Management of Ionizing Radiation Injuries and Illnesses, Part 3: Radiobiology and Health Effects of Ionizing Radiation

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Ionizing radiation exposure can induce profound changes in intracellular components, potentially leading to diverse health effects in exposed individuals. Any cellular component can be damaged by radiation, but some components affect cellular viability more profoundly than others. The ionization caused by radiation lasts longer than the initial inciting incident, continuing as 1 ionization incident causes another. In some cases, damage to DNA can lead to cellular death at mitosis. In other cases, activation of the genetic machinery can lead to a genetic cascade potentially leading to mutations or cell death by apoptosis. In the third of 5 articles on the management of injuries and illnesses caused by ionizing radiation, the authors provide a clinically relevant overview of the pathophysiologic process associated with potential exposure to ionizing radiation.

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Purposeful exposure of patients to ionizing radiation has been a staple in the practice of medicine since the use of the first x-rays more than 100 years ago. Whether for general radiologic study or for targeted administration in cancer therapy, most physicians will, on a daily basis, encounter a patient who has been exposed to ionizing radiation. To appreciate the systemic pathophysiologic process of ionizing radiation injuries and illnesses, it is necessary to understand how ionizing radiation causes subcellular, cellular, tissue, and organ damage. In contrast to the nontherapeutic radiologic/nuclear incidents and disaster scenarios discussed in the previous article in the series,[1] the present article explores issues associated with routine and accidental exposure from administration of ionizing radiation during routine clinical practice. We provide key background material required to successfully diagnose and manage this patient population, and we report clinically relevant principles of radiobiology that all physicians, regardless of specialty, should be familiar with.

Ionization and Free Radical Formation

Free radicals are atoms or molecules carrying an unpaired orbital electron in the outer shell. As soon as ionization occurs in tissue and free radicals are formed, the ionization becomes progressive up to and including lipid peroxidation of cellular membranes, which can also result in cellular death, as demonstrated by the following equations:

(1) $H_2O + \text{ionizing radiation} \rightarrow H_2O^+ + e^-$

(2) $H_2O^+ + H_2O \rightarrow OH + H^3O^+$

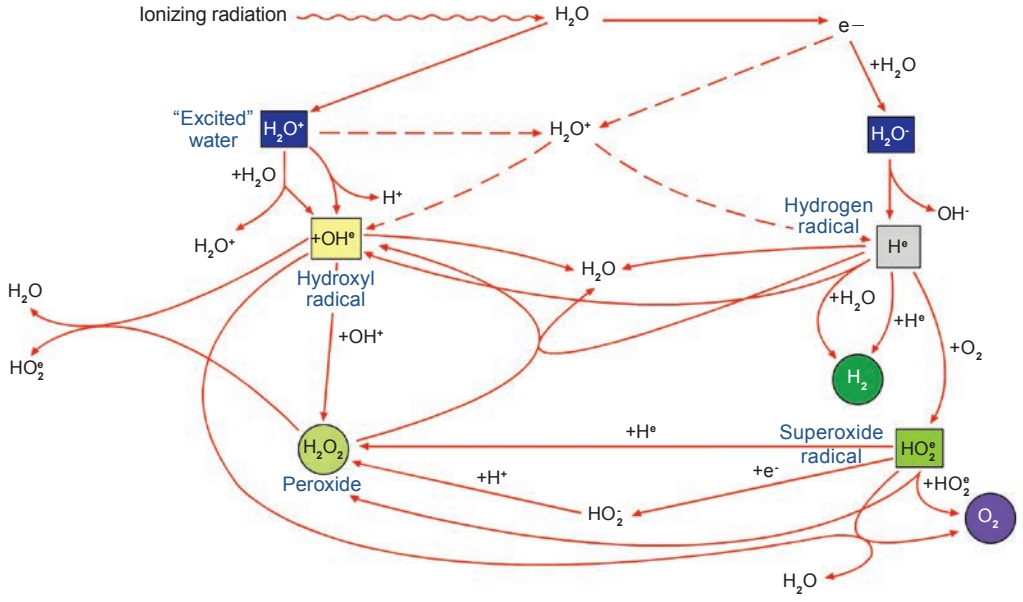

Figure 1.
Cascade of effects from the ionization of water.

