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Hematologic consequences of exposure to ionizing radiation

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From the early 1900s, it has been known that ionizing radiation (IR) impairs hematopoiesis through a variety of mechanisms. IR exposure directly damages hematopoietic stem cells and alters the capacity of bone marrow stromal elements to support and/or maintain hematopoiesis in vivo and in vitro. Exposure to IR induces dose-dependent declines in circulating hematopoietic cells not only through reduced bone marrow production, but also by redistribution and apoptosis of mature formed elements of the blood. Recently, the importance of using lymphocyte depletion kinetics to provide a "crude" dose estimate has been emphasized, particularly in rapid assessment of large numbers of individuals who may be exposed to IR through acts of terrorism or by accident. A practical strategy to estimate radiation dose and triage victims based upon clinical symptomatology is presented. An explosion of knowledge has occurred regarding molecular and cellular pathways that trigger and mediate hematologic responses to IR. In addition to damaging DNA, IR alters gene expression and transcription, and interferes with intracellular and intercellular signaling pathways. The clinical expression of these disturbances may be the development of leukemia, the most significant hematologic complication of IR exposure among survivors of the atomic bomb detonations over Japan. Those at greatest risk for leukemia are individuals exposed during childhood. The association of leukemia with chronic, low-dose-rate exposure from nuclear power plant accidents and/or nuclear device testing has been more difficult to establish, due in part to lack of precision and sensitivity of methods to assess doses that approach background radiation dose. Nevertheless, multiple myeloma may be associated with chronic exposure, particularly in those exposed at older ages. **© 2002 International Society for Experimental Hematology. Published by Elsevier Science Inc.**

Life forms developed and evolved on earth in a radiation field that was much stronger than that existing today [1]. Nevertheless, experimental exposure to ionizing radiation (IR) has been long known to be associated with changes in hematopoietic tissue and sometimes death [2,3]. This review is written in an effort to pique the interest of experimental hematologists in this apparent paradox.

Common forms of IR include electromagnetic radiation (x-rays and γ rays, neither of which contain mass or charge) and particulate radiation, including electrons, protons, neutrons, and α particles. While electrons have a small mass (9.1×10^{-31} kg) and negative charge, protons have a relatively large mass (approximately 2000 times that of an electron) and are positively charged. The mass of neutrons is approximately equivalent to that of protons, while an α particle consists of the helium nucleus (two protons + two neutrons). Electrons can be accelerated to nearly the speed of light and decelerate upon entry into tissue, resulting in a limited amount of penetration. By contrast, protons abruptly stop when entering tissues, depositing their energy and inducing ionization in an area known as the Bragg peak. The amount of ionization deposited along a track of radiation defines whether IR is low linear energy transfer (LET), where ionization (or energy deposited) is sparse, or high LET, where ionization is dense. X-rays and γ rays are examples of low-LET radiation, while α particles and neutrons are forms of high-LET radiation.

Special features of IR that may predict a biological response include its quality (for example, 131-iodine is selectively concentrated in the thyroid gland while 90-strontium is selectively deposited in bone), half-life (i.e., the half-life of 131-iodine is 8 days while that of 239-plutonium is 24,000 years), dose rate (i.e., the rate at which energy is transferred), and dose. From animal studies, it has been suggested that IR delivered at a high dose rate is more carcinogenic than that

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delivered at a low dose rate, although data in man are insufficient to ascertain a value for the magnitude of this effect [4].

Measurements of IR dose and dosimetry

Of all features of IR, dose is critical for predicting an effect on hematologic (and other) tissue of the body. Table 1 provides definitions and useful conversions for radiation units that are commonly used to quantitate radiation exposure. For comparison, the average annual dose in persons residing in the United States is approximately 3.6 mSv (i.e., the dose equivalence of 3.6 mGy) [5]. Another way of reporting the same dosage is 360 mrem or 0.36 rem (i.e., the dose equivalence of 0.36 rad). Natural radiation is the largest source of IR dose to man, with radon contributing over half of the average annual effective dose [5]. Imaging tests for medical diagnosis contribute the largest amount of dose of all man-made sources of IR [5]. Useful reference doses are those received from medical imaging tests, including a standard chest x-ray (dose equivalence of 0.02 rem), a Sesta Mibi stress test (dose equivalence of 0.04 rem), and a barium enema (dose equivalence of approximately 2 rem).

Unlike other reports (where low dose is considered to be $\leq$1 rad), for the purpose of this review, radiation exposure is divided into low-dose ($\leq$1 Gy) and high-dose ($>$1 Gy). Varying degrees of clinical toxicity from ionizing radiation may develop after a mild (1–2 Gy), moderate (2–4 Gy), severe (4–6 Gy), very severe (6–8 Gy), or lethal ($>$8 Gy) exposure. Whether or not a threshold dose of IR exists for a biological effect (i.e., a dose below which there is no biological effect) remains debatable [7].

Direct measurement of radioactivity in living subjects and matter remains the cornerstone of dosimetry. Sensitive physical measurements of individual dose may be made, using a whole-body radiation dosimeter [8]. Physical dosimeters are also available for rapid assessment of dose in common materials (such as air, soil, water, brick, etc.), and accelerator mass spectroscopy has been used in order to measure long-lived isotopes in Hiroshima and Chernobyl [9,10]. Since many types of building materials have relatively higher levels of external absorbed doses, dose rate may be increased by up to 50% in persons residing indoors [11]. Accordingly, environmental measurements have been combined with time-integrated activity in order to develop sensitive and accurate dose reconstruction [12]. Although labor intensive, the latter approach appears to have potentially great sensitivity, an important issue when assessing exposure to low doses. The technical aspects of dose reconstruction are complex and include appropriate use of mathematical models, pathway analysis (to examine transport of released radionuclides through environmental pathways), epidemiologic design (accounting for size and demographic structure of a potentially affected population), uncertainty analysis (to ascertain whether uncertainty arises from an unexplained variable in the observed data vs results from lack of information about the true value), and sensitivity analysis [13].

Biological markers have been used to indicate an exposure, an effect, or a susceptibility to radiation injury [13]. The landmark observation of Bender and Gooch that the formation of dicentric chromosome aberrations correlates with dose [14] represented a major change in how IR dose could be assessed. The slope and shape of the dose-response curve for dicentric formation is steep and nearly linear for high-LET radiation, and linear-quadratic for low-LET radiation [7]. With the recent application of molecular techniques to define biological response to IR (see below), new biomarkers have emerged [15], all of which must perform against the "gold standard" benchmark of chromosomal analysis. Before one can reliably use newly identified biomarkers to assess an IR-induced response, it is necessary that transitional epidemiological studies be performed in order to validate that the biomarker response measures exposure [16,17]. Furthermore, since chronic, low-dose exposure may result in a different biological response from that elicited by acute, high-dose exposure, evaluation of biomarkers must take into account the type of radiation exposure [18].

