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Effects Of Nuclear Weapons On The Gastrointestinal System

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Introduction

When physicians think of the effects of nuclear weapons upon the human body, there is a natural tendency to focus on the radiation aspects. Whilst this is undoubtedly important, it should be remembered that blast and thermal radiation will be more immediately debilitating, and that debility may increase radiation exposure (1).

For a low altitude atmospheric detonation of a moderate sized weapon in the kiloton range, the energy is distributed roughly as follows (1):

- 50% as blast;
- 35% as thermal radiation; made up of a wide range of the electromagnetic spectrum, including infrared, visible, and ultraviolet light and some soft X-ray emitted at the time of the explosion; 15% as nuclear radiation; including 5% as initial ionizing radiation consisting chiefly of neutrons and gamma rays emitted within the first minute after detonation, and 10% as residual nuclear radiation. Residual nuclear radiation is the hazard in fallout.

The radii of these effects are illustrated in Table 1. Thermal radiation will not greatly affect the gut, but blast injury and nuclear radiation will both have profound effects upon the gastrointestinal system.

Table 1. Radii of effects Nuclear Weapons (From NATO Handbook On The Medical Aspects of NBC Defensive Operations).

Effect	1 Kt	10 Kt	100 Kt	1000 Kt
Ionising Radiation (50% latent lethality)	800m	110m	1600m	3200m
Ionising Radiation (50% immediate transient ineffectiveness)	600m	950m	1400m	2900m
Blast (50% casualties)	140m	360m	860m	3100m
Thermal (50% casualties with 2nd degree burns under uniform)	369m	110m	3190m	8020m

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Pathophysiology of Blast Injury

In passing through the atmosphere, the blast wave imparts its energy to the molecules of the surrounding air, setting them into motion in the direction of the advancing shock front. The motion of these air molecules is manifested as severe transient winds, known as "blast winds," which accompany the blast wave. The destructive force associated with these winds is proportional to the square of their velocity and is measured in terms of dynamic pressure. These winds constitute decay forces which produce a large number of missiles and tumbling of objects. These dynamic forces are highly destructive (1).

Most of the material damage caused by a nuclear air burst is caused by a combination of the high static overpressures and the dynamic or blast wind pressures. The relatively long duration of the compression phase of the blast wave is also significant, in that structures weakened by the initial impact of the wave front are literally torn apart by the forces and pressures which follow. The compression and drag force phases together may last several seconds or longer, during which, forces many times greater than those in the strongest hurricane are present. These persist even through the negative phase of a blast wave when a partial vacuum is present because of the violent displacement of air (1).

Primary pulmonary and intestinal blast injuries are the most significant lesions; lung contusions, pneumothorax and pulmonary oedema can develop rapidly. Primary intestinal blast injuries usually present as a perforated viscus or gastrointestinal bleeding and the treatment of such injuries is not dissimilar to that of any other cause of abdominal trauma (2). Major morbidity or mortality among immediate survivors is caused by delayed perforation of intestinal mural contusions. Laparotomy remains the only way to reliably assess these contusions in the small bowel, as the development of ileus prevents the use of such modalities as Video Capsule Endoscopy. Previous studies have suggested that small bowel and colonic contusions larger than 10 mm in diameter are at high risk (3-7). A further study subjected large white pigs to blast injury and found that some 16 per cent of small bowel and 12 per cent of colonic contusions were at high risk of late perforation. Small bowel contusions larger than 15 mm in diameter

had a worse histological grading than those smaller than 15 mm. Contusions that extended over more than half the bowel circumference and those affecting the mesenteric border were more severe injuries. Colonic contusions larger than 20 mm in diameter had a worse histological grading than smaller ones. Confluent, rather than diffuse, colonic contusions were more severe injuries (8). If these experimental guidelines were adopted and small bowel contusions less than 15 mm in diameter and colonic contusions smaller than 20 mm were left alone, the number of small bowel contusions requiring excision would be reduced by one-quarter and colonic contusions by two-thirds (8). Experiments looking at using protective equipment materials to reduce the severity of blast injury in the gut have shown some promising results in the small bowel, using a combination of two densities of glass-reinforced plastic plate and Plastazote foam (GRP/PZ), but unfortunately this had no impact on large bowel lesions (9).

Pathophysiology of Radiation Injury

A typical time course for events after radiation exposure is as follows:

Prodromal Phase: The prodrome is characterized by the relatively rapid onset of nausea, vomiting, and malaise. This is a nonspecific clinical response to acute radiation exposure. An early onset of symptoms in the absence of associated trauma suggests a large radiation exposure. Radiogenic vomiting may easily be confused with psychogenic vomiting that often results from stress and realistic fear reactions. Use of oral antiemetics, such as Granisetron and Ondansetron, may be indicated (10).