Water is the most abundant constituent of cells and tissues—thus, the breakdown of H_2O molecules by means of radiation (ie, radiolysis) is an important means of generating free radicals.[2(p9)] An electron not only revolves around the nucleus of the atom but also spins on its own axis. When the number of electrons spinning clockwise matches the number spinning counterclockwise, a state of electronic equilibrium exists and the atom or molecule is in a state of chemical stability.

In contrast, an atom or molecule that has lost an electron through oxidation by ionization will have an odd number of electrons. As a consequence, it lacks an electron with an opposing spin. This unpaired electron is associated with a high degree of chemical reactivity. Because 80% of a cell is water, there are numerous opportunities for atoms of water to interact with x-rays, γ-rays, or charged particles such as electrons or protons. This interaction is shown in equation (1), where H_2O^+ is an ion radical that reacts with another water molecule to form the highly reactive hydroxyl radical (OH). The hydroxyl radical possesses 9 electrons; thus, 1 electron is unpaired. This free radical is highly reactive and can diffuse a short distance to reach a critical target in a cell. It has been estimated that approximately two-thirds of the x-ray damage to DNA in mammalian cells is caused by the hydroxyl radical.[2]

The ionization of water is a seminal incident in human disease caused by ionizing radiation. *Figure 1* depicts the cascade of ionizations that result.

Types of Ionizing Radiation

Ionizing radiation is categorized as either direct or indirect.[2(pp7,89)] Particulate forms of radiation, such as α-particles, have sufficient kinetic energy to readily (ie, directly) disrupt the atomic structure of the absorber and thus produce chemical and biological changes. In contrast, electromagnetic radiation (ie, x-rays and γ-rays) is indirectly ionized: it does not cause substantial chemical and biological damage by itself. Instead, it deposits en-

ergy by means of ionization into the medium through which it passes. This process results in "liberated" electrons (charged particles), which in turn produce ionization along their respective paths.

The average energy deposited per unit of path length is defined as the linear energy transfer (LET),[2(pp9,104-106)] which is most often set in units of kiloelectron volts per micron (keV/μm) of path length. The notion of LET is an important concept in radiobiology because both chemical and biological effects are directly linked to the magnitude of ionization in the tissue. In many materials, the energy required to produce an ion pair—that is, the removed electron and remaining positively charged particle—is estimated to be between 30 and 40 electron volts (eV).[3] This energy is more than enough to break a double bond linking one carbon atom to another, as found abundantly in the base pairs of DNA.

Table 1 lists common types of radiation, radiation energies, and LET values. As can be seen, photons (x-rays and γ-rays) are not very efficient at creating ionizations along their paths, unlike α particles and neutrons, which are very efficient.

Relative Biological Effectiveness

Biological damage produced by radiation increases as the LET of radiation increases. As a result, equal doses of different types of radiation do not produce equal biologic effects. Thus, 1 Gy of neutrons produces a greater biologic effect than 1 Gy of x-rays. Relative biological effectiveness is a factor used to compare the biological effectiveness of different types of ionizing radiation.[2(pp108-110)] According to a report by the National Council for Radiation Protection and Measurements,[4] relative biological effectiveness is defined as the ratio of absorbed dose of a reference radiation necessary to produce a given effect in a biological system to the absorbed dose of a specific radiation to produce an equal response.

Table 1.
Types of Radiation, Associated Energies, and LET Values

Radiation	Energy	LET, keV/μm
X-ray	250 keV	3.0
Cobalt-60 γ	1.17 MeV, 1.33 MeV	0.3
X-ray	3 MeV	0.3
β-particle	1 MeV	0.25
Neutron	2 MeV	20
α-particle	5 MeV	100

Abbreviation: LET, linear energy transfer.