Radiation dose response for normal lymphohem atopoietic tissue

As with all tissues composed of short-lived cells, hematopoietic tissue is directly (and indirectly) affected by IR. De-

Table 1. Radiation units and definitions

*Unit	Quantity measured	Definition
Roentgen (R)	Exposure	Charge (ionization) produced in air by x-rays or gamma rays
Rad	Dose	100 ergs deposited per gram of tissue
Gray (Gy)	Dose	SI unit of dose; equals 100 rad
Rem	Dose equivalence	Unit that reflects biologic response; used to compare various types of radiation
Sievert (Sv)	Dose equivalence	SI unit of dose equivalent; equals 100 rem
Becquerel (Bq)	Exposure	Disintegration per second; 1 Bq = 2.7×10^{-11} Curie (Ci); 1 Ci = 3.7×10^{10} Bq or 37 GBq
KERMA	Exposure	Kinetic energy released in matter

*Submultiples: 10^{-2} = centi(c); 10^{-3} = milli (m); 10^{-6} = micro. Multiples: 10^{3} = kilo (k); 10^{6} = mega (M); 10^{9} = giga (G).

Abbreviations: Rad—radiation absorbed dose; Rem—roentgen equivalent in man; SI—Systeme International.

Modified from (6).

From Chinsoo Cho L, Glatstein E (1998) Radiation injury. In AS Fauci, E Braunwald, KJ Isselbacher, et al. (eds): Harrison's Principles of Internal Medicine. New York: McGraw-Hill, p. 2559. Used with permission of The McGraw-Hill Companies.

pending on the dose (and dose rate), effects may be exerted predominantly through cell renewal, apoptosis, or redistribution of lymphohematopoietic cells.

Hematopoietic stem cells and bone marrow stroma

Survival curves for normal clonogenic cells have been derived for many tissue types. While the linear shape and slope of the curve are generally similar for all tissues, considerable variation is present in the width of the shoulder [8]. The average value of the effective D_0 (i.e., the dose that gives an average of one hit per cell or the dose that reduces the number of survivors to 37% on the exponential region of the survival curve) for human cells is approximately 3 Gy [8]. From the studies of Till and McCulloch using the spleen colony-formation assay (colony forming units–spleen or CFU-S) [19], a single-exponential radiation survival curve was developed for murine hematopoietic stem cells. Enumeration of spleen colonies in recipients that were irradiated with 9–10 Gy with a knowledge of the number of cells required to produce a colony in unirradiated animals (i.e., plating efficiency) permitted calculation of the surviving fraction for a dose D. Figure 1 shows the γ ray survival curve for a range of doses. Murine bone marrow stem cells were determined to be the most sensitive of all mammalian cells undergoing mitotic death (D_0 = 0.95 Gy or 95 rad), with a minimal shoulder (indicating increased efficiency of cell killing) to the curve.

Given the remarkable degree of heterogeneity in cell type, proliferative capacity, and cell cycle status within the bone marrow, the hypothesis that subpopulations of stem cells (or other cell types in the marrow microenvironment) are selectively resistant to radiation damage has been proposed and tested [21–24]. Substantial evidence has accumulated to suggest that a fraction of hematopoietic stem cells survive radiation at doses as high as 6 Gy [23]. Figure 2 shows the survival curve for CFU-S as curvilinear, following a multiphasic, concave model. This observation suggests that members of the stem cell pool are variously sensitive to IR. Moreover, irradiation at different stages of development may have distinct effects on primitive repopulating hematopoietic cells. Whereas irradiation with 1–3 Gy of 17-day-old fetuses and 12-week-old adult mice impaired the proliferative capacity of multipotent, lymphohematopoietic bone marrow cells in a competition assay, there was no effect observed in repopulation assays when exposure occurred during early embryonic life (4-day-old embryos) [25].

The possibility that damage to hematopoiesis is mediated by nonhematopoietic, regulatory cells by altering the pro-

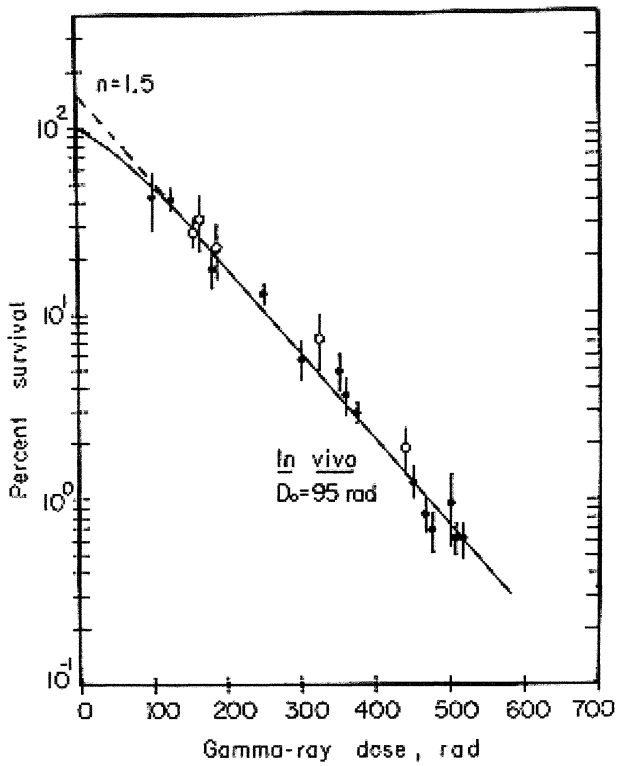

Figure 1. γ-ray survival curve for CFU-S. The surviving fraction for a dose D = colonies counted/cells inoculated × plating efficiency. Modified figure from [8], originally published in [20]. Used with permission of Lippincott Williams & Wilkins for [8] and Radiation Research (Academic Press) for [20].

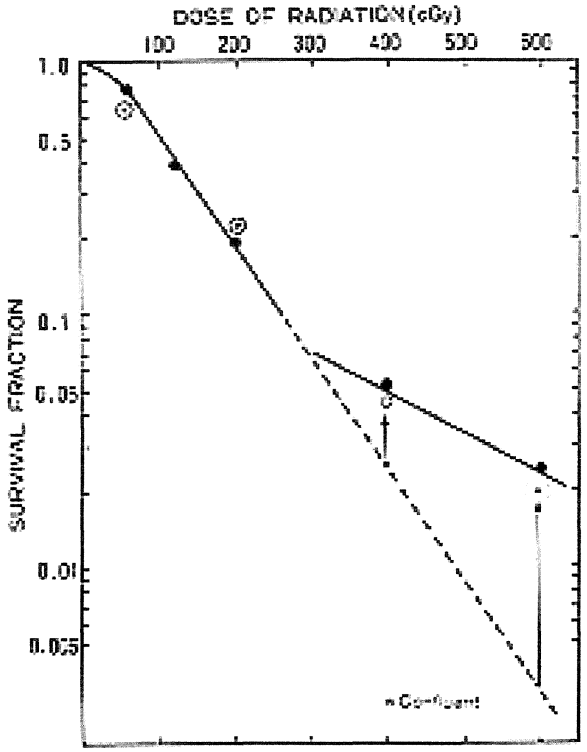

Figure 2. Survival curve for CFU-S. A single exponential curve is evident with a small shoulder between doses of 0.8 and 2.0 Gy. However, a larger than expected surviving fraction of cells is measured between 4.0 and 6.0 Gy (indicated by actual counts and solid line), compared to anticipated counts from following a single exponential curve (dashed line). Redrawn figure from [23] with permission from the International Society for Experimental Hematology.