Latent Period: Following recovery from the prodromal phase, the exposed individual will be relatively symptom free. The length of this phase varies with the dose. The latent phase is longest preceding the bone-marrow depression of the haemopoietic syndrome and may vary between 2 and 6 weeks. The latent period is somewhat shorter prior to the gastrointestinal syndrome, lasting from a few days to a week. It is shortest of all, preceding the neurovascular syndrome, lasting only a matter of hours. These times are exceedingly variable and may be modified by the presence of other disease or injury.

Manifest Illness: This phase presents with the clinical symptoms associated with the major organ system injured (marrow, intestinal and neurovascular).

At sufficiently high doses, cell necrosis occurs. High but sub-lethal doses may interfere with cell proliferation by decreasing the rate of mitosis, by slowing DNA synthesis, or by causing cells to become polyploid. In tissues that normally undergo continual renewal (such as bowel epithelium, bone marrow and gonads) radiation produces dose-dependent progressive hypoplasia, atrophy, and eventually fibrosis. Some cells, injured but still capable of mitosis, may pass through one or two generative cycles, producing abnormal progeny (e.g. giant metamyelocytes, hypersegmented neutrophils) before dying (11).

The somatic and genetic effects of doses < 100 mGy are usually estimated by linear extrapolation from studies of higher doses, because few objective data on the effects of very low doses are available. Some researchers postulate a threshold effect, which is not fully understood (11).

Acute Radiation Syndromes can be divided into cerebral, polmonary haemopoietic and gastrointestinal depending on dose, dose rate, body area, and time after exposure.

Gastrointestinal Radiation Syndrome

This is produced by whole-body doses of >= 4 Gy. Thus, it is always found in association with the haematological syndrome. It is characterized by:

- Nausea
- Vomiting
- Malabsorption & Diarrhoea
- Ileus
- Fluid & Electrolyte shifts
- Gastrointestinal Bleeding
- Bacterial translocation & sepsis

Pathophysiology

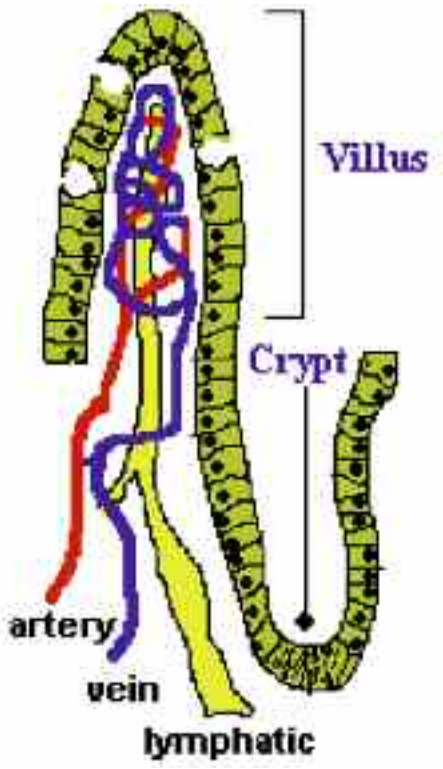

Fig 1. The Structure of Small Intestinal Mucosa.

