

Chapter 2

ACUTE RADIATION SYNDROME IN HUMANS

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INTRODUCTION

Victims of acute radiation events in radiological and nuclear incidents require prompt diagnosis and treatment of medical and surgical conditions as well as of conditions related to possible radiation exposure. Emergency personnel should triage victims using traditional military medical and trauma criteria. Radiation dose can be estimated early following the event using rapid-sort, automated biodosimetry and clinical parameters, such as the clinical history and timing of symptom complexes, the time to emesis (TE), lymphocyte depletion kinetics,^{1,2} and various multiparameter biochemical tests.³⁻¹⁷ Acute high-level radiation exposure should generally be treated as a case involving multiorgan failure (MOF).¹⁸ Various radiation severity grading schemes are currently used by the medical community.^{7,14,19}

Radiation-induced multiorgan dysfunction (MOD) and MOF refer to progressive dysfunction of two or more organ systems, the etiological agent being radiation damage to cells and tissues over time. Radiation-associated MOD appears to develop in part as a consequence of the systemic inflammatory response syndrome and in part as a consequence of radiation-induced loss of vital organs' functional cell mass. A worldwide consensus conference considering many different historical radiation accidents has recently addressed radiation-related MOD and MOF.^{11,20-25} Besides providing modern guidance to medically managing radiation-induced MOF, the conference proceedings are also a comprehensive educational resource for the physician likely to be involved in managing patients in a radiation incident.

As a resource to physicians, the Strategic National Stockpile Radiation Working Group and other working groups have recently issued recommendations on medically managing acute radiation syndrome (ARS).^{12,26-28} ARS has been an important part of radiation medicine for many years and the basic pathophysiology and treatment protocols are summarized in various textbooks.²⁹⁻³⁴ In addition, the Radiation Emergency Assistance Center / Training Site, a medical asset of the US Department of Energy, sponsors periodic symposia and short courses on the medical management of radiation accidents.³⁵⁻³⁸ Likewise, the Armed Forces Radiobiology Research Institute (AFRRI) provides the Medical Effects of Ionizing Radiation course for military and ancillary personnel and has long been a guiding influence in developing improved treatment methods for ARS.

Radiation sensitivity data on humans and animals has made it possible to describe the symptoms associated with ARS. ARS results from high-level external

exposure to ionizing radiation, either of the whole body or a significant portion (> 60%) of it. For this purpose, "high-level" means a dose greater than 1 Gy delivered at a relatively high dose rate. From a physiological standpoint, ARS is a combination of syndromes. These syndromes appear in stages and are directly related to the level of radiation received. They begin to occur within hours after exposure and may last for several weeks. ARS includes a subclinical phase (< 1 Gy) and three syndromes resulting from either whole-body irradiation or irradiation to a significant fraction of the body: hematopoietic syndrome (approximately 1-8 Gy), gastrointestinal syndrome (approximately 6-20+ Gy), and neurovascular syndrome (20-50+ Gy).

Radiation accidents have historically fallen into certain major categories, including low-dose incidents in which the patient shows essentially no signs or symptoms; higher dose, acute whole- or partial-body incidents with significant systemic signs and symptoms associated with ARS and often MOF; local radiation injury arising primarily from lost radiation sources and involving a regional portion of the body, often the hands; and inhalation or ingestion of radioactive material, often without systemic signs and symptoms. In a tactical event, it is possible to have ARS from exposure to a lost or stolen source, from an improvised nuclear weapon, or from inhalation or ingestion of radioactive material. However, the latter is expected to be rare. This chapter will focus on evaluation and management of ARS, regardless of the etiology of the event, although high-level external radiation dose will most likely be the etiology. From a medical viewpoint, patient mortality from radiation exposure is generally associated with a high-level gamma or neutron dose delivered over a short period of time.

Goans has provided an analysis of the recent history of radiation medicine that shows many cases of delayed diagnosis, even with the presentation of classical symptoms. In a review of four recent major gamma radiation incidents involving lost high-level gamma sources (Goiânia, Brazil [September 1987]; Tammiku, Estonia [October 1994]; Bangkok, Thailand [February 2000]; and Meet Halfa, Egypt [May 2000]), the average time from beginning of the accident until definitive diagnosis averaged 22 days.³⁸ However, in the severe criticality event in Tokaimura, Japan (September 1999), awareness of the accident was immediate because it occurred in an industrial environment.³⁹

Radiation incidents will be seen by physicians in a dichotomous fashion: either soon after the event or 2

to 4 weeks or more later (as in the case of lost sources found in the public domain or stolen covertly), when the patient becomes ill secondary to radiation-induced

neutropenia or pancytopenia. The clinical presentation of the externally irradiated patient will be much different in these two scenarios.⁴⁰

PATHOPHYSIOLOGY

The etiology of organ damage from high-level radiation exposure results from the radiosensitivity of certain cell lines.⁴¹ Cell radiosensitivity in various tissue systems is the basis for the distinction among the three acute radiation syndromes, as described below. Specifically, cells are radiosensitive if they replicate rapidly, are immature (eg, blast cells), and have a long mitotic future (law of Bergonie and Tribondeau). For example, spermatogonia, lymphocytes, blast cells (various types), other hematopoietic cells, and cells of the small intestine, stomach, colon, epithelium, and skin are radiosensitive, while cells of the central nervous system, muscle, bone, and collagen are much less sensitive. In addition, more highly differentiated cells are less radiosensitive. Lymphocytes are an exception to the law of Bergonie and Tribondeau⁴¹ because they have a long life span, but they do have a very large nucleus, encompassing almost all of the cytoplasm, thereby producing an excellent target for radiation damage.

In radiation medicine, ARS is classically divided into hematopoietic, gastrointestinal, and neurovascular syndromes, each with increasing dose, although there is some overlap, particularly within the first two. Each of these syndromes has been further divided into four clinical stages: prodromal, latent, manifest illness, and recovery or death. Prodromal symptoms begin a few hours after exposure and the time of onset is generally related to the severity of dose and dose rate. During the latent period, the patient may appear relatively clinically normal and generally symptom free. In the hematopoietic syndrome, during the period of manifest illness, significant issues to address are neutropenia and possibly pancytopenia. Therefore, medical treatment during the first 6 weeks after exposure to approximately 2 to 6 Gy is focused toward managing pancytopenia, controlling infection, and managing possible MOF in places other than the hematological system.

Hematopoietic Syndrome

Hematopoietic syndrome occurs after whole-body or significant partial-body irradiation of greater than 1 Gy delivered to the bone marrow. The radiosensitive cells of the hematopoietic tissue are the various lineages of stem cells.⁴²⁻⁴⁶ Their anatomical location in the bone marrow distributes them throughout the body. A

dose-dependent suppression of bone marrow at doses greater than 2 to 3 Gy leads to eventual neutropenia and possibly pancytopenia. Prompt radiation dose (within minutes to an hour) of approximately 3 to 8 Gy will cause significant damage to the bone marrow. A dose of approximately 3 to 4 Gy may result in death to 50% of exposed individuals without significant medical support.⁴⁷⁻⁴⁹ Radiation exposure causes the exponential biological death of bone-marrow stem and progenitor cells. If it is possible in tactical situations, shielding is the best method to protect bone marrow.^{50,51}

Prodromal symptoms after high-level radiation exposure often last for 1 to 3 days and include nausea, emesis, anorexia, and diarrhea. Generally, the earlier the onset of nausea and emesis, the higher the dose, if one excludes the possibility of psychogenic emesis. An approximate dose dependence for nausea and emesis was compiled from prior, unpublished research at Oak Ridge Associated Universities in the 1970s in conjunction with the US space program. From this research, the ED₅₀ (effective dose; the amount of drug that produces a therapeutic response in 50% of the subjects taking it) was found to be approximately 1.6 Gy and 2.4 Gy for nausea and emesis, respectively (Figure 2-1).