duction and/or release of signal molecules has been extensively investigated (reviewed in [26]). Using an ectopic transplantation model with bone marrow from irradiated (7 Gy) mice relocated to the area beneath the renal capsule of unirradiated mice, Grande and Bueren argued that long-term (i.e., one-year) damage to the capacity of stromal cells to support stem cell proliferation results from IR exposure [27]. However, irradiation of the stroma appeared to improve the self-renewal capacity of lodged unirradiated CFU-S [27]. Debate concerning the relative contribution of hematopoietic stem cell function and nonhematopoietic cell function in the response to IR remains vigorous [28–30]. Until highly purified populations of progenitor cells at various stages of differentiation are studied, estimation of D_0 values ranging from 0.86 to 2.02 Gy, 1.11 to 1.44 Gy, and 1.29 to 2.40 Gy for human CFU-GEMM, CFU-GM, and BFU-E, respectively [30], will remain imprecise. In view of recent advances in our understanding of molecular responses to IR exposure (see below), significant opportunities exist for improving our understanding of mechanisms by which radiation preferentially alters the function of stem cells and stromal elements of the bone marrow.

Circulating cells

IR dose-dependent declines in all hematopoietic cell lines have been carefully documented by Cronkite, Fliedner, and colleagues [31–33]. In general, declines in the lymphocyte, granulocyte, and erythrocyte counts occur over hours, days, and weeks, respectively. Platelets also decline over a period of days, consistent with their half-life. Of all hematopoietic cells, the small lymphocyte has the greatest radiosensitivity (D_0 of 0.2–0.3 Gy) [34]. In fact, a decline in absolute lymphocyte count has been felt by many to be the most practical and best laboratory test to assess IR dose in the early phase of observation after exposure [35–37]. Table 2 provides a correlation between absolute lymphocyte count and IR dose.

Mechanisms by which rapid reduction in the lymphocyte count takes place have been investigated. Redistribution of lymphocytes and/or radiation-induced apoptosis may take place within hours. Lymphocyte redistribution from the circulation to lymph nodes is believed to occur predominantly via precapillary venules, which function as afferent lymphatic vessels. This process may be facilitated by the presence of highly radiosensitive cells in the capillary bed [38]. The relative contribution of lymphocyte redistribution vs apoptosis of lymphocytes (a process that is completed within 16–18 hours after radiation exposure; [39]) is unknown.

Table 2. Absolute lymphocyte count and IR dose

Degree of ARS$^+$	Dose (Gy)	Lymphocyte Ct*
Mild	1.0–2.0	0.7–1.5
Moderate	2.0–4.0	0.5–0.8
Severe	4.0–6.0	0.3–0.5
Very Severe	6.0–8.0	0.1–0.3
Lethal	>8.0	0.0–0.1

*Expressed as 10^9 cells/L.

$^+$ARS—acute radiation syndrome (exposure).

Data derived from text of Diagnosis and Treatment of Radiation Injuries (35).

Although leukoneutropenia occurs following whole-body IR exposure, the decline in granulocyte count requires more than 1–2 days and does not reach a nadir until 3–4 weeks following exposure to moderate IR dose [40]. The decline is often preceded by an initial phase of granulocytosis, an event that is believed to be due to demargination of granulocytes and release of mature and early precursors from the relatively large pool of granulocytic cells within the bone marrow compartment. The granulocyte count normalizes over 1–3 months (and may rise to higher than normal values), in distinction from lymphopenia, which may persist for many years after exposure. An interesting "abortive rise" in granulocyte count may occur after exposure to moderate doses of IR [40]. This transient rise toward (but rarely reaching) a normal level typically occurs between 5 and 10 days following IR exposure and may be due to maturation of the differentiated progeny of "injured" hematopoietic progenitor cells.

The platelet count typically declines 5–10 days following exposure to a mild or moderate IR dose. The duration of thrombocytopenia correlates directly with IR dose and platelet utilization at sites of active bleeding (due to nonhematologic sequelae of IR exposure such as gastrointestinal injury, trauma, etc.). Although declines in circulating granulocyte and platelet counts correlate with IR dose, they do not necessarily predict subsequent hematologic recovery [41]. For example, Baranov and coworkers have observed spontaneous recovery of granulocyte counts at 20–30 days following exposure among clean-up workers from Chernobyl whose circulating counts rapidly declined to less than 100 per mm^3 within 7–14 days [42]. These responses might be explained by persistence of radioresistant subpopulations within hematopoietic stem cell and progenitor cell compartments.

Lymphocyte subpopulations

Given the profound effect of IR on lymphocyte number, investigation of relative radiosensitivity of subpopulations of lymphocytes has been vigorous; however, the results have been somewhat conflicting. Differences in radiosensitivity have been documented by most investigators, with cytotoxicity for B cells and T cells. Since activation of lymphocytes may reduce these differences in radiosensitivity [43,44], and because the quality of antibodies used to quantify lymphocyte subtypes may vary depending on the subtype [44], it is not surprising that relative radiosensitivity has varied, depending on methods employed [43–48]. Accordingly, investigators have reported that IR-induced cytotoxicity is greater for CD4 cells than for CD8 cells after exposure in vitro [43,44,48]. Recently, Kusunoki and coworkers have reported

that interleukin (IL)-2 production by T cells is reduced in atomic bomb survivors receiving high-dose exposure [49], an effect that correlates with IR dose (>1.5 Gy) and that is unchanged when all cancer cases are removed from the cohort [50]. Using direct in situ hybridization, we have observed that the percent peripheral blood lymphocytes containing mRNA for IL-5 increased as a function of IR dose among Belarussians exposed to low-dose radiation (4–10 mSv) released during the Chernobyl accident [51]. Together, these reports suggest that a long-lasting effect persists among individuals who are exposed in vivo to IR, resulting in a relative depletion of TH-1–type cells and proliferation of TH-2–type cells, respectively [49,51]. They are further supported by reports of IR-induced TH-2–type responses in irradiated pulmonary tissue [52] and irradiated brain [53]. Interestingly, transcriptional regulation of the human IL-5 gene promoter by IR has been demonstrated as well [54].