DNA Damage and Mitotic Death

If a photon or energetic particle causes ionization in a biologically important molecule, then the connections holding the structure together are threatened. With DNA, for example, the DNA strands can break.[2(pp12-16)] A single-strand break can be repaired by intranuclear enzymes, after which the chromosomes may function normally.[2(pp16-23)] If a break occurs in both sister chromatids or both chromosomes, exchanges of DNA between the 2 strands can occur, called double-strand breaks. Enzymes can also repair double-strand breaks; if the exchange is of the same DNA sequence on each sister chromatid (ie, a symmetrical exchange), there may be no net effect on cellular function and the chromosome may function normally. If, however, the exchange is asymmetrical and is not repaired properly, the cell may not be able to function normally and will eventually die. A centromere is a constriction point along the linear course of DNA strands. If the asymmetrical exchange results in 1 chromosome having 2 or more centromeres (eg, dicentric chromosome, tricentric chromosome) and the other having no centromere (ie, having an acentric fragment), then the chromosomes will not be able to divide at mitosis and the cell undergoes a mitotic death (*Figure 2*).

The other important method of cell killing is by apoptosis, which may occur by means of the normal physiological processes or by means of a toxicant such as ionizing radiation.

Apoptosis, Programmed Cell Death, and Cellular Suicide

Apoptosis is called *programmed cell death* when it occurs as a normal physiological phenomenon, one which allows the body to remove senescent cells, cells that are functioning abnormally, or cells that are cancerous. Ionizing radiation, however, can induce the genetic expression of the enzymes that result in cellular suicide, a pathologic process. Ionizing radiation may also result in death by means of apoptosis. Apoptosis in ionizing radiation injuries and illnesses may be even more important than mitotic death. The molecular biology underlying apoptosis is complicated and involves an enzymatic cascade that eventually results in production of executioner caspases that activate genetic and other cellular mechanisms—again, resulting in cell death.[2(pp35,41-42,46-47,304-330),3(pp11-12)]

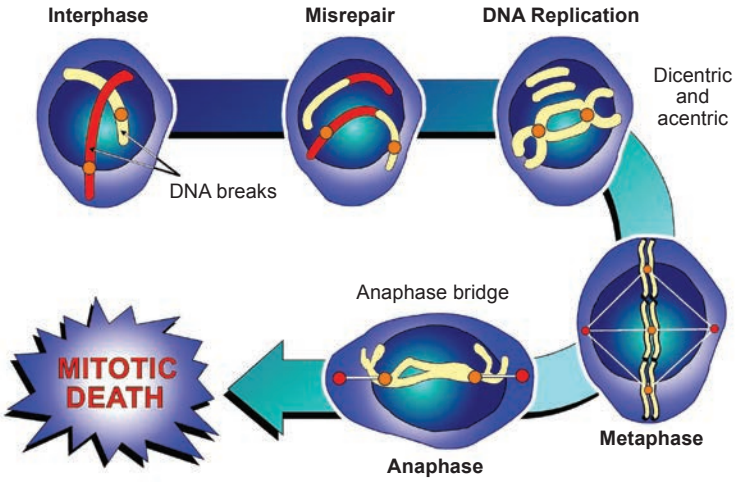

Figure 2.
Asymmetrical exchange of DNA.

Radiosensitivity and Radioresistance

Some cells are more sensitive to damage by ionizing radiation than others, a tendency discovered by the French scientists Bergonié and Tribondeau.[5,6(pp14,333-334)] The *Bergonié-Tribondeau law*, as it is now known, states that cells that are rapidly dividing (ie, that have a high mitotic index) and cells that are more immature (ie, which are more undifferentiated) are more sensitive to ionizing radiation.[7] The obverse is that cells that are not mitotically active and cells that are more differentiated are more radioresistant. In general, the law means that the sensitivity of cells to radiation is related directly with the reproductive capacity of the cells and inversely with their degree of differentiation.