The prodromal symptoms are followed by 2 to 3

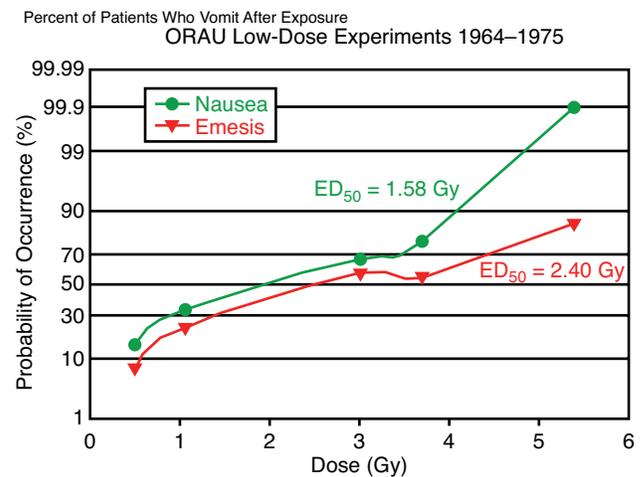


Figure 2-1. Incidence of nausea and emesis as a function of dose. Research performed at Oak Ridge Associated Universities for the National Aeronautics and Space Administration. Adapted with permission from Taylor and Francis and Oak Ridge Associated Universities.

weeks of latency, during which the patient will suffer from significant fatigue and weakness. The clinical symptoms of manifest illness appear approximately 21 to 30 days after exposure and may last up to 2 weeks. Sepsis associated with pancytopenia from bone-marrow suppression and severe hemorrhage from platelet loss are often the lethal factors in hematopoietic subsyndrome.^{46,49} Platelet counts of fewer than 20,000/mm³, moderately decreased erythrocyte counts, and severely suppressed neutrophil counts (fewer than 500/mm³) may also be seen. The treating physician will consequently be required to use current medical therapy for severe neutropenia in the setting of MOF.

Clinical hematological profiles over the period of manifest illness generally follow a course similar to that shown in Figure 2-2. There is a progressive decrease in lymphocytes, neutrophils, and platelets with increasing radiation dose. From traditional medical guidance, a 30% to 50% decrease of absolute lymphocytes within the first 24 hours is suggestive of serious and potentially lethal injury.⁵² More recently developed guidelines have been presented for early determination of the severity of radiation injury using both hematological kinetics and the appearance and severity of various clinical symptoms.^{15,28,40,53-58} Subpopulations of selectively radioresistant stem cells or accessory cells often exist^{49,59-62} and play an important role in hematologic reconstitution. Moreover, the radiation exposure is often inhomogeneous. The patient's physical environment and distance from the source may afford

partial shielding, accounting for dose variability, and this may result in areas of viable hematopoietic stem cells. Such a reservoir of stem cells may contribute to the future reestablishment of hematopoiesis.

The onset of radiation-induced cytopenia is variable and dose dependent. Granulocytes may experience a transient rise prior to decrease in patients exposed to less than 5 Gy. The transient increase prior to decline is termed an "abortive" rise, a finding that may be clinically helpful because it may indicate a more survivable exposure. The time to onset and duration of the nadir are variable.^{43,63} Indeed, the nadir may not occur for 3 to 4 weeks, particularly at lower doses. The duration of neutropenia is often extensive, requiring prolonged administration of hematopoietic growth factors, blood product support, and antibiotics. Patients with burns or wounds also experience poor wound healing, bleeding, and infection because of hematopoietic suppression. Impaired wound healing may be due in part to radiation-induced endothelial damage, which significantly depresses the revascularization of injured tissue.^{52,64,65}

Gastrointestinal Syndrome

Gastrointestinal syndrome and hematopoietic syndrome occur simultaneously at high radiation doses, beginning at 6 to 8 Gy. Consequences of gastrointestinal syndrome are more immediate and less amenable to treatment. The prodromal stage includes severe nausea, vomiting, watery diarrhea, and cramps occurring within hours after irradiation. At higher doses, bloody diarrhea, hypovolemia, shock, and death may ensue.^{52,66-70} At radiation doses above 10 to 12 Gy, patients will die sooner than if they just had hematopoietic syndrome. In a mass casualty event, these patients will likely be triaged expectant.

From a pathology viewpoint, the intestinal mucosa experiences severe radiation-induced damage following high-dose exposure.^{43,52} A shorter latent period is observed clinically because of the observed turnover time of 3 to 5 days for intestinal mucosal epithelial cells. Damaged crypt stem cells do not divide and therefore the damaged mucosal lining is shed and not replaced.⁵² The ability to absorb food is greatly reduced because of the disrupted mucosal lining and because of vascular coalescence. The damage to the mucosal lining also provides a portal for intestinal flora to enter the systemic circulation and serve as a nidus for sepsis.⁵² In addition, severe mucosal hemorrhage has been seen in experimental animal models. The overall intestinal pathology includes disturbance of absorption and secretion, glycocalyx disruption, mucosal ulceration, alteration of enteric flora, depletion of gut lymphoid

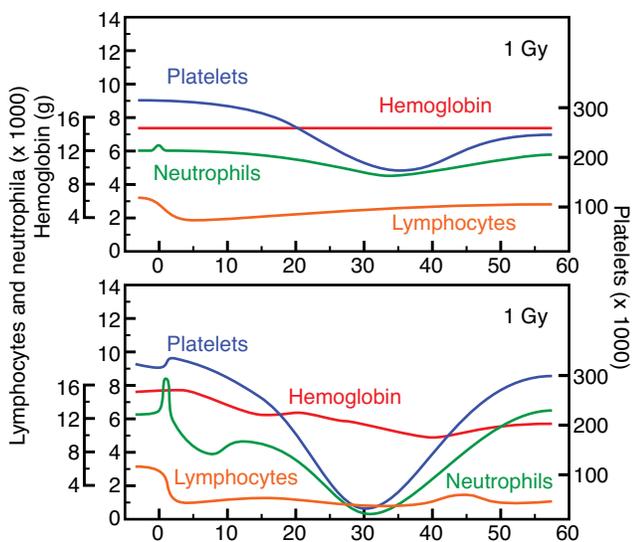


Figure 2-2. Cellular kinetics for the hematopoietic syndrome as a function of days following irradiation. Graphic courtesy of the US Armed Forces Radiobiology Research Institute.

tissue, and motility disturbances.^{34,71,72}

Medical issues associated with the gastrointestinal syndrome include malnutrition resulting from malabsorption, emesis, ileus, dehydration, possible acute renal failure, and cardiovascular collapse resulting from shifts in fluids and electrolytes. It is also possible to observe anemia from prolonged gastrointestinal bleeding and sepsis resulting from entry of bacteria into the systemic system via the damaged endothelial lining.^{34,52,69,73–75}