Molecular and cellular basis of the hematologic response

Several reviews have summarized molecular pathways and mechanisms of IR-induced injury to mammalian cells [55–58]. The reader is referred to these reviews of the published literature concerning IR effects directed at DNA, gene expression, and protein production by cells directly targeted by IR and neighboring cells that may be affected by an exposure (i.e., "bystander" cells).

Direct effects on DNA

The critical target for IR-induced cell death has been generally considered to be DNA. Although double-strand breaks (DSBs) and the associated DSB repair response appear to correlate with cytotoxicity [59,60], mathematical models have predicted that IR induces the formation of more complex lesions [61]. Multiply damaged sites (MDS) (i.e., DSBs, single-strand breaks, base damage, base loss, etc.) within one or two helical turns of DNA may result in mutations and cell death [62,63]. The degree of complexity of such damage is predicted to increase with LET [64]. Indeed, unanticipated IR-induced lesions have been documented by nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry [65]. The finding of clustered lesions in DNA from human cells receiving 0.1- to 1-Gy doses of high-LET radiation [66] raises the possibility that repair-resistant, premutagenic damages may result from low-dose exposure. Results of studies of irradiated *E. coli* mutant cells support the concept that DNA glycosylases create DSBs during abortive repair at sites of clustered damages [67].

Because IR induces the formation of reactive oxygen species [68–70], it has been difficult to identify intracellular targets that are essential to cell death. Results of studies of survival of CHO cells suggest that damage to non-DNA molecules in the cell is required for IR-induced cell death [71], a notion that is consistent with the importance of an adequate response of base excision repair pathways [63,72].

Effects on gene expression

Woloschak and coworkers have reported that exposure to low-dose IR (90 cGy of rays) induces changes in mRNA levels for a variety of genes, including c-jun, H4-histone, and Rb [73,74]. Interestingly, the latter genes were not induced by exposure to 21 cGy of JANUS fission-spectrum neutrons [74], raising the possibility that biological response in this dose range may be distinct for high-LET and low-LET radiations. Given the complexity of DNA damage resulting from IR exposure, assessment of IR-induced damage would be facilitated by an approach that simultaneously measures a large number of cellular responses. The development of cDNA microarray technology, coupled with sequencing of the human genome, has provided the technology for a practical approach to assess transcriptional responses to exposure to IR.

Amundson and colleagues have applied microarray hybridization to examine the expression of genes known to be involved in the stress response and cell-cycle progression [75–77]. They assessed transcriptional responses to known levels (0.2–20.0 Gy) of IR in vitro, using a human myeloid cancer cell line (ML-1) and human peripheral blood lymphocytes. Dose-dependent increases in mRNA for CIP1/WAF1, GADD 45, MDM2, ATF3, and BAX were observed in the leukemia cell line at 4 hours after exposure to 20 Gy [75]. Increases in the expression of DDB2 (a gene that codes for a subunit of the XPE protein which plays a role in repair to ultraviolet light–induced damage), CIP1/WAF1, and XPC were observed in irradiated lymphocytes with a linear dose response between 0.2 and 2 Gy [76]. Interestingly, the pattern of gene expression varied, depending on tissue type (spleen, liver, or thymus) in mice receiving 2 Gy in vivo [77]. Likewise, lymphoblastoid cell type, culture methods, and IR dose may all contribute to differences in response pattern [78].

We have recently used cDNA microarray technology to assess response to low-dose exposure in vivo among Belarussians residing near Chernobyl [79,80]. Using arrays with probes for growth factors, cytokines and their receptors, protein kinases, and pro-apoptotic proteins, we observed differences in patterns of expression for subjects exposed to greater than 10 mSv, compared to those exposed to less than 10 mSv. Genes encoding proteins associated primarily with the proliferation or apoptotic death of monocytes and T cells were upregulated (see Table 3). While cDNA microarray technology is a powerful and versatile tool that may detect radiation-associated transcriptional responses, the enormous amount of data generated by this method requires careful analysis with cross-validation, particularly as larger data sets are analyzed [80]. Given the potential enthusiasm for identifying "signature" patterns of response [73–80], particularly at low-dose, low-dose-rate levels, standard-

ization of formats for describing microarray data is essential before gene profiling may be formally assessed as a biomarker of exposure.

Apoptotic pathways

Apoptotic pathways are triggered by IR [57,58]. Receptors belonging to the tumor necrosis superfamily are integrally linked with physiological cell death [81]. The most common studied receptor in this family involved with cell death is TNFRSF6 (i.e., Fas). Belka and coworkers have shown that in lymphocytes, IR-induced apoptosis proceeds through mutual interaction of TNFRSF6 and TNFSF6 (Fas ligand) [82]. In studies of lymphoid cells from healthy individuals and patients with ataxia-telangiectasia or AT (an autosomal recessive disease characterized by cerebellar degeneration, oculocutaneous telangiectasia, and increased risk for development of malignancy of the lymphoid system with hypersensitivity to IR), we have shown that TNFRSF6 is upregulated at the cell surface by IR. This dose-dependent effect (between 0.1 and 10 Gy) can be partially prevented by inhibition of caspase-8 [83], an enzyme that is activated during apoptosis, forming a death-inducing signaling complex [84]. Nevertheless, treatment with antagonistic anti-TNFRFS6 antibody does not prevent apoptosis [83], suggesting that hyperradiosensitivity of AT cells is not due to functional activity of TNFRSF6 receptor.

Apoptosis is accompanied by not only caspase activation but also ceramide formation [85]. While the relative importance of the ceramide pathway has been debated [86,87], the importance of hydrolysis of sphingomyelin to ceramide at the cell surface during the execution phase of apoptosis has been emphasized [88]. IR produces numerous effects that are directed at the plasma membrane [39,89]. Haimovitz-Friedman and coworkers have emphasized the potential role of ceramide production in response to IR [90,91]. In turn, ceramide may stimulate the stress-activated protein kinase/JUN kinase (SAPK/JNK) cascade [92,93]. Regardless of the details of the molecular mechanisms of ceramide-mediated cell death, evidence is accruing to suggest that the plasma membrane, by virtue of its sphingomyelin content, plays an important role in IR-induced apoptosis. Alterations in relative amounts of ceramide, sphingomyelin, or lipids regulating the fluidity of plasma membranes, may be used as an indicator of exposure [39,89].

Direct vs bystander effects

It has been known for nearly 50 years that radiation induces responses in unirradiated cells, an observation referred to as the "bystander effect" [56]. Moreover, it has been long known that individuals receiving localized therapeutic radiation may respond to therapy in distant sites of the body that are remote from the original irradiated field (i.e., abscopal effects) [94–96]. Utilizing a microbeam that delivers precise radiation amounts to individual cells, investigators at Columbia University (USA) and the Gray Laboratory (UK) have confirmed that a greater than expected effect is observed when low numbers of particles are delivered to a field of cells [97–99].