The clinical implication of this law for practicing physicians is that the relative sensitivity of hematopoietic progenitor cells, epidermal stem cells, gastrointestinal stem cells (ie, "crypt" cells), and endothelial cells will result in the manifestation of damage to these cells in acute radiation syndrome (ARS). *Figure 3* summarizes these principles. The other types of cells play less of a role in acute radiation illnesses but may play a substantial role in acute high-dose local radiation injury. These types of illnesses will be detailed in the final article in this series.[6,8,9]

We note, however, some exceptions to the Bergonié-Tribondeau law. Agranulocytes—particularly lymphocytes—are exquisitely radiosensitive but do not undergo mitosis at all and thus are terminally differentiated. In fact, the damage to lymphocytes can be monitored with serial complete blood cell counts. White blood cell differentials in substantial radiation injuries will show a dose-response decrease in the absolute lymphocyte count (ALC).[10,11] Lymphocyte depletion kinetics—which involves measuring serial complete blood cell counts over time (generally every 6 to 12 hours) and comparing measurements with a previously established curve[12]—is used to perform what is called *laboratory radiation biologic dosimetry* (biodosimetry), which is used to estimate a radiation dose that can serve as a guide to medical management.

Depletion of lymphocytes will lead to a certain degree of immunologic incompetence. More importantly, lymphocyte depletion using the ALC can be used to esti-

More Radiosensitive
Mature lymphocytes
Hematopoietic progenitor cells
Mitotically Active
Epidermal stem cells
Undifferentiated
Spermatogonia
More Metabolically Active
Gastrointestinal stem ("crypt") cells
Endothelial cells
Salivary gland cells (parotids primarily)
Gastric gland cells
Osteoblasts
Not Mitotically Active
Chondroblasts
More Differentiated
Spermatocytes
Less Metabolically Active
Granulocytes
Osteocytes
Spermatozoa
More Radioresistant
Erythrocytes

Figure 3.
Relative radiosensitivity of different types of cells. Cells at the top of the list are more radiosensitive than those at the bottom. From a medical standpoint, mature lymphocytes, hematopoietic progenitor cells, epidermal stem cells, gastrointestinal ("crypt") cells, and endothelial cells are the most important not necessarily because they are so radiosensitive but because damage to these cell populations at survivable doses can wreak medical havoc.

mate radiation dose to predict what will happen to the neutrophil count. Substantial depletion of neutrophils will lead to further immunologic incompetence with concomitant infections, a major cause of morbidity and mortality following acute whole-body exposures to ionizing radiation. One would ideally like to know the extent to which the immune system will be compromised to prophylactically manage impending leukopenias and associated infections.

As demonstrated in *Figure 4*, the various progenitor (precursor) cells are more radiosensitive than their more mature and differentiated daughters. The term *progenitor* is used to distinguish these cells—which have the ability to form more than 1 kind of mature cell, a state known as being multipotent—from those that do not have the ability to form all kinds of mature cells. Hematopoietic stem cells can form all types of blood cells and are therefore also multipotent. It is important to be able to distinguish embryonic stem cells from hematopoietic and other kinds of stem cells. Embryonic stem cells are truly capable of forming all types of bodily cells and are thus defined as totipotent.

As the various formed elements of blood (*Figure 5*) differentiate and mature, they are less radiosensitive according to the Bergonié-Tribondeau law. Furthermore, cells like erythrocytes and platelets are very radioresistant because they are terminally differentiated and have no nuclei or genome to guide cell division. Thus, such cells are not mitotically active. Beginning with mature lymphocytes—which are exquisitely sensitive to ionizing radiation and therefore exempt from the Bergonié-Tribondeau law—precursors to other formed elements of blood are not as radiosensitive. Depletions of the numbers of granulocytes, platelets, and erythrocytes will therefore occur later.

Genetics Overview

The structure and behavior of chromosomes provide the physical basis of most genetic phenomena. During somatic cell division (ie, mitosis), the genetic material in a cell is first replicated then divided equally and exactly between 2 daughter cells. The mammalian cell cycle consists of 4 mitotic stages (ie, prophase, metaphase, anaphase, and telophase) and the subsequent interphase stage can be divided into 3 stages: gap 1, synthesis, and gap 2. Gap 1 is defined as the period between the previous mitotic phase and the subsequent synthesis, or biosynthesis, phase, and gap 2 is the period between completion of the biosynthesis stage and next mitotic stage (*Figure 6*).