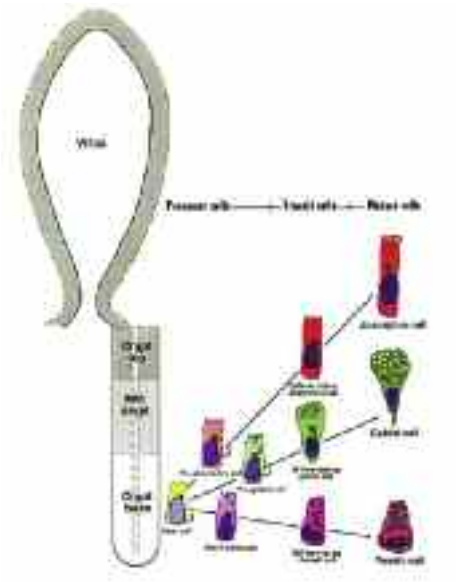

Fig 2. Maturation of Small Intestinal Stem Cells

The mucosa of the small intestine is divided into villi (Figure 1), projections into the lumen covered predominantly with mature absorptive enterocytes, and crypts which are moat-like invaginations of the epithelium around the villi, and are lined largely with younger epithelial cells which are involved primarily in secretion. Toward the base of the crypts are stem cells, which continually divide and provide the source of all the epithelial cells in the crypts and on the villi. The four cell renewal compartments are: stem cell and proliferating cell compartment, maturation compartment, functional compartment, and the extrusion zone. Stem cells and proliferating cells move from crypts into a maturing only compartment at the neck of the crypts and base of the villi. Functionally mature epithelial cells then migrate up the villus wall and are extruded at the villus tip. The overall transit time from stem cell to extrusion on the villus for humans is estimated as being 7 to 8 days (Figure 2). It was thought that all radiation-induced cell death was induced as a direct effect of radiation breaking DNA and leading to apoptosis, but there have been recent papers suggesting that death of epithelial stem cells in gut may be a secondary event resulting from the demise of the endothelial cells on which they depend (11,12). Emerging data suggest that radiation acts directly on the plasma membrane of several cell types, activating acid sphingomyelinase, which generates ceramide by enzymatic hydrolysis of sphingomyelin (13). Ceramide then acts as a second messenger in initiating an apoptotic response via the mitochondrial system. Radiation-induced DNA damage can also initiate ceramide generation by activation of mitochondrial ceramide synthase and de novo synthesis of ceramide (13).

Hyporesponsiveness of the intestinal epithelium to secretagogues also occurs in different models of intestinal injury, including radiation enteropathy. While this impairment of barrier function has been linked to increased inducible nitric oxide synthase (iNOS) activity, the cellular target of nitric oxide (NO) in this phenomenon is not known, although recent studies suggest that some isoforms of adenylate cyclase are inhibited by NO. A recent study has also shown NO inhibitable isoforms of adenylate cyclase are expressed in mouse and human secretory colonic epithelia, and appear to be the target of radiation induced NO to reduce the responsiveness to cAMP dependent secretagogues (14). Cytokines such as transforming growth factor beta, interleukin 6 and interferon appear to increase the gut lethality of radiation, whereas cytokines such as interleukin 1, tumor necrosis factor, stem cell factor and interleukin 12 protect mice from radiation lethality when given before irradiation (15). The actions of ceramide, NO and cytokines give some insight into the mechanisms of gut injury by radiation, and may offer some avenues for prophylaxis or therapy in the future, but to date there are no useful agents.

Once radiation damage occurs in the gut, there is tissue necrosis, progressive atrophy of GI mucosa and a breakdown in the mucosal barrier which leads to haemorrhage and massive loss of plasma into the intestine. The loss of mucosal barrier also leads to bacterial translocation and sepsis (11). These events normally occur within 1 to 2 weeks after irradiation.

Treatment

The medical management of radiation and combined injuries to the gut can be divided into three stages: triage, emergency care, and definitive care (10). During triage, patients are prioritised and rendered immediate lifesaving care. From the gastrointestinal viewpoint this is likely to involve fluid resuscitation for those patients suffering from blast injury. Emergency care includes therapeutics and diagnostics necessary during the first 12 to 24 hours and with regards to the gut again primarily relates to blast injury. Continuing fluid resuscitation may be needed. Laparotomy may be required to remove missiles generated by the blast wave, establish haemostasis or to repair a perforated viscus (1,7). Use of oral antiemetics, such as Granisetron and Ondansetron, may be indicated to treat radiation induced nausea (1,10,16).

At the level of definitive care, management needs to address both blast wave and radiation syndrome treatment. Regarding blast injury, a laparotomy may be needed to prevent or treat the late

perforation of intestinal mural contusions (8). Treatment of an emerging gastrointestinal radiation syndrome will involve the following steps:

Fluid Resuscitation

As the gut mucosal barrier breaks down, there will be massive fluid shift into the gut and bacterial translocation. This may develop into frank septic shock and will require aggressive fluid resuscitation (16).

Isolation & reverse barrier nursing

The patient will become neutropenic as a haemopoietic syndrome supervenes or as septic shock from bacterial translocation overwhelms the failing haemopoiesis.

Prophylactic selective gut decontamination

This aims to suppress aerobes but preserve anaerobes and so reduce bacterial translocation. The rationale for this is that life-threatening, gram-negative bacterial infections are universal among neutropenic patients, but the prevalence of life-threatening, gram-positive bacterial infections varies greatly among institutions (10). Ciprofloxacin has been shown to have good activity against gram-negative anaerobes (17) and would be a reasonable first line choice.