Several mechanisms may explain the bystander effect. These include the formation of gap junctions through which signal molecules may pass from one cell to another [100–102], and the release of soluble or membrane-associated growth factors and proapoptotic proteins [103–106]. To my understanding, evidence for a gap junction effect is indirect (primarily through inhibition of gap junction formation, using agents such as lindane), and direct visualization of gap junctions (through various electron microscopy methodologies) has not been demonstrated. Since gap junctions form among cells of the bone marrow in vivo and between cells of developing hematopoietic colonies (reviewed in [107]), analysis of IR effects on gap junction communication in the hematopoietic system may provide new insights into how IR-induced signaling takes place.

Removal of medium conditioned by irradiated cells has resulted in the transfer of a factor (or factors) that reduce clonogenic survival of unirradiated cells [103]. This simple but elegant approach of Mothersill and Seymour provides strong evidence that direct cell-cell contact is not required for a bystander effect [104]. It is well known that soluble cytokines such as IL-8 may be produced in response to exposure to IR [105]. We have presented results indicating that plasma membrane–derived vesicles shed into medium condi-

Table 3. Genes expressed in mononuclear cells from chernobyl victims

Gene	Subgroup/cluster	Principle cluster
Monocyte chemotatic 1, IL-1β	1	A
M-CFSR, M-CSF	2	A
IGF-2, membrane Fas, IL-12β	3	B
IGFBP3, MPL, TcR, apoptosis-related protein, LERK-1, IL10R, IL-2, IL-10, leukemia inhibitory factor	4	B
IL-2β. soluble Fas, β subunit of IFN-δR, IFN-δR, IL-12α subunit	5	C
TNF-β, TNF-α, IL-8	6	D

Dendrograms were created and analyzed to identify principal clusters of expressed genes in microarrays prepared with RNA from peripheral blood mononuclear cells of six healthy subjects exposed to 10–50 mSv in vivo resulting from the Chernobyl accident. Listed are overexpressed genes, relative to those from mononuclear cells of individuals exposed to <10 mSv. Modified from [80]. Used with permission of the British Institute of Radiology.

tioned by irradiated cells contain increased levels of TNFSF6, whose signal may be communicated from one cell to another [106]. Our finding that bioactive TNFSF6 is expressed on membrane-derived vesicles [108] has been confirmed by several laboratories [109–112]. Because exfoliation of cell-surface components occurs in vivo [107,113,114], shed TNFSF6 may provide a mechanism for abscopal effects of IR.

Other signal molecules may be released from cells targeted by IR. Gorbunov and coworkers reported that high-dose radiation (2–50 Gy) induces the release of nitric oxide from bone marrow stromal cells in vivo and in vitro, which in turn may place recipient mice at risk for leukemia [115]. IR-induced signaling among cells requires additional study, particularly in assessing biological effects in the low-dose range, where the magnitude of the bystander effect may be greatest [116]. Results of such investigation may have several applications. For example, understanding bystander effects of high-LET galactic cosmic rays may help in assessing radiation risks associated with travel in free space [117]. Moreover, knowledge of how exfoliation of membrane-bound growth factors [107,118–120] takes place, and of the role of exfoliation in autocrine signaling [107,121], may lead to new approaches to prevention of IR-induced injury, analogous to antagonism of shed growth factor effects [122].

Clinical effects of acute exposure to high-dose-rate radiation

Except for a few accidental high-dose-rate exposures of a handful of individuals, exposure to IR at a high dose rate has been limited to atomic bomb survivors. The study of atomic bomb survivors is the largest, longest, and most comprehensive assessment of radiation carcinogenesis [123]. Overall, very few excess cancer deaths in this population can be attributed to radiation (estimated as less than 430) [123].

Atomic bomb survivors

The release of radiation from the atomic bombs detonated over Hiroshima and Nagasaki was rapid, resulting in high-dose-rate exposure. Although dose rate was very high, the dose range was wide, with approximately one-half of exposed individuals receiving bone marrow doses of 5 mSv or less [124,125]. Follow-up of an IR-exposed cohort of more than 86,000 people by the Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, has contributed a wealth of information concerning the association of exposure to IR with leukemia and possibly other hematologic disorders. Results of the Life Span Study (LSS) cohort of atomic bomb survivors have been published by several organizations [126–129], and updates have been periodically published [130–132].

Analysis of data from the LSS cohort using the French-American-British (FAB) leukemia classification system indicates that the highest excess absolute risk (EAR) was for acute myelogenous leukemia (AML) (1.1 cases per 10^4 person-years [PY] Sv), followed by chronic myelogenous leukemia (CML) (0.9 cases per 10^4 PY Sv) and acute lymphoblastic leukemia (ALL) (0.6 cases per 10^4 PY Sv) [125,133]. These risks correlate with highest excess relative risks (ERR) of 9.1 per Sv for ALL, 6.2 per Sv for CML, and 3.3 per Sv for AML. Analysis of the age-time patterns for cancer excess risks in atomic bomb survivors may provide insights into the nature of IR-associated leukemia [134]. Accordingly, descriptions of EAR and ERR have taken into consideration age, gender, and other factors that may be important for a radiation-associated effect. Preston and coworkers have reported observed and expected leukemia cases in the LSS cohort by age and IR dose [133,135].

Figure 3 shows fitted ERR and EAR function for leukemia incidence data. Overall, the risk for leukemia is greatest in the early years after exposure. Folley and colleagues have estimated a latent period of 2 to 3 years between exposure and disease for IR-related leukemia [136]. The risk for IR-associated leukemia is highest for individuals who are under 10 years or over 50 years of age at the time of exposure [137]. For any given age, the absolute risk for males observed at approximately 5 years after exposure is greater than that for females. However, as the risk declines with attained age, the rate of fall is lower for females than for males (see Fig. 3). Another difference by gender is leukemia subtype. For males, approximately 60% of leukemia is represented by ALL and CML [125]. For females, AML was more frequent than ALL or CML in women diagnosed with leukemia under the age of 40 years [125,133].

The bone marrow dose-response curves for all types of leukemia appear to be linear-quadratic over the 0- to 4-Gy range [133]. Dose-response curves for ALL and CML appear to be linear, while that for AML appears to be quadratic. Finch suggests that the concave upward dose-response curve for AML may account for the slight curvature of the dose-response curve for all leukemias [125]. Molecular pathways, intercellular sig-

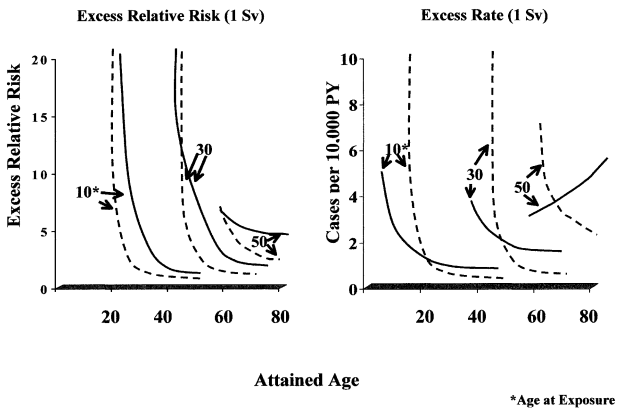

Figure 3. Leukemia incidence, 1950–1987 LSS cohort. Shown are fitted ERR (left panel) and EAR (right panel) at 1 Sv for individuals of different attained age. Age at exposure is indicated for each pair (males, broken line; females, solid line) of plots. Modified from [135]. Used with permission of Stem Cells.

naling within the bone marrow, and endocrine signaling may all contribute to differences in the dose dependence relationship by mechanisms that remain undefined today.