In other words, the cells undergo a regular alternation of chromosome replication and segregation at mitosis to maintain bodily organs, replenish with new cells, and sustain the organism. Chromosomes are central to the entire organism because they reproduce themselves and the genetic content (the genome) with a high degree of precision. The replication and repair of DNA within the chromosomes comprise the basic processes involved in the maintenance of genetic stability. That ionizing radiation can perturb these basic processes is not surprising because alterations in the structural features of DNA and chromosomes can lead to mutagenesis, carcinogenesis, or cell death by mitotic death or apoptosis.

The cell cycle can be divided into 2 major parts: interphase (the period between mitotic divisions) and mitosis. *Figure 6* depicts this process. Some important functions activate before mitosis to enable the daughter cells to have the full complement of chromosomes and organelles. The cell cycle is most sensitive during the period of synthesis and shortly thereafter when the sister chromatids have formed.[2(p54-58,117)] Phytohemagglutinin is used to stimulate mitosis and is an essential part of the process of the dicentric chromosome assay (DCA).[13,14]

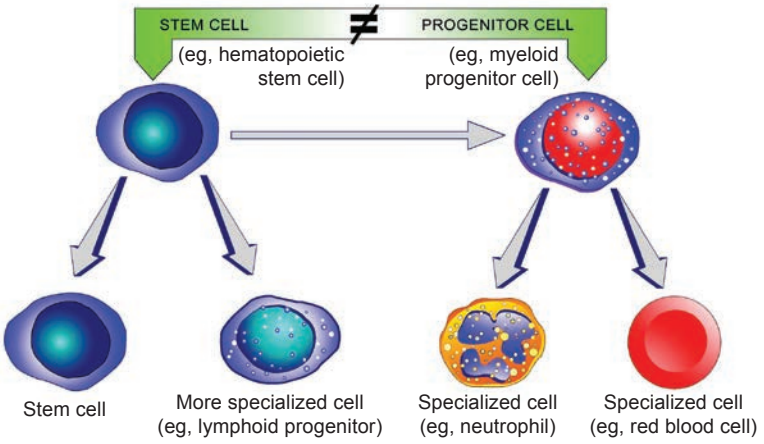

Figure 4.
The various progenitor (precursor) cells, seen here, are more radiosensitive than their more mature and differentiated daughters.

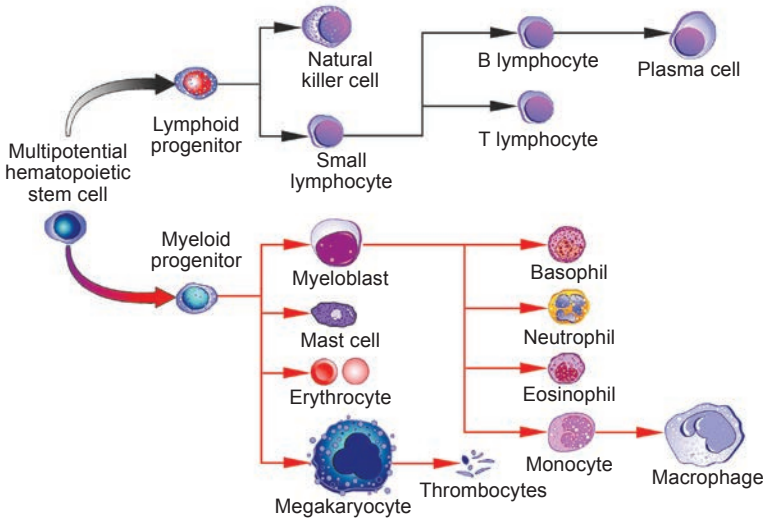

Figure 5.
The various formed elements of blood.