Neurovascular Syndrome

Neurovascular syndrome is less well defined than the others.^{76,77} Generally, patients with this syndrome have experienced a lethal dose over 30 Gy, but there is relatively little clinical experience at these doses for human exposure and the mechanism of death is unclear. Cardiovascular shock accompanies such high doses, resulting in a massive loss of serum and electrolytes through leakage into extravascular tissues. The ensuing circulatory problems of edema, increased intracranial pressure, and cerebral anoxia can bring death within 2 days.^{23,34,52,77,78}

The prodromal stages of the neurovascular syndrome are compressed. The patient may experience a burning sensation occurring within minutes; nausea

and vomiting within 1 hour; and confusion, prostration, and loss of balance (ataxia). During the latent period, apparent improvement for a few hours is likely to be followed by severe manifest illness. Within 5 to 6 hours, the overt clinical picture proceeds with the return of severe watery diarrhea, respiratory distress, and gross central nervous system signs.^{34,52} MOF is the final common pathway in the neurovascular syndrome.^{11,23,79}

The histopathology of the neurovascular syndrome appears to be due to massive endothelial damage in the microcirculation.^{34,52,65} This has been postulated as a causative mechanism in the damage of some organs. Preliminary experimental evidence indicates that the cause of initial hypotension may be an early, overwhelming surge of histamine released from degranulated mast cells.³⁴ The radiation threshold for the neurovascular symptom complex is not well defined. Experimental evidence in animals and in a few human radiation accidents indicates that 30 to 50 Gy will elicit the neurovascular syndrome and all doses in this range will eventually cause a lethal outcome.⁵²

The natural history of ARS shows that the time to death in an untreated patient is approximately 20 to 30 days in a severe hematopoietic case, 8 to 14 days in a patient with gastrointestinal syndrome, and 1 to 3 days with neurovascular syndrome.

DETERMINANTS OF RADIATION EFFECTS ON HUMANS

Radiation Lethality Curve

The slope of a radiation lethality curve is weighted heavily by data at each extreme of its distribution.^{34,52} This fact underscores the importance of reliable dosimetry, not only in the experimental situation but also in accurately determining the human exposure after a nuclear incident. In spite of the heterogeneity surrounding LD₅₀ values, it is possible to conclude that the doses giving between 90% and 95% mortality in most animal experiments are about twice those giving 5% to 10% mortality.^{47,51,80} In a recent review of animal data, a uniform dose (D) normalized to the LD₅₀ (D/LD₅₀) revealed that no deaths occurred when D/LD₅₀ was less than 0.54. When D/LD₅₀ was greater than 1.3, mortality was 100%.^{47,48,52,81,82} Therefore, total survival in a population can apparently be changed to total mortality by increasing the radiation dose by a factor of approximately 2.4.³⁴ Relationships between dose and lethality, drawn from a large number of animal studies, emphasize two important points on extrapolation to the human radiation response: reliable dosimetry is extremely valuable, and either therapy or trauma can significantly shift the dose–response relationship. An

error in dosimetry of 0.5 to 1 Gy can result in large shifts along the dose–response curve, and effective therapy can increase the LD₅₀ by 1 Gy or more. Radiation lethality appears to be a consequence of changes in the cellular kinetics of renewal systems critical for survival.

Factors such as trauma, stress, and poor nutritional status that compromise or damage the hematopoietic system or the immune system negatively affect the dose–response curve.³⁴

The goal of modern medical management of ARS is to shift the mortality curve to the right, which will result in saving more lives.^{83–86} This can be accomplished by good medical and nursing care, intravenous (IV) hydration, antibiotic coverage (as indicated), early use of cytokine growth factors, and possibly the use of stem cell transplants in the higher dose ranges (> 6–8 Gy).

Influence of Trauma on LD₅₀

A recent consensus committee has examined modern scientific aspects of combined injury (radiation plus burns or trauma).⁸⁶ The combination of radiation exposure and trauma produces a clinical dilemma not encountered by most military and civilian physicians.

In combined injury, two (or more) injuries that are sublethal or minimally lethal when occurring alone will act synergistically with radiation injury, resulting in much greater mortality than the simple sum of what all injuries would have produced.^{9,34,52,85-89}

Human radiation exposure events, such as the Hiroshima and Nagasaki bombings⁹⁰⁻⁹⁴ or the Chernobyl accident,^{63,95,96} were often coupled with other forms of injury, such as wounds, burns, blunt trauma, and infection. Radiation-combined injury would also be expected after a radiological or nuclear attack. Few animal models of radiation-combined injury exist, and mechanisms underlying the high mortality associated with complex radiation injuries are poorly understood. Medical countermeasures are currently available for managing the nonradiation components of radiation-combined injury, but it is not known whether treatments for other insults will be effective when the injury is combined with radiation exposure. Further research is needed to elucidate mechanisms behind the synergistic lethality of radiation-combined injury and to identify targets for medical countermeasures.⁸⁶

The mechanisms responsible for combined injury sequelae are unknown, but they can significantly increase the consequences of radiation exposure across the entire dose-response curve.⁵² It must be emphasized that the survival of a patient following exposure in the hematopoietic dose range requires the following: (a) a minimum critical number of surviving stem cells to regenerate a competent host defense system, (b) the functional competence of surviving cells composing the specific and nonspecific immune system, or (c) effective replacement or substitution therapy during the critical postexposure cytopenic phase.⁵² Trauma alone, depending on its intensity, may also effectively depress host resistance to infection.⁹⁷⁻⁹⁹

When trauma is imposed on a physiological system with even mild radiation injury, the outcome can be lethal. In most instances, trauma symptoms will either mask or exacerbate the first reliable signs of radiation injury. This will cloud the situation if one is relying on

prodromal symptoms to estimate dose. In addition, the choice of treatment in these cases should include consideration of not only the patient's initial status, but also the condition that will exist 7 to 21 days later, when the radiation effects are seen. An open skin wound (combined injury) markedly increases the chances of infection. Therefore, immediate wound closure has been recommended. Injuries to the abdomen may also present significant problems to the irradiated subject. Blast overpressure, blunt trauma, and penetrating trauma are all significant causes of abdominal injury in a tactical situation.⁵²

Effect of Clinical Support on the LD₅₀ Dose Effect Curve

Modification of survival throughout the LD₅₀ dose range is achievable using a simple regimen of clinical support to replace or substitute the depleted functional cells after stem cell destruction.^{34,52-70} Experimental work over the last 20 years showed the efficacy of supportive care centered on systemic antibiotics and transfusions of fresh platelets.^{49,100} Several canine studies indicated that antibiotics, individually or in combination, were successful in reducing mortality in the LD₅₀ range. Combination antibiotics, in conjunction with fresh whole-blood transfusions and parenteral fluids, have been effective in controlling dehydration and thereby reducing mortality.^{34,52} These studies have been extended over a dose range that can determine the significant shift in LD₅₀ that results from treatment. It must be emphasized that the practical application of these concepts requires that the damage to the stem cell system be reversible; that is, the surviving fraction of hematopoietic stem cells must be capable of spontaneous regeneration. Carefully controlled experiments clearly indicate that supportive treatment will elevate the estimate of the LD₅₀ by as much as 30%. Based on the range of values discussed, the recommended value for the LD₅₀ is approximately 3.6 to 3.9 Gy, but a mild dose-rate dependence has been demonstrated.³⁴

CLINICAL ASPECTS OF THE US CRITICALITY EXPERIENCE

Only a small number of radiation accidents in the United States have been severe enough to result in ARS-related MOF. Since 1945, four deaths have resulted from criticality accidents. The four criticality cases are particularly relevant for analysis of MOF because medical treatment was supportive and did not appreciably perturb the clinical evolution of radiation injury. In addition, these cases illustrate the clinical and pathological expression of the various ARS syndromes.^{101,102}

Two criticality events occurred with the same 6.2-kg, delta-phase plutonium sphere at Los Alamos National Laboratory in New Mexico. The first incident occurred on August 21, 1945, when a worker was preparing a critical assembly by stacking tungsten carbide bricks around the plutonium core as a reflector. He moved the final block over the assembly but, noting that this block would make the assembly supercritical, he withdrew it. The brick fell onto the center of the assembly, resulting in a super-prompt critical state. The worker sustained



Figure 2-3. Los Alamos criticality victim (LA-1) on day 24, prior to death.