Although an extensive amount of information is available concerning overall IR dose and bone marrow (weighted) dose in atomic bomb survivors [138], imprecision (resulting in uncertainty of 20–40%) is inherent in radiation dose estimates [139]. Moreover, systematic discrepancy appears to exist in the DS86 neutron dosimetry for Hiroshima [140]. Straume suggests that underestimates of organ dose due to neutrons may be of a magnitude that is sufficient to have an impact on risk estimates for IR-related cancer [141]. In fact, 2/7 survivors of high-dose neutron exposure from a critical accident at Los Alamos subsequently died of AML [142]. An updated estimate of doses based on revised neutron calculations (DS02) should be completed this year (T. Straume, personal communication). Uncertainty and imprecision potentially complicate projection of IR-induced risk to populations chronically exposed to low-dose IR. The dose-rate effectiveness factor (DREF) must also be considered when such extrapolations are made [143]. Nevertheless, actual and projected mortality from leukemia using specific age rates for women, according to a report of the Committee on Biological Effects of Ionizing Radiation (BEIR), showed very close agreement [144].

Other hematologic disorders have been thought to be related to IR exposure in the LSS cohort. Initial LSS mortality study data suggested that multiple myeloma increased significantly with a latent period of approximately 20 years [145,146]. However, later analyses indicate that the increases in multiple myeloma are insignificant [147]. For the 41,000 persons who received more than 10 mSv and a mean dose of 230 mSv, 30 cases of multiple myeloma were observed and 29 cases were expected over 1 million PY of study. This discrepancy in findings may be due, in part, to exclusion of several of the cases in the original analysis based upon pathologic review and/or dose-range restriction [148]. On the other hand, the association of multiple myeloma with low-dose-rate exposure to low-LET radiation may be significant (as described below). Similarly, initial reports of the association of aplastic anemia in atomic bomb survivors proved on subsequent analysis to show no association between IR exposure and incidence of confirmed cases of aplastic anemia [149].

In general, studies have consistently shown a lack of association between IR exposure and risk for Hodgkin's disease in the LSS cohort [148]. Data are inconsistent with regard to an association between IR exposure and risk for non-Hodgkin's lymphoma. The most recent analysis of the LSS cohort showed no significant increase, with 76 cases of non-Hodgkin's lymphoma observed and 72 cases expected [133].

Other exposures

It is well known that individuals who are accidentally exposed to high-dose, high-dose-rate radiation may develop fulminant marrow failure [150]. Since these individuals often develop acute radiation syndrome, death may be due to the failure of one or multiple organs.

Hematologic response to chronic, low-dose-rate exposure

Most studies designed to assess the development of leukemia and exposure to natural background radiation levels have shown no significant correlation between the two events [151–153]. Studies of accidental exposure to low-dose IR from nuclear power plant accidents and atomic weapons testing have shown conflicting results regarding the association of leukemia and radiation exposure. The following review is intended to highlight several instances of accidental exposure to IR, rather than to provide a comprehensive review of all accidents. The reader is referred to Mettler and Upton [7] for a more complete compendium.

Nuclear power plant accidents

The Chernobyl nuclear power plant disaster of April 26, 1986 resulted in the release of the largest amount of radioactivity on record [154]. Although this accident created a setting for studying the biological effects of low-level IR exposure, difficulties in assessing very low doses have limited the amount of new information derived from the exposed population. Given the limitations of uncertainty and imprecision in dose reconstruction, establishment of a relationship between leukemia risk and IR exposure has been difficult. Several studies have been conducted in populations exposed to fallout from the Chernobyl accident [155–161]. Two long-term studies are in progress (a National Cancer Institute study and a case-control study of the International Consortium for Research on the Health Effects of Radiation) in the former Soviet Union.

Results of the majority of studies of leukemia suggest that there is no increased risk of disease among individuals exposed to IR from the Chernobyl disaster [155–158]. This includes analysis of both adult leukemia and childhood leukemia. Nevertheless, reports based on registries of clean-up workers (i.e., liquidators) suggested that nearly all types of leukemia and lymphoma were increased in the exposed group [162–165]. Reanalysis of the data revealed that several of the cases were miscoded and that case ascertainment may have been incomplete in the "unexposed" population (S. Finch, personal communication). More recently, Noshchenko and coworkers reported that there is an apparent 3.4-fold increase in the incidence rate ratio for ALL in children born in the "contaminated" region of Zhitimir of the Ukraine, compared to that in the "clean" region of Poltava [159]. However, this ecological study suffers from a broad range of doses (0.1–200 mSv) in the "exposed" individuals, lack of individual dosimetry, low number of ALL cases (13 vs 4), and inattention to population migration between and among oblasts and outside of the Ukraine.

A similar level of confusion has emerged with respect to the risk for infant leukemia after in utero exposure to IR from the Chernobyl accident. Petridou and colleagues reported that infants born between July 1, 1986 and December 31, 1987 in Greece who were "exposed" in utero to IR from the Chernobyl accident had a 2.6-fold increase in incidence of leukemia, compared to "unexposed" children born before December 31, 1985 or after January 1, 1988 [160]. However, the numbers of leukemia cases were small (1 vs 7 vs 4 cases for $<$100, 100–999, and $>$1000 Bq/kg, respectively), and this observation could not be duplicated when a similar definition of exposure was applied to an analysis of data from the German Childhood Cancer Registry [161].

If intrauterine exposure to IR indeed results in excess infant leukemia rates, the largest excess would be anticipated to occur in Belarus, the country receiving approximately 75% of the total radiocontamination, with levels exceeding by an order of magnitude those found in Greece. While a trend of increased infant leukemia rates was observed in a similarly defined "exposed" cohort of children from Belarus overall and from the most heavily contaminated oblasts (i.e., regions) of Belarus, the observed excess cases were not larger than that found in Greece [166]. Recently, we have analyzed leukemia incidence rates for 1987–1992 and 1993–1997 among Belarussian children under 1 year of age and children 1–4 years old at the time of diagnosis for areas of Belarus classified by radioactive contamination at the rayon level (i.e., smaller units within oblasts) and migration characteristics. Since migration of younger adults (of childbearing age) out of heavily contaminated rayons was generally known to occur after the nuclear power plant disaster, one might expect that fewer live births (and hence, smaller populations of children 0–4 years) would have occurred in rayons of the two most heavily contaminated oblasts (i.e., Gomel and Mogilev). When the size of populations at risk by age is taken into account, infant leukemia rates were found to be higher in the early years after the disaster in contaminated regions with low migration, and leukemia rates among children 1–4 years were significantly higher (at the 90% certainty level) in the latter time period (unpublished data). Our results suggest that the size of the population at risk should be considered in light of resettlement; they are consistent with the hypothesis that low-dose fetal irradiation may present a leukemogenic risk [131,167,168].

Several studies have been published addressing risk of leukemia among nuclear facility workers [169–172]. Given that individuals in the workforce may be of younger age than the general population, the standardized mortality ratio may be less than unity, requiring the use of internal cohorts in order to adjust for a "healthy worker effect." Moreover, confounders must also be considered (such as exposure to chemicals, cigarettes, etc.). In spite of these limitations, information may be gathered regarding leukemia among nuclear power plant workers. Table 4 provides a summary of four studies that show different results.

No apparent increase in the standardized mortality ratio was observed for leukemia deaths or all cancer deaths in a study of nearly 40,000 subjects in the United Kingdom [169]. Another study of individuals working at the Mound facility in Ohio demonstrated an increased mortality from leukemia only when chronic lymphocytic leukemia (CLL) was also included in the analysis. Since CLL in man has never been shown to be associated (among atomic bomb survivors or elsewhere) with IR exposure, the results are suspect. A combined cohort study of workers at the Hanford, Rocky Flats, and Oak Ridge facilities showed no apparent leukemia risk [171]. Finally, a study reporting on mortality in workers at the Chelyabinsk reactor and reprocessing plant in the Russian Federation reported that those who worked in the reprocessing plant between 1949 and 1953 (average dose of 2.45 Gy) had an increase in leukemia cases (25 observed vs 7 expected cases) [172]. For those working between 1954 and 1958 (average dose of 7.16 Gy), 6.0 cases were observed (vs 3.6 cases expected). Other occupational studies have been reported in the radiation epidemiology literature, as reviewed by Mettler and Upton [7].

An explosion at a nuclear facility in the southern Urals took place in 1957, resulting in radioactive waste reaching the Techa River (exposure of up to 4 Gy). A comparison of incidence of leukemia cases in approximately 28,000 exposed persons was made to that in 394,000 unexposed persons [173]. A significant increase in incidence of leukemia was observed with an ERR per Sv of 1.9. This represents only 50% of the leukemia risk for atomic bomb survivors

Table 4. Leukemia in nuclear facility workers

Site (years)	Design	No. subjects	Risk
UK Atomic Energy Authority (1946–1979)[1]	Cohort	39,546	None
Mound Facility, Ohio (1947–1979)[2]	Cohort	—	Increased only if CLL included
Hanford, Rocky Flats, Oak Ridge[3]	Combined Cohort	H-23,704 (492,000 PY) RF-5897 (83,000 PY) OR-6332 (130,000 PY)	None
Chelyabinsk, Mayak[4] (1949–1953) (1954–1958)	Cohort	931 worker with av. dose of 2.45 Gy (1949–1953) 1479 workers with av. dose of 7.16 Gy (1954–1958)	25 obs/7 exp (1949–1953) 6obs/3.6 exp (1954–1958)

Results summarized from text of (170)[1], (171)[2], (172)[3], and (173)[4].
Abbreviations: Obs—observed cases, Exp—expected cases, H—Hanford, RF—Rocky Flats, OR—Oak Ridge.

(ERR = 4.4 per Sv). Additional studies of this population may explain whether reduced risk of leukemia in the Techa River incident relates to a dose-rate effect, accuracy of dosimetry, case ascertainment, and/or differences in biological response. Results of such studies must be interpreted in the context of reported declining health in the Russian Federation [174].

Finally, clusters of leukemia have been reported in children of nuclear power plant workers [175–178]. Gardner and coworkers reported an eightfold increase in risk for children of fathers who were exposed to IR before conception [175]. They postulated that childhood leukemia (and non-Hodgkin's lymphoma) may be caused by a father's exposure to IR prior to conception of the child. The Gardner hypothesis has not been validated when subject to further scrutiny [176]. Nevertheless, several additional case-control studies have been performed to suggest that clusters may potentially exist among children of nuclear facility workers [177–179]. In a study of a population exposed near the La Hague plant in Normandy, the relative risk for individuals using local beaches was 2.87 (95% confidence interval [CI], 1.05–8.72) and that for consumption of local fish was 2.67 (95% CI, 0.91–9.51) [177]. Other studies in the United Kingdom have suffered from low case numbers and the lack of an observed dose response [178,179].

Aside from radiation-associated leukemia, a hallmark of cancer death associated with IR exposure is its occurrence at an age that is typical for the onset of a malignancy. For example, multiple myeloma has been associated with exposure to low-dose IR in individuals at older ages of exposure who have worked at the Hanford, Los Alamos, Oak Ridge, and Savannah River facilities [180,181]. Results of a large international worker study (covering over 2.1 million PY and over 15,800 deaths) did not support an association between exposures at older ages and development of myeloma [182]. However, others have confirmed that there is an effect for older-age individuals in both cohort and nested case-control studies of multiple myeloma, with different dose-response relationships than those for individuals who have younger ages at exposure [183,184]. Accordingly, older adults may be more sensitive than younger adults to IR with respect to risk for myeloma and other cancers.

Other accidental exposures

Populations downwind of nuclear weapons test sites have been assessed for hematologic complications of exposure to IR. Based on the previous discussion, it is clear that the most sensitive indicator of a hematologic effect is mortality from leukemia. Weak or insignificant associations between mortality and incidence of leukemia have been documented in the literature [185–191].

Between 1946 and 1958, the Marshall Islands were used to test nuclear devices. On March 1, 1954, a thermonuclear device was detonated on the Bikini Atoll, after which an unexpected wind shift resulted in radioactive fallout deposition on inhabited atolls [185,186]. This resulted in dose-dependent suppression of hematopoiesis, which resolved after several weeks, although mild depression of blood counts persisted for several years. A single case of infant leukemia was reported after exposure to 1.9 Gy [185,186].

A weak association between childhood leukemia and IR exposure from the Nevada Test Site was reported by Lyon and coworkers [187]. However, individual dosimetry was lacking for the exposed population. Of more importance was the anonymously low incidence rate of leukemia in Utah in the years prior to the Nevada Test Site testing (1944–1949). Finally, there was an insignificant association between leukemia and estimated bone marrow dose [191]. The results of the "smoky" bomb test in 1957 indicated that 9 cases of leukemia occurred (where 3.5 cases were expected) [188]. This analysis suggested an absolute risk of 160 cases per 1 million persons annually for 10 mGy. Mean bone marrow dose was 5.3 mGy. However, the low number of cases makes it difficult to generalize from this report. Finally, no association between leukemia rates and exposure have been documented for weapons test sites in the United Kingdom and Nordic countries [189,190].