Table 2.
Effects of γ-Ray Dose on Dicentric Chromosome Frequency

Dose, Gy	Cells Scored, No.	Total Dicentrics	Dicentrics/Cell
0	2000	3	0.0015
0.25	2000	29	0.0145
0.50	2000	53	0.0265
1.00	1832	200	0.1092
2.00	488	201	0.4119
3.00	262	200	0.7634
4.00	154	201	1.3052
5.00	134	202	1.5075

Cytogenetic Biodosimetry

Modifications of chromosome number or structure are known to occur in all organisms. In humans, such changes may occur spontaneously or be associated with exposure to chemical, biological, and physical agents. Ionizing radiation is a particularly powerful agent because of its unique ability to cause direct or indirect damage to chromosomal DNA. The damage to DNA increases with the absorbed dose. Biological dosimetry is an essential tool for radiation dose assessment when exposures are unexpected and physicians are unable to rely on instruments of physical dosimetry (eg, film badges, other kinds of cumulative radiation dosimeters). Lymphocytes can serve as biosensors of radiation exposure because of their sensitivity, accessibility, and whole-body distribution, as well as their ability to record chromosomal DNA damage in a reproducible, dose-dependent manner.

Because of constant exposure to ambient terrestrial and cosmic radiations, most humans have a very low spontaneous frequency (approximately 0.5 to 1 per 10^3 cells) of dicentric chromosomes in their peripheral blood lymphocytes whether or not they have been directly exposed to medical or industrial sources.[15,16] The numbers of these dicentric chromosomes are independent of both age and sex and are relatively easy to identify. The DCA was first introduced in the 1960s and has now been validated by its use in a number of radiation accidents that occurred in Goiânia, Brazil[17]; Chernobyl, Ukrainev[18]; and Tokai-mura, Japan.[19] The DCA remains the standard assay for estimating radiation dose.[20] After whole-body exposure to low-LET radiation, doses down to about 100 to 200 mGy (10-20 rem) are detectable with the DCA.

A DCA involves the following steps: (1) lymphocyte culture, (2) cell fixation, (3) slide preparation and staining, and (4) scanning individual cells at the metaphase stage for the presence of chromosomes with 2 or more centromeres. To perform the DCA, peripheral blood is drawn and put into tissue culture for 48 hours. During this time, lymphocytes are artificially stimulated to divide using the chemical phytohemagglutinin and then the division process is stopped in metaphase with the chemical colcemid. Cells with chromosomes that have undergone double-strand breaks and asymmetrical DNA exchanges are unable to divide at metaphase. The dicentric chromosomes are counted and then compared with dose-response curves that have been predetermined on the basis of measures of human blood that has been irradiated to known doses with a variety of radiation sources. At the Radiation Emergency Assistance Center/Training Site (REAC/TS), we use human blood that has been irradiated with cobalt-60 (Co-60 or 60Co) γ-rays, 250 keV x-rays, and californium-252 (Cf-252 or 252Cf) neutrons at various doses to develop the dose-response curves against which a patient's numbers of dicentric chromosomes are compared. *Figure 7* reproduces a photomicrograph of a metaphase spread used for the DCA.

Although the DCA is the standard of radiation biodosimetry,[21] it is labor intensive, time consuming, and costly. Other cytogenetic biodosimetry techniques are available, including premature chromosome condensation, fluorescence in situ hybridization, and the micronucleus assay. Each technique has its own advantages and disadvantages and not all are available to all cytogenetics laboratories. Unfortunately, there are only 2 federally funded cytogenetic biodosimetry laboratories in the

United States: REAC/TS in Oak Ridge, Tennessee, and the Armed Forces Radiobiology Research Institute in Bethesda, Maryland. There are more than 100 laboratories in the United States that are accustomed to performing cytogenetics techniques; however, they are in the business of analyzing chromosomes for the purposes of family genetic counseling and are not in the business of performing radiation biodosimetry. Efforts are underway at REAC/TS to collaborate with these genetics laboratories using online distance scoring of chromosomes to increase cytogenetic throughput nationally.[22] These efforts are in preparation for radiologic/nuclear incidents such as those that were discussed in part 2 of this series.[23]

The number of abnormal (eg, dicentric) chromosomes increases in a dose-responsive manner up to about 5 Gy, at which point a person is considered to have acute whole-body irradiation. Above that dose, circulating lymphocytes have usually been so depleted that by the time the DCA is performed, a person does not have enough lymphocytes that will grow in culture. Therefore, at doses ⩾5 Gy, other cytogenetic techniