuppression induced by ionizing radiation as measured by delayed hypersensitivity response reflecting a T lymphocyte function.³¹ Furthermore, Roy and Petrella³² determined serum hemagglutination titers (HA) to sheep red blood cells in mice subjected to irradiation and maintained on vitamin E deficient diets for 8 weeks. Vitamin E injection increased IgG titers and partially reversed radiation-induced depression of lymphocyte response.

This radioprotection against the hemopoietic system may be used as a model for GI radioprotection. Paulus et al. compared the hematopoietic stem cells to the stem cell equivalent (crypts) of the digestive tract, demonstrating that the regulatory processes were very similar in the two systems.³³ More recently GI mucosal injury due to oxidative stress in experimental animals was shown to be prevented by vitamin E administration.³⁴ Further, Empey et al.³⁵ have shown in their experiments with local irradiation of the abdomen that vitamin E administration preserved the GI structure.

In recent years, the importance of diet therapy in the treatment of gastrointestinal diseases has become better defined.³⁶ A number of elemental diets containing predigested proteins and various amounts of

carbohydrates and fats have been shown to alleviate various clinical conditions.³⁷ However, hypoplasia of the small bowel mucosa and loss in functional integrity has been noted during prolonged feeding of an elemental diet.³⁸ Further, increased bacterial translocation have also been documented. Recent evidence indicates that the increased bacterial translocation attributable to elemental diet therapy can be controlled by incorporation of dietary fiber or by treatment with hormones such as bombesin or somatostatin.³⁹

The effectiveness of elemental diet protection against radiation-induced intestinal injury was studied in experimental animals. It was observed that elemental diet facilitated mucosal healing by maintenance of glycocalyx and its normal content of disaccharides.⁴⁰ However, the nutritional management of patients with chronic radiation enteropathy depends on a variety of factors such as the degree of damage, the functionality, the region affected, etc. Many metabolic changes such as malabsorption of protein, fat soluble vitamins and micronutrients might ensue after irradiation. Clinical studies reveal that continuous feeding of elemental diets starting three days before irradiation and continued after irradiation significantly minimized mucosal damage attributable to radiation.⁴¹ Furthermore, other investigators have also shown the beneficiary effects of elemental diet in the prevention of acute and delayed radiation enteropathy as well as in Crohn's disease.⁴² To summarize, the approach of using elemental diets to minimize or prevent GI damage caused by various agents such as chemicals or ionizing radiation appears promising and should be pursued in greater detail.

IV. ROLE OF GLUTAMINE IN THE PROTECTION AGAINST RADIATION-INDUCED GI DAMAGE

The GI tract is the major organ of glutamine utilization. Glutamine is taken up by the epithelial cells that line the intestinal villi. There are dietary and arterial supplies of glutamine to the intestinal mucosa. Historically, the role of glutamine in ammonia metabolism was first demonstrated in kidneys by Sir Hans Krebs in 1935. Glutamine was shown to be essential for mammalian cells in culture by Eagle in 1955.

Studies in rats have shown that the rate of utilization of glutamine in the jejunum is comparable when the glutamine is derived from the lumen or from the arterial blood.⁴³ After a protein meal, the dietary source of glutamine is in the form of oligopeptides. Metabolic studies indicate that glutamine dipeptide is absorbed as such and is then hydrolyzed intracellularly.⁴⁴ Further, parenteral administration of either glutamine or glutamine dipeptide brings about similar metabolic effects.⁴⁵

The importance of dietary glutamine in reversing the hypoplasia of GI tract in glutamine-deficient rats has been established.⁴⁶ Further, glutamine feeding resulted in adaptive hyperplasia after partial intestinal resection in experimental animals.⁵⁰ The mucosal atrophy observed in experimental

animals on total parenteral nutrition solution correlates with the deficiency of glutamine. In addition, changes in tissue glutamine concentrations have also been shown to correlate with net protein turnover. The mechanism of this effect of glutamine is unclear. Recent in vitro data suggest that, although epidermal growth factor (EGF) directly activates the early growth response genes that encode nuclear transcription factors, glutamine is a necessary cofactor for the actual synthesis of nucleic acids and proteins.⁴⁷ Glutamine also plays an important role in regulating the metabolism during the catabolic state. It is released from muscle and is utilized by the kidney, macrophages, and lymphocytes as well as by intestinal mucosal cells. Recent studies have shown that glutamine may be a conditionally essential nutrient and that its requirement may increase two- to threefold during postoperative conditions.⁴⁸ During stress and organ failure, the GI tract is severely challenged, and its support requires particular attention. Several authors have compared the protective effect of arginine, xylitol, growth hormone, glutamine, and branched chain amino acids.¹⁴ They found that glutamine appeared to be the most effective agent in protecting the GI tract. Glutamine supplementation has also been shown to be beneficial in rats during septic shock⁴⁹ and in dogs after small bowel resection.⁵⁰ Therefore, glutamine or glutamine peptides appear to play an important role in GI mucosal integrity.

The beneficial effect of glutamine in combination with an elemental diet was demonstrated in the sarcoma rat model.⁵¹ In this model, the toxicity of methotrexate was reduced, and its tumoricidal effectiveness was enhanced by glutamine administration. In contrast, Xu et al.⁵² were unable to demonstrate the effectiveness of glutamine in reversing the increased bacterial translocation observed after prolonged feeding of an elemental diet. Further, these authors were unable to demonstrate the beneficial effect of glutamine on immunosuppression observed after feeding elemental diet.

Souba et al.⁵³ demonstrated the role of nutrients such as glutamine in preventing subacute GI tissue damage due to ionizing radiation. Bacterial translocation was studied in rats exposed to 10 Gy X-radiation (dose rate 2.27 Gy/min) to the abdomen, with the thorax, head, gonads and extremities shielded. Glutamine was provided through drinking water. The animals receiving glutamine showed lower culture positive lymph nodes (20%) as compared to a greater culture positive lymph nodes (89%) in unsupplemented animals. The predominance of gram negative rods (*Escherichia coli*) in the culture positive lymph nodes indicated that the bacterial flora of the gut was involved in translocation and that such a translocation was inhibited by glutamine administration. The protective effect of oral glutamine after abdominal radiation (10 Gy) was studied in experimental animals.⁵³ The survival rate was 100% in animals receiving glutamine when compared with 45% in animals receiving glycine. Glutamine ingestion diminished bloody diarrhea and the incidence of bowel perforation. Another study evaluated the

effect of glutamine along with elemental diet on the intestinal mucosal growth and function.⁵⁴ 10 Gy of X-irradiation were delivered to the abdomen of rats which were given 4 days of either glutamine-enriched or glutamine-free elemental diet. After irradiation, all animals received a glutamine-free diet. Four days later, animals fed the glutamine-enriched elemental diet had a significant increase in the number and height of jejunal villi compared to animals fed the glutamine-free diet. This protection of the small bowel mucosa appeared to be mediated by a glutamine-induced increase in crypt cell proliferation. Recently, Klimberg et al.⁵⁵ have shown that glutamine given with elemental diet before radiation significantly increased the jejunal villous number, villous height, and number of metaphase mitosis per crypt.

Nutritional support has been considered to play a key role in preventing metabolic failure.⁵⁶ The catabolic states resulting from trauma, sepsis or surgery are associated with net skeletal muscle breakdown. The positive role of glutamine-enriched parenteral nutrition in improving nitrogen balance has been documented in postoperative patients^{7,57} (Table 2). The purpose of these studies was to improve nitrogen retention and reduce hospital stay in patients who undergo radiotherapy for bone marrow transplantation. Results revealed that nutrient intake was comparable between control and glutamine-supplemented groups. However, nitrogen balance was improved significantly in the glutamine-treated group. The clinical infection rate was also significantly reduced although the number of antibiotic days was similar. The hospital stay was reduced from an average of 36 days in the control group to 29 days in the glutamine-supplemented group. Recently, Schloerb and Amare⁵⁸ following the same protocol of glutamine administration in BMT patients subjected to radiotherapy confirmed the earlier observations of Zeigler et al.⁷. A significant reduction in days of hospitalization was again noted in patients on glutamine-supplemented total parenteral nutrition. Glutamine supplementation also benefitted patients with solid tumors undergoing BMT. However, hospitalized patients receiving standard total parenteral nutrition for reasons other than bone marrow transplantation did not significantly benefit from incorporation of glutamine in the parenteral solution.⁵⁸ These results suggest that, although the potential benefits induced by glutamine administration in TPN patients are apparent, additional studies are required to establish the conditions wherein the efficacy of glutamine is optimal.

Thus experimental and clinical evidence clearly demonstrates the beneficial effects of glutamine administration on GI protection under various conditions such as after exposure to ionizing radiation or after certain chemical or drug therapy. However, glutamine may not be effective under certain conditions as has been noted in the clinic.⁴⁵ Scott and Moellman⁵⁹ also observed that intravenous glutamine administration did not accelerate small bowel mucosal

indwelling catheters were inserted in the jugular veins of rats which subsequently received 10 Gy of abdominal irradiation. Isonitrogenous and isocaloric intravenous total parenteral nutrition containing either 0 or 2% glutamine was given for 5 days postirradiation. Irradiation caused a similar 40% decrement in both the villous height and the DNA content of intestinal segments in the two groups of animals.

Table 2.
Effect of Parenteral Nutrition with or without Glutamine on Various Parameters in Patients Subjected to Total Body Radiation for Bone Marrow Transplantation (After Ziegler et al.⁷)

Variable	Standard Parenteral	Glutamine Supplemented
Number	21	24
Hospital stay	36 days	29 days*
Nitrogen bal	-4.2 g/D	-1.4 g/D
Total N bal	-29.6 g/7 D	-9.7 g/7 D*
No. positive culture	1	10*
+ stool culture	16	10*
+ throat culture	18	13*
Clin. infection	9	3
Total antibiotic	15 days	13 days

*Significantly different from standard

These contradictory observations indicate that the route of administration and the experimental conditions appear to modify the radioprotective effect exerted by glutamine on the GI tract. Scott and Moellman⁵⁹ showed that i.v. glutamine was ineffective in experimental conditions involving combined injury of radiation and surgery, while both experimental and clinical studies have demonstrated the beneficial effects of dietary glutamine.⁵⁴ Therefore it appears that additional investigations will be required to clarify the role of glutamine in the protection of GI structure and function during stress.

V. CONCLUSIONS

The role of nutrition on the GI structure and function has been clearly established by several investigators although in many instances it has not been possible to identify specific changes attributable to individual nutrients. Electron microscopic studies reveal that there are microscopic changes in different cell types of the intestine which should be taken into account while evaluating the alterations to the GI tract after exposure to ionizing radiation.

There is some indication that nutritional supplements may provide a low risk, cost effective intervention that could limit the adverse effects of ionizing radiation on the gut and reduce mortality due to ionizing radiation. Further, experimental and clinical studies indicate that the amino acid glutamine may be a promising nutrient in protecting the GI tract from the ill-effects of ionizing radiation. In many tissues, glutamine appears to serve as an ammonia scavenger and as a nitrogen donor for the biosynthesis of a number of important compounds such as nucleotides, aminosugars and amino acids. Recent clinical studies have aroused considerable interest in the role of glutamine in critical care situations. The results of parenteral administration of glutamine have shown the beneficial role of glutamine against the mucosal atrophy generally associated with total parenteral nutrition.^{60,61} Finally, a recent review of the current status of glutamine in hospitalized patients indicates that glutamine supplementation may become a common practice in the near future.⁶²

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