Reproduced with permission from Hempelmann LH, Lisco H, Hoffman JG. The acute radiation syndrome: a study of nine cases and a review of the problem. *Ann Intern Med.* 1952;36:279–510 (Plate XVIII).

an average whole-body dose of approximately 5.1 Gy neutrons and gammas and a dose to the right hand of approximately 100 to 400 Gy. The patient died of sepsis 24 days later (Figure 2-3).^{35,103,104}

The second criticality accident occurred in 1946 during an approach-to-criticality demonstration at which several observers were present. The operator used a screwdriver as a lever to lower a hemispherical beryllium shell reflector into place. While holding the top shell with his left thumb in an opening at the spherical pole, the screwdriver slipped and caused a critical configuration. The operator received an estimated acute whole-body dose of approximately 21 Gy, with a dose to the left hand of 150 Gy and somewhat less to the right hand. Seven observers were exposed in the range of 0.27 to 3.6 Gy. The operator died 9 days later.^{35,103}

A third Los Alamos event was a liquid criticality event. On December 30, 1958, during purification and concentration of plutonium, unexpected plutonium-rich solids were washed from two vessels into a single large vessel that contained layered, dilute aqueous and organic solutions. The tank contained approximately 295 liters of a caustic stabilized organic emulsion. The added nitric acid wash is believed to have separated the liquid phases. Accident analysis shows that the aqueous layer was initially slightly below delayed critical (approximately 203-mm thick, with critical thickness being 210 mm). When the stirrer was started, the central portion of the liquid system was thickened, changing system reactivity to super-prompt critical. Bubble generation was the negative feedback mechanism for terminating the

first neutron spike. The system was driven permanently subcritical by mixing the two layers. This accident resulted in the death of the operator 36 hours after the accident. The dose to the upper extremity is estimated to have been 120 Gy, plus or minus 50%. Two other persons received acute doses of 1.34 Gy and 0.53 Gy.¹⁰⁵

The last fatal US criticality case occurred at Wood River Junction, Rhode Island. This liquid process accident occurred on July 24, 1964, at the United Nuclear Fuels Recovery Plant. A chemical processing plant was designed to recover highly enriched uranium from scrap material left over from the production of fuel rods. Uranyl nitrate solution U(93) was poured into a carbonate reagent vessel. The critical excursion occurred when nearly all of the uranium had been transferred. It is probable that the system oscillated, resulting in a series of neutron excursions. The acute dose to the operator was estimated to be 100 Gy. Two supervisory personnel received approximately 1 and 0.6 Gy. The operator died 49 hours later (Figure 2-4).^{106,107}

Clinical Course of the Criticality Cases

Radiation histopathology is an important adjunct to the clinical aspects of radiation medicine and has been examined by various authors.^{108–114}

Case Study 2-1: Los Alamos Plutonium Sphere (hematopoietic syndrome; cutaneous radiation injury syndrome; whole-body dose approximately 5.1 Gy; dose to right hand 100–400 Gy). The patient was a 26-year-old male whose past



Figure 2-4. Wood River Junction, Rhode Island, patient postaccident.

Reproduced with permission from Karas JS, Stanbury JB. Fatal radiation syndrome from an accidental nuclear excursion. *N Engl J Med.* 1965;272:755–761. Article DOI:10.1056/NEJM196504152721501.

medical history was significant only for Wolff-Parkinson-White syndrome diagnosed 3 years prior to the incident. On admission to the hospital, his vital signs were within normal limits and his only initial complaint was numbness and tingling of both hands. The initial physical examination was also within normal limits.

Within 30 minutes after the accident, the patient's right hand had become diffusely swollen. Emesis began approximately 1.5 hours after the event, and nausea continued intermittently for the next 24 hours. The patient experienced subjective improvement but had a mild temperature, mild gastric distress, and weakness during days 3 to 6. By day 5, the patient experienced a distinct rise in temperature with tachycardia and began to appear increasingly toxic. On day 10, he developed severe stomatitis, a paralytic ileus, and diarrhea. Clinical signs of pericarditis were noted on day 17, and the patient's mental status became irrational. The clinical course is notable for progressive pancytopenia.

Within 36 hours after the accident, blisters were noted on the volar aspect of the right third finger, and within 24 hours thereafter, extensive blistering was noted on both palmar and volar surfaces of the hand. A decision was made on day 3 to surgically drain the blisters, but by the third week the right hand had progressed to a dry gangrene. Desquamation of the epidermis involved almost all of the skin of the dorsum of the forearm and hand. In addition, epilation was almost complete at the time of death.

On day 24, the patient's temperature had risen to 41.1°C. He had lost a great deal of weight, developed thoracic-abdominal erythema, and had signs of sepsis. On day 24, the patient became comatose and died. During the patient's clinical admission, treatment consisted of fluid support, penicillin antibiotic therapy, thiamine, and two blood transfusions.

On autopsy, severe skin necrosis was observed as well as overt dry gangrene. The cardiorespiratory system was significant for pericarditis, cardiac hypertrophy, pulmonary edema, and alveolar hemorrhage. The spleen was noted to have no germinal centers and the mucosa of the large bowel was ulcerated, as well as that in the buccal mucosa. The bone marrow was noted to be hypoplastic with foci of bac-

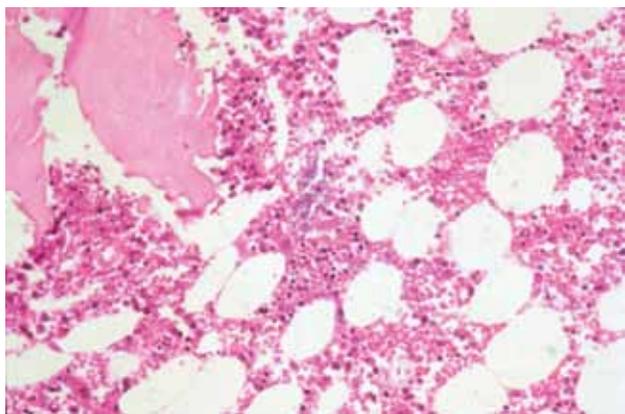


Figure 2-5. Hypocellular marrow with bacteria present centrally (hematopoietic syndrome). Slide courtesy of the US Department of Energy.

teria (Figure 2-5) and lymph nodes also showed significant lymphocyte depletion. The testes demonstrated significant atrophy with aspermia. A solitary ulcer was noted in the large colon, as was a right renal infarct.

Case Study 2-2: Los Alamos Plutonium Sphere (gastro-intestinal syndrome; cutaneous radiation injury syndrome; acute dose approximately 21 Gy; dose to the left hand 150 Gy). The patient was a 32-year-old male, admitted to the hospital within 1 hour after the accident. His medical history is generally unremarkable. His occupational history is significant only for several prior, generally chronic occupational exposures, none exceeding 0.005 Gy in a week. The patient complained of nausea in the hour prior to admission and vomited once in that time.

The general condition of the patient was quite good in the first 5 days following the accident. On the fifth day, there was a precipitous drop in his leukocyte count, and his condition began to decline rapidly. The patient rapidly lost weight, became mentally confused on day 7, became comatose, and died in cardiovascular shock on the ninth day.

Medical therapy during the 9-day course was largely symptomatic. Penicillin was given (50,000 U every 3 hours intramuscularly) beginning on day 5 because of granulocytopenia. Blood transfusions were also given daily after the fifth day. On day 6, fever and tachycardia developed, and on the seventh day, the patient developed a severe paralytic ileus. At the time of death, both hands showed extensive radiation damage.

On autopsy, examination of the skin was remarkable for early vesicle formation in the abdominal skin and marked epidermal damage. The cardiorespiratory system was remarkable for cardiac hemorrhage and myocardial edema, and the terminal bronchi showed features of aspiration pneumonia. The spleen exhibited no germinal centers and mucosa of most of the gastrointestinal tract showed atrophy and sloughing, most pronounced in the jejunum and ileum (Figure 2-6). Widespread degenerative changes were noted in the adrenal cortex as well as hyaline degeneration in the

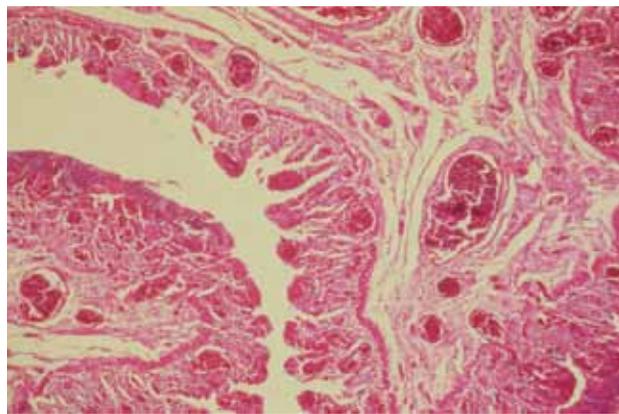


Figure 2-6. Intestinal specimen illustrating villous atrophy, congestion, and hemorrhage (gastrointestinal syndrome). Slide courtesy of the US Department of Energy.

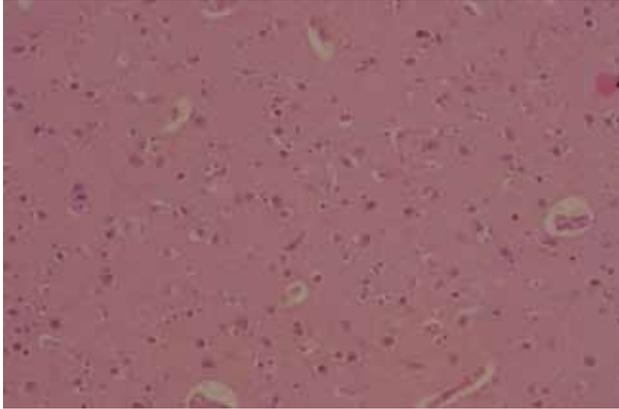


Figure 2-7. Neurovascular syndrome with brain perivascular edema (Virchow-Robins space). Slide courtesy of the US Department of Energy.

renal tubular epithelium. Examination of the red bone marrow showed it to be of liquid consistency.

Case Study 2-3: Los Alamos Liquid Criticality Event (central nervous system syndrome; dose to the upper extremity 120 Gy \pm 50%). The patient was a 50-year-old male with no significant past medical history. The clinical course has been divided into four separate phases. Phase 1 (20–30 min after the event) included immediate physical collapse and mental incapacitation, progressing eventually into semiconsciousness. Phase 2 (90 min after the event) consisted of signs and symptoms of cardiovascular shock accompanied by severe abdominal pain. Phase 3 (4 h after the event) included subjective minimal clinical improvement. Phase 4 (28 h after the event) was characterized by rapidly appearing irritability and mania, progressing to coma and death. The clinical course was remarkable for continuing, profound hypotension; tachycardia; and intense dermal and conjunctival hyperemia. The patient died 35 hours after exposure.

On autopsy, examination of the bone marrow was most significant for absence of mitotic activity. The lungs showed pyknotic, degenerating cells in the pleura, degenerating

lymphocytes and neutrophils in the subpleural connective tissue, and many areas of focal atelectasis interspersed with foci of emphysema. All lymph nodes were markedly atrophic and lymphoid follicles in the spleen were greatly depleted.

Examination of the heart showed acute myocarditis, myocardial edema, cardiac hypertrophy, and a fibrinous pericarditis. Examination of the brain demonstrated cerebral edema, diffuse vasculitis, and cerebral hemorrhage. The gastrointestinal system showed necrosis of the anterior gastric wall parietal cells, acute upper jejunal distention, mitotic suppression throughout the entire gastrointestinal tract, and acute jejunal and ileal enteritis.

Case Study 2-4: Wood River Junction (neurovascular syndrome; approximately 100 Gy). The patient was a 38-year-old male with a negative medical history. Following the initial criticality excursion, the patient appeared stunned, ran from the building, and immediately vomited. He also experienced immediate diarrhea and complained of severe abdominal cramping, headache, thirst, and profuse perspiration. His initial vital signs showed borderline blood-pressure elevation and tachycardia. Approximately 4 hours after the accident, the patient experienced transient difficulty in speaking, hypotension, and tachycardia. A portable chest radiograph 16 hours after admission showed hilar congestion. The physical examination also showed the left hand and forearm to be edematous, as well as left-sided conjunctivitis and periorbital edema. On day 2, the patient became disoriented, hypotensive, and anuric. The patient died 49 hours after the accident in cardiovascular shock.

At autopsy, interstitial edema of the left hand, arm, and abdominal wall was noted. Examination of the heart, lungs, and abdominal cavity revealed acute pulmonary edema, bilateral hydrothorax, hydropericardium, abdominal ascites, acute pericarditis, interstitial myocarditis, and inflammation of the ascending aorta. Examination of the gastrointestinal tract showed severe subserosal edema of the stomach and of the transverse and descending colon. The bone marrow was noted to be aplastic, and lymph nodes, spleen, and thymus were depleted of lymphocytes. The brain showed minimal change, with rare foci of microglial change and perivascular edema (Figure 2-7). The testes also showed interstitial edema and overt necrosis of the spermatogonia.