Treatment of haemopoietic syndrome

Gastrointestinal death after total body irradiation is influenced by bone marrow depletion (18). The detailed management of the haemopoietic syndrome is covered elsewhere in this issue. It should be noted that mouse studies have shown that administration of Granulocyte Colony Stimulating Factor unexpectedly increased the gut bacterial translocation in 8 Gy-irradiated mice (19). The same study showed that combined treatment with G-CSF and OK-432 (a pharmaceutical preparation of low-virulence Streptococcus pyogenes) decreased bacterial translocation and prevented death (19). Further studies are needed in this area.

Treatment of established infections

Once a patient develops overt infection then the organism should be identified and appropriate antibiotic therapy commenced. As previously mentioned, these patients will become neutropenic as haemopoietic syndrome supervenes and antibiotic regimen may need to be revised accordingly.

Early oral feeding

Once ileus has resolved, early oral feeding has been shown to stimulate villi growth and prevent atrophy. Active mucosa helps to limit translocation of bacteria and a stimulated immune system clears limited volume of translocated bacteria. These effects are lost with parenteral nutrition. A study performed in rats has shown that dietary arginine supplementation enhanced bacterial clearance from mesenteric lymph nodes and also improved intestinal mucosal recovery following abdominal irradiation (20) but data are too sparse to recommend dietary arginine supplementation in humans at present.

Follow Up

Even performing a simple abdominal X-ray carries a risk of inducing cancer in 1:300,000 to 1:800,000 cases (21), so it will come as no surprise that survivors of nuclear irradiation have an increased cancer risk in the small and large bowel. Large bowel tumours appear to follow the adenoma to carcinoma route (22-24), and in the small bowel there have been descriptions of radiation induced angiosarcomas (25,26) and leiomyosarcomas (27,28).

Precise figures for the increased cancer risk are somewhat difficult to find. A review of therapeutic pelvic irradiation found several reports of rectal carcinoma. The average interval between irradiation and diagnosis of the rectal cancer was 15.2 years, the range being from one year two months to 33 years (23). Continuing studies of Hiroshima survivors found 347 deaths from bowel cancer, an excess of 23 deaths when compared to a non-irradiated control group (29-31). The excess solid cancer risks appeared to be linear in dose even for doses in the 0 to 150 mSv range. While excess rates for radiation-related cancers increased throughout the study period, a new finding was that relative risks declined with increasing attained age, as well as being highest for those exposed as children. A useful representative value was that for those exposed at age 30 the solid cancer risk was elevated by 47% per sievert at age 70 (31).

Survivors of nuclear irradiation may benefit from a screening program of colonoscopy to detect and remove adenomas in the colon, but as yet no guidelines exist and there is no published data on whether it would be clinically worthwhile and cost effective.

Summary

Nuclear weapons have both blast injury and radiation effects on the gut. The successful management of survivors requires a combined medical and surgical approach, and is likely to need at least 5 – 6 weeks of in-patient therapy for gastrointestinal radiation syndrome. It should be remembered that the haemopoietic syndrome is an invariable companion. The chance of survival for people with acute radiation syndrome decreases with increasing radiation dose. Most people who do not recover from ARS will die within a few weeks of exposure. The cause of death in most cases is the destruction of the bone marrow, which results in infections and internal bleeding. For the survivors, the recovery process may last from several weeks up to 2 years. Long term survivors face an increased solid cancer risk of approximately 47% per sievert.

References

1. NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B). United States Departments of the Army, the Navy and the Air Force, 1996.
2. Cripps NP, Glover MA, Guy RJ. The pathophysiology of primary blast injury and its implications for treatment. Part II: The auditory structures and abdomen. [Review] [125 refs]. Journal of the *Royal Naval Medical Service* 1999; **85**(1):13-24.
3. Flint LM, Malangoni MA. Abdominal Injuries. In: Richardson JD, Polk HC, Flint LH, editors. Trauma: Clinical Care and Pathophysiology. Chicago: Year Book Medical, 1987.
4. Johansson L, Norrby K, Nystrom PO, Lennquist S. Intestinal intramural haemorrhage after abdominal missile trauma--clinical classification and prognosis. *Acta Chir Scand* 1984; **150**(1):51-56.
5. Paterson-Brown S, Francis N, Whawell S, Cooper GJ, Dudley HA. Prediction of the delayed complications of intestinal and mesenteric injuries following experimental blunt abdominal trauma. *Br J Surg* 1990; **77(6)**:648-651.
6. Tatic V, Ignjatovic D, Jevtic M, Jovanovic M, Draskovic M, Durdevic D. Morphologic characteristics of primary nonperforative intestinal blast injuries in rats and their evolution to secondary perforations. *J Trauma* 1996; **40**(3 Suppl):S94-S99.
7. Thal ER. Abdominal Trauma. In: Shires GT, editor. Principles of Trauma Care. New York: McGraw Hill, 1985: 291-344.
8. Cripps NP, Cooper GJ. Risk of late perforation in intestinal contusions caused by explosive blast. *British Journal of Surgery* 1997; **84**(9):1298-1303.
9. Cripps NP, Cooper GJ. The influence of personal blast protection on the distribution and severity of primary blast gut injury. *Journal of Trauma-Injury Infection & Critical Care* 1996; **40**(3 Suppl):S206-S211.
10. Medical Management of Radiological Casualties. Bethesda: Military Medical Operations Office, 1999.
11. Radiation Reactions & Injuries. In: Beers MH, Berkow R, editors. The Merck Manual of Diagnosis and Therapy. Merck & Company, Incorporated, 1999.
12. Paris F, Fuks Z, Kang A, Capodieci P, Juan G, Ehleiter D et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice.[see comment]. *Science* 2001; **293**(5528):293-297.
13. Kolesnick R, Fuks Z. Radiation and ceramide-induced apoptosis. *Oncogene* 2003; **22**(37):5897-5906.
14. Freeman SL, MacNaughton WK. Nitric oxide inhibitable isoforms of adenylate cyclase mediate epithelial secretory dysfunction following exposure to ionising radiation. *Gut* 2004; **53**(2):214-221.
15. Neta R. Modulation of radiation damage by cytokines. *Stem Cells* 1997; **15** Suppl 2:87-94.
16. Advances in the Treatment of Radiation Injuries. Oxford: Elselvier Science, 1996.
17. Rudin JE, Norden CW, Shinners EM. In vitro activity of ciprofloxacin against aerobic gram-negative bacteria. *Antimicrob Agents Chemother* 1984; **26**(4):597-598.
18. Terry NH, Travis EL. The influence of bone marrow depletion on intestinal radiation damage. *Int J Radiat Oncol Biol Phys* 1989; **17**(3):569-573.
19. Nose M, Uzawa A, Ogyu T, Suzuki G. OK-432 reduces mortality and bacterial translocation in irradiated and granulocyte-colony stimulating factor (G-CSF)-treated mice. *J Radiat Res (Tokyo)* 2001; **42**(2):191-200.
20. Gurbuz AT, Kunzelman J, Ratzer EE. Supplemental dietary arginine accelerates intestinal mucosal regeneration and enhances bacterial clearance following radiation enteritis in rats. *J Surg Res* 1998; **74**(2):149-154.
21. Vogel H. [Radiation-risk in roentgendiagnostic of the gastro-intestinal tract (author's transl)]. [German]. Rontgen-Blatter 1979; **32**(6):314-318.
22. Morita H, Koyama N, Tamura Y. Development of flat adenoma and superficial rectal cancer after pelvic radiation. *Journal of Clinical Gastroenterology* 1998; **26**(3):171-174.
23. Martins A, Sternberg SS, Attiyeh FF. Radiation-induced carcinoma of the rectum. *Diseases of the Colon & Rectum* 1980; **23**(8):572-575.
24. Qizilbash AH. Radiation-induced carcinoma of the rectum. A late complication of pelvic irradiation. *Archives of Pathology & Laboratory Medicine* 1974; **98**(2):118-121.
25. Hansen SH, Holck S, Flyger H, Tange UB. Radiation-associated angiosarcoma of the small bowel. A case of multiploidy and a fulminant clinical course. Case report. *APMIS* 1996; **104**(12):891-894.
26. Hwang TL, Sun CF, Chen MF. Angiosarcoma of the small intestine after radiation therapy: report of a case. *Journal of the Formosan Medical Association* 1993; **92**(7):658-661.
27. Langlands AO. Radiation-induced leiomyosarcoma of the small intestine.[comment]. *Journal of the Royal College of Surgeons of Edinburgh* 1989; **34**(3):170-171.
28. McCue LJ, Norton AJ. Radiation-induced leiomyosarcoma of the small intestine.[see comment]. *Journal of the Royal College of Surgeons of Edinburgh* 1988; **33**(3):162-164.
29. Miyake M, Yokoyama T, Yamaguchi K, Hara M, Sugano H. Pathology of early death in atomic bomb casulties in Hiroshima. Morphological features and physical analysis of causative factors. *Acta Pathologica Japonica* 1967; **17**(4):517-533.
30. Charles MW. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *J Radiol Prot* 2003; **23**(4):457-459.
31. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 2003; **160**(4):381-407.