Management of early hematologic complications of radiation exposure

The threat of large-scale incidents [192] has heightened awareness of the role of physicians as early responders to chemical, infectious, and radiation accidents and to the intentional use of weapons of mass destruction [193–194]. Hematologists will be likely involved in early evaluation of victims experiencing one or more cytopenias resulting from such exposures. Guidelines have been reviewed for the management of acute radiation exposure [40,195]. The reader is referred to these publications for further discussion of approaches that include replacement of blood components, administration of replacement therapy, growth factors, and transplantation with allogeneic bone marrow, peripheral blood stem cells, and cord blood cells.

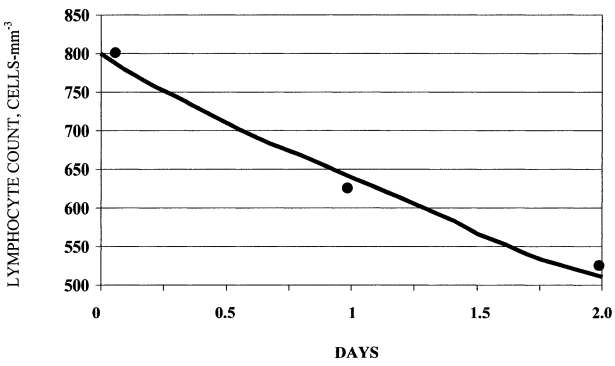

Figure 4. Lymphocyte kinetics after IR exposure. Decrease in absolute lymphocyte count is shown at 0–2 days after a neutron-γ mixed field accident with a γ equivalent dose of approximately 3.5 Gy. Modified from [197]. Used with permission of Health Physics.

Table 5. Hematopoietic response to IR exposure

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes[1]	$\geq 1.5 \times 10^9$/l	<1.5–1×10^9/l	<1–0.5×10^9/l	$<0.5 \times 10^9$/l
Granulocyte changes[2]	$\geq 2 \times 10^9$/l	$<2 \times 10^9$/l	0.5–1×10^9/l	$<0.5 \times 10^9$/l or initial granulocytosis
Thrombocyte changes[3]	$\geq 100 \times 10^9$/l	<100–50×10^9/l	<50–20×10^9/l	$<20 \times 10^9$/l
Infection	local; no antibiotic therapy required	local; only local antibiotic therapy required	systemic; oral antibiotic treatment sufficient	sepsis; intravenous antibiotics necessary
Blood loss	petechiae; easy bruising; normal Hb	mild blood loss with $<10\%$ decrease in Hb	gross blood loss with 10–20% decrease in Hb	Spontaneous or blood loss with $>20\%$ decrease in Hb

Reference values: 1.5–4×10^9/l[1], 4–9×10^9/l[2], 140–400×10^9/l[3]
Modified from [40], p. 59. Used with permission of the British Institute of Radiology.

Initial assessment of radiation exposure requires an estimate of radiation dose. Recently, the importance of monitoring the decrease in absolute lymphocyte count has been emphasized in early dose assessment [196,197]. Figure 4 depicts lymphocyte kinetic data from an individual who was accidentally exposed to 3.5 Gy (as measured by whole-body dosimetry). From a practical viewpoint, early estimates may be obtained by examining the lymphocyte depletion rate and multiplying by a factor of 8.6 [197]. Approximations can be obtained for γ radiation or mixed-field radiation at doses of greater than 50 cGy and less than 8–10 Gy by this simple technique. Since the defined dose range includes virtually all doses at which therapeutic options (other than observation alone for low-dose exposure and supportive therapy alone for exposure to lethal doses) must be thoughtfully exercised, determination of lymphocyte depletion kinetics is practical for early dose estimation. Although recent approaches have assessed dose by biological response only [40], dosimetry using cytogenetics or γ-spectrophotometry may be extremely valuable [198,199].

Based on analysis of historical data and computer modeling, Fliedner and colleagues have estimated severity of biological response by measuring the absolute level of lymphocytes, granulocytes, and platelets in the absence and presence of infection or blood loss (see Table 5). Using the degree of hematopoietic response, one may develop an algorithm according to which patients may be triaged to observation in an ambulatory setting, observation on a hospital medical floor, or admission to the medical intensive care unit. Therapy is based upon the degree of hematopoietic response (see Fig. 5). For further detail, the reader is referred to the Manual on the Acute Radiation Syndrome [40], a publication sponsored by the Nuclear Fission Safety Program of the European Atomic Energy Community, and report No. 138 of the National Council on Radiation Protection and Measurements [196].

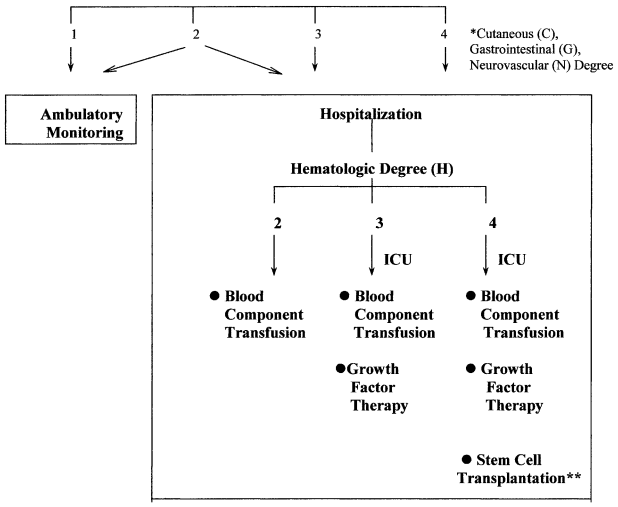

Figure 5. Overall approach to therapy of radiation victims. *Systems include cutaneous system (1: minimal, transient rash; 2: moderate rash of <10 cm^2, $<10\%$ body surface area or BSA; 3: marked rash, 10–40% BSA with onycholysis; 4: severe rash, $>40\%$ BSA with onycholysis), gastrointestinal system (1: 2–3 stools/day with minimal abdominal pain; 2: 4–6 stools/day with moderate pain; 3: 7–9 stools/day with severe pain; 4: ≥ 10 stools/day with excruciating pain), and neurovascular system (1: mild nausea with vomiting 1×/day, BP $>100/70$, normal neurological exam; 2: vomiting 2–3×/day, BP $<100/70$and $>90/60$, focal neurological deficits and memory loss; 3: vomiting 6–10×/day, BP $\leq 90/60$ and >80 palpable, prominent neurological deficits, major intellectual impairment). **Presence of G4, C4, and/or N4 degree indicates probable death. Supportive therapy alone is indicated (fluids, blood components, antibiotics, pain Rx, counseling).

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