CURRENT TREATMENT OF ACUTE RADIATION SYNDROME

Radiation damage results from the inherent sensitivity of certain cell types to radiation, with the most undifferentiated and mitotically active cells being the most sensitive to acute effects. The inherent sensitivity of these cells results in a constellation of clinical syndromes that occur with radiation exposure. The clinical components of ARS include hematopoietic, gastrointestinal, and neurovascular syndromes and are reviewed above. The medical management of patients with acute, moderate to severe radiation exposure (effective whole-body dose > 3 Gy) should emphasize early initiation of colony-stimulating factor (CSF),

transfusion support as needed, antibiotic prophylaxis, and treatment of febrile neutropenia.^{45,49,53,86,115} Additional supportive medications may include antiemetics, antidiarrheals, fluid and electrolyte replacement, and topical burn creams. In the case of coexisting trauma (combined injury), wound closure should be performed within 24 to 36 hours.⁸⁶

The merits of modern supportive care lie in its significant prolongation of survival. The LD_{50/60} (the dose at which 50% of the exposed population will die within 60 days) is approximately 3.5 Gy in persons managed without supportive care. The LD_{50/60} may be

increased to 4 to 5 Gy when antibiotics and transfusion support are provided. The lethal dose may also be somewhat higher with early initiation of CSFs.^{83,84,116} Casualties whose radiation doses are most amenable to treatment will be those who receive between 2 and 6 Gy. The primary goal of medical therapy is to shift the survival curve to the right by 2 Gy or more. Many casualties whose doses exceed 6 to 8 Gy will also have significant blast and thermal injuries that will preclude survival when combined with the radiation insult. If there is little to no trauma, some authorities would consider stem cell transplant (peripheral or cord blood) for victims in this dose range.¹²

Currently, the only hematopoietic CSFs that have marketing approval from the US Food and Drug Administration (FDA) for managing treatment-associated neutropenia are the recombinant forms of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), and the pegylated form of G-CSF. All have been explored and have some efficacy in irradiated preclinical models of radiation-induced marrow aplasia. The rationale for using CSFs in irradiated humans is derived from three sources: their enhancement of neutrophil recovery in oncology patients, their perceived benefit in a small number of radiation-accident victims, and several prospective trials in canines and nonhuman primates exposed to radiation.

The most convincing data, which provides the proof of principle, is the demonstration of not only enhanced neutrophil recovery, but more importantly a significant survival advantage in nonhuman primates and canines if the CSF is given less than 24 hours after

irradiation (Figures 2-8 and 2-9).^{83,84} However, there appears to be less efficacy with a delay in treatment, but the interval required before the survival advantage is lost is unknown. The current data strongly suggest that CSFs should be initiated as early as possible in those exposed to a survivable whole-body dose of radiation and who are at risk of the hematopoietic syndrome (> 3 Gy).^{83,84}

These data collectively demonstrate that CSFs and extensive medical support may not only ameliorate radiation-induced neutropenia¹¹⁷ but also offer a survival advantage, especially if employed early. These data justify the treatment recommendations recently published by the Strategic National Stockpile Radiation Working Group.¹² The following cytokines are choices available for patients expected to experience severe neutropenia:

- Filgrastim (G-CSF) 2.5–5 $\mu\text{g}/\text{kg}/\text{d}$ every day subcutaneously, or the equivalent (100–200 $\mu\text{g}/\text{m}^2/\text{d}$)
- Sargramostim (GM-CSF) 5–10 $\mu\text{g}/\text{kg}/\text{d}$ every day subcutaneously, or the equivalent (200–400 $\mu\text{g}/\text{m}^2/\text{d}$)
- Pegfilgrastim (pegG-CSF) 6 mg once subcutaneously

Treatment with CSFs for expected exposures greater than 2 Gy should begin within 2 days.¹¹⁸ CSFs have been associated with rare splenic rupture and, more commonly, bone pain.¹¹⁹ Allogeneic stem cell transplantation may have limited use due to severe morbidity and mortality associated with concurrent

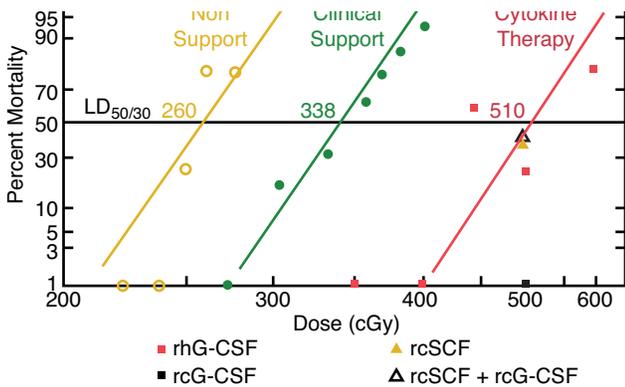


Figure 2-8. Influence of clinical support and cytokine therapy on canine mortality at 3.5 Gy. Graph courtesy of Dr Thomas MacVittie.

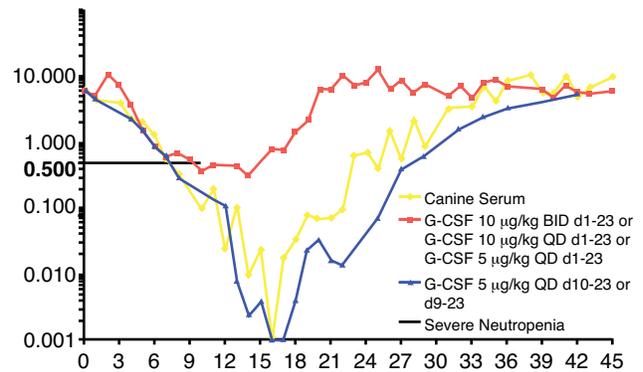


Figure 2-9. Onset of neutropenia and recovery after placebo and colony-stimulating factor given early (day 1) or late (day 10); x-axis is days postirradiation, y-axis is white blood cell count. Graph courtesy of permission Dr Thomas MacVittie.

nonhematopoietic injuries sustained at marrow-lethal doses of radiation.¹⁸

Various hospital issues are clinically important when managing patients who have sustained doses greater than 2 to 3 Gy, including:

- antibiotic prophylaxis, as well as antiviral and antifungal agents;
- barrier isolation and gastrointestinal decontamination;
- early cytokine therapy;
- early surgical wound closure and avoidance of unnecessary invasive procedures;
- isolation rooms for ARS patients with whole-body doses greater than 2 to 3 Gy (medical personnel should also be aware of the need for rigorous environmental control, including potential laminar flow isolation, strict hand washing, and surgical scrubs and masks for staff);
- physiological interventions, including maintaining gastric acidity, avoiding antacids and H2 blockers, and using sucralfate for stress-ulcer prophylaxis, when indicated, to reduce gastric colonization and pneumonia (early oral enteral feeding is highly desirable when feasible); and
- povidone-iodine or chlorhexidine for skin disinfection and shampoo, as well as meticulous oral hygiene.

Supportive Care

Transfusion of cellular components, such as packed red blood cells and platelets, is required for patients with severe bone-marrow damage and is an important component of clinical management. Fortunately, this complication does not typically occur for 2 to 4 weeks after the exposure unless losses from concur-

rent trauma are present. All cellular products must be leukoreduced and irradiated to 25 Gy. The latter prevents transfusion-associated graft-versus-host disease in immunosuppressed patients.

In nonneutropenic patients, antibiotics should be directed toward the foci of infection and the most likely pathogens. For those who experience significant neutropenia (absolute neutrophil count < 500 cells/mm³), broad-spectrum prophylactic antimicrobials should be given during the potentially long duration of neutropenia.⁴⁹ Prophylaxis should include a fluoroquinolone (FQ), an antiviral agent (if indicated, as discussed below), and an antifungal agent. The justification for FQ prophylaxis includes preclinical and clinical studies demonstrating decreased infectious episodes in irradiated animals and neutropenic oncology patients, respectively.^{13,120,121} Streptococcal coverage with the addition of penicillin or amoxicillin should also be considered, if not inherently covered by the FQ, given the increased treatment failure observed due to this pathogen and the benefit demonstrated with expanded antistreptococcal coverage in neutropenic animals.¹³

Antimicrobials should be continued until the patient experiences a neutropenic fever and requires alternate coverage or experiences neutrophil recovery (absolute neutrophil count > 500 cells/mm³). In patients who experience fever first, traditionally the FQ is stopped and therapy is directed at gram-negative bacteria (in particular, *Pseudomonas aeruginosa*), as infections of this type may be rapidly lethal. Antipseudomonal coverage serves as the foundation antibiotic, and additional coverage is then added to address other foci of infection, such as mucosal or integument injury. Empiric therapy of patients with febrile neutropenia with or without a focus of infection should be guided by the current recommendations of the Infectious Diseases Society of America.^{122–126} Any focus of infection that develops during the neutropenic period will require a full course of therapy.

MEDICAL ISSUES IN PATIENT MANAGEMENT

ARS is seen to be a sequence of phased symptoms. It is characterized by the relatively rapid onset of nausea, vomiting, malaise, and anorexia. An early onset of prodromal symptoms in the absence of associated trauma suggests a large radiation exposure. The medical management of ARS has two primary goals: hematological support to reduce both the depth and duration of neutropenia, and prevention and management of neutropenic fever.

The onset and depth of neutropenia is directly determined by the severity of the accident. In order to gauge the severity of an incident, radiation dose

to a patient can be estimated early after the event using rapid-sort, automated biodosimetry^{127–130} and clinical parameters such as the onset of various clinical symptom complexes,¹³¹ TE,^{13,54,57,85,132} and lymphocyte depletion kinetics,^{13,40,55} and through combinations of various biochemical entities.^{3,5,6,127,133} No single technique is satisfactorily sensitive, but multiparameter techniques have been shown to have good predictive value.^{5,127,133–135}

For external doses less than 1 Gy, the patient is generally asymptomatic and blood parameters will be within the normal range. Upon admission to

emergency care following the incident, it is always appropriate to obtain a complete blood count with differential, either as a baseline level or as a beginning step for lymphocyte kinetic analysis. TE, measured from the irradiating event, generally decreases with increasing dose. For TE between 1 and 2 hours, the effective whole-body dose is likely at least 3 to 4 Gy. If TE is less than 1 hour, the whole-body dose likely exceeds 4 to 6 Gy. In a mass casualty tactical event, patients who experience emesis less than 4 hours after the accident should be triaged to professional medical care, while those with emesis after more than 4 hours can be instructed to receive delayed medical attention. Patients who experience radiation-induced emesis within 1 hour after a radiation incident will require extensive and prolonged medical intervention, and an ultimately fatal outcome will occur in many instances.

Patient radiation dose and expected prognosis in a radiation event may be estimated from the medical history and timing of symptom complexes, serial lymphocyte counts, TE, and confirmatory chromosome-aberration cytogenetics. In addition, close collaboration with health physics experts is critical, since dose reconstruction personnel often have access to an array of sophisticated mathematical analysis techniques to estimate the dose field.

The prodromal symptoms of nausea and emesis will be particularly troublesome to patients. The following dosages of selective 5-HT₃ receptor antagonists are recommended for radiation-induced emesis:

- Ondansetron: initially 0.15 mg/kg IV; a continuous IV dose option consists of 8 mg followed by 1 mg/h for the next 24 hours. Oral dose is 8 mg every 8 hours as needed.
- Granisetron (oral dosage form): dose is usually 1 mg initially, then repeated 12 hours after the first dose. Alternatively, 2 mg may be taken as one dose. IV dose is based on body weight; typically 10 µg/kg (4.5 µg/lb) of body weight.

The patient history, physical examination, and early estimate of the severity of the radiation incident may be rapidly analyzed, using multiple clinical and dosimetric parameters, into a clinically meaningful estimate of radiation exposure using the AFRRRI Biodosimetry Assessment Tool software package, which is available at no cost (www.afri.usuhs.mil). Estimation of dose purely from the lymphocyte depletion rate constant is a quantitative enhancement of the classical Andrews model.^{1,136,137} Two additional Web resources are useful to the physician charged with treating radiation casualties. The radiation event medical management Web site (<http://www.remm.nlm.gov/>) developed by the US

Department of Health and Human Services, National Cancer Institute, and the National Library of Medicine is an important resource in patient management. In addition, the Centers for Disease Control and Prevention has a useful compendium of radiation medicine information and protocols (<http://www.bt.cdc.gov/radiation/>). As an additional medical resource, the recommendations of the Strategic National Stockpile Radiation Working Group¹² are considered to be a primary reference document for modern medical management of ARS.

When the irradiated patient is first evaluated, the following laboratory test results are important to acquire, as time permits.

- Required initial laboratory test results (in the field or in the emergency department):
 - complete blood count with differential (repeat every 6 h) to evaluate lymphocyte kinetics and calculate the neutrophil-lymphocyte ratio, and
 - serum amylase (baseline and daily after 24 h). A dose-dependent increase in amylase is expected after 24 hours.
- Other important laboratory test results to obtain:
 - blood FMS-like tyrosine kinase 3 ligand levels (marker for hematopoietic damage),
 - blood citrulline (decreasing citrulline indicates gastrointestinal damage),
 - cytogenetic studies with overdispersion index to evaluate for partial-body exposure,
 - interleukin-6 (blood marker is increased at higher radiation doses),
 - quantitative G-CSF (blood marker is increased at higher radiation doses), and
 - C-reactive protein (increases with dose as an acute-phase reactant; shows promise to discriminate early between minimally and heavily exposed patients).

For a small-volume scenario¹² (< 100 casualties), consider early cytokine therapy, fluid support, and antibiotic prophylaxis in the dose range of 2 to 6 Gy, if there is no significant trauma. At doses greater than 6 Gy without trauma, it is also prudent to consider stem cell transplantation therapy.¹² With doses in the region of 2 to 6 Gy and with burns or trauma, cytokines and antibiotic therapy are warranted. For doses greater than 6 Gy with burns or trauma, the patient is probably expectant. The severely neutropenic patient must be evaluated carefully, using the Infectious Disease Society of America's recommendations and other expert guidelines for the treatment of neutropenic fever.¹³⁸⁻¹⁴⁶

SELECTED ASPECTS OF CURRENT RESEARCH

The field of ARS research is progressing rapidly and any discussion is likely to be just as rapidly dated. However, many promising avenues of treatment have been shown in the preclinical phase or in early clinical evaluations.

AFRRI and a research partner recently achieved FDA clearance for 5-androstenediol (5-AED) to be evaluated in Phase 1 human clinical trials. Cytokines, as discussed above, are useful but costly to transport and store, unstable at room and high environmental temperatures, and must be used under the care of a physician. Those limitations make cytokines impractical for use in a mass casualty radiation scenario, which could leave many victims without access to physicians, hospitals, or roads to access either. Moreover, while G-CSF causes elevations in certain types of white blood cells, it does not stimulate production of platelets. AFRRI's preclinical trials for 5-AED showed an excellent safety and efficacy profile. Therefore it appears to be useful as a single therapy, without need for physician or medical support, in a mass casualty scenario. Research on 5-AED addresses two of the major problems causing mortality after irradiation—loss of infection-fighting white blood cells and loss of platelets—which lead to excessive bleeding. 5-AED also ameliorates the drop in red blood cells seen after high-level external irradiation (Figure 2-10).¹⁴⁷⁻¹⁵⁴ The AFRRI Radiation Countermeasures Branch continues to develop additional pharmacological countermeasures to radiation injury that can be used by military personnel and by emergency responders and to develop a better understanding of the biology of radiation injury and radiation countermeasure drugs. Knowledge of biochemical processes involved in radiation injury and countermeasures can be used to identify and assess novel drug candidates. AFRRI actively collaborates with other research institutions, pharmaceutical firms, and government agencies to develop and obtain approval for radiation countermeasures for use in the field and the clinic.

Possible countermeasures to ionizing radiation can be broadly categorized into three groups: (1) drugs that prevent the initial radiation injury (free-radical antioxidants, hypoxia-generating drugs, and enzymatic detoxification and oncogene targeting agents); (2) drugs that repair the molecular damage caused by radiation either by hydrogen transfer or enzymatic repair; and (3) drugs that stimulate proliferation of surviving stem and progenitor cells, such as immunomodulators and growth factors and cytokines. The availability of medical facilities for radiation casualties after a nuclear detonation near a city will be problem-

atic. In light of the logistical realities of likely nuclear disaster scenarios, much of the current focus is on drug candidates with extremely low toxicity and ease of administration, suitable for use outside the clinic without physician supervision.

Radiation countermeasure candidates tested for efficacy at AFRRI are chosen based on extensive basic research, which increases the probability of eventual clinical success. All four ARS countermeasures currently with FDA investigational new drug status (2010) are AFRRI products. Two (5-AED and BIO 300 [Humanetics, Eden Prairie, MN]) were conceived, initiated, and developed at AFRRI. The two others (Ex-RAD [Onconova, Newtown, PA]; and CBLB502 [Cleveland BioLabs, Inc, Buffalo, NY]) were the subjects of company-initiated research programs that AFRRI joined at early stages. Furthermore and as noted above, the current standard, off-label treatment for ARS, administration of hematopoietic cytokines such as G-CSF, was conceived, initiated, and developed at AFRRI. AFRRI has an ongoing in-vivo efficacy-screening program and is frequently approached by organizations for research collaboration and consultation regarding its promising countermeasure can-

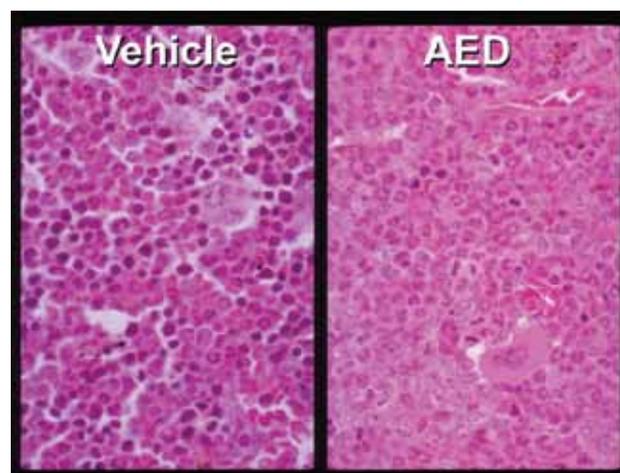


Figure 2-10. Bone marrow from a mouse treated with 5-androstenediol (right), compared with marrow from a mouse treated with placebo (left). The many small, round, dark objects in the control section are nuclei in progenitors of red blood cells. Progenitors of granulocytes (mostly neutrophils) and monocytes possess lighter nuclei, often horseshoe-shaped. Four days after 5-androstenediol treatment, there was a proliferation of granulocyte/monocyte progenitors. Slide courtesy of the US Armed Forces Radiobiology Research Institute.

didates. This screening program is supplemented by a robust research program that provides supporting data for approval of existing drugs and identification of potential drug targets.

Radioprotectants are another class of drugs that are designed to be used before or shortly after exposure. These include antioxidants such as gamma tocotrienol (a vitamin-E moiety),^{155,156} or genistein (a soy by-product) to increase survivability. Assessed effects of genistein on hematopoietic progenitor cell recovery in irradiated mice have documented that genistein operates on radiation-responsive gene expression. Genistein also protects against delayed radiation effects in the lungs and induces cytokine production in whole-body gamma-irradiated mice.¹⁵⁷ The use of advanced nutraceuticals as radioprotectants has shown that vitamin E is an effective radioprotectant. This research has also characterized the radioprotectant properties of soy-derived isoflavones and has demonstrated induction of cytokines by vitamin-E-related analogs. In addition, tocopherol succinate has been found to be a promising radiation countermeasure. A tocol antioxidant, gamma-tocotrienol, acts as a potent radioprotector, and alpha-tocopherol succinate has been shown to protect mice from gamma-radiation by induction of G-CSF and by preventing persistent DNA (deoxyribonucleic acid) damage. A recent review

article describes the history and scope of radioprotectants in research and in clinical radiation medicine.¹⁵⁸

An entity important in the clinical management of ARS is severe mucositis, which often appears in patients with high-dose external irradiation. Keratinocyte growth factor (KGF) has been shown to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies who are receiving myelotoxic therapy and require hematopoietic stem cell support. The safety and efficacy of KGF have not been established in patients with nonhematologic malignancies¹⁸; however, it is likely that KGF would be of use in the treatment of ARS.

Another severe manifestation of high-level dose—gastrointestinal syndrome—has defied effective treatment over the years.^{75,159–162} Currently, mixed data is available for treating and mitigating gastrointestinal syndrome. Current treatment modalities include gastrointestinal decontamination with FQs, vancomycin, polymyxin B sulfate, and antifungals (as medically indicated). In addition, L-glutamine has been found to be a helpful adjunct, along with supportive care. Nutrition options include total parenteral nutrition, elemental diets, and fluid and electrolyte repletion. There is also active current research on the use of growth factors to protect intestinal stem cells from radiation-induced apoptosis.^{163–165}

SUMMARY

Victims of acute radiation events in radiological and nuclear incidents will require prompt diagnosis and treatment of medical and surgical conditions as well as conditions related to possible radiation exposure. Emergency personnel should triage victims using traditional military medical and trauma criteria. Radiation dose to military personnel can be estimated early after the event using rapid-sort, automated biodosimetry and clinical parameters, such as the clinical history and timing of symptom complexes, TE, lymphocyte depletion kinetics, and various multiparameter biochemical tests. Acute high-level radiation exposure should be clinically treated as a medical case

involving MOF. Radiation-induced MOD and MOF refer to progressive dysfunction of two or more organ systems with the etiological agent as radiation damage to cells and tissues over time. Radiation-associated MOD appears to develop in part as a consequence of the systemic inflammatory response syndrome and in part as a consequence of radiation-induced loss of the functional cell mass of vital organs. Modern guidance to the medical management of radiation-induced MOF is presented in this chapter and it is hoped that this will serve as a comprehensive educational resource for the physician likely to be involved in managing patients in a radiation incident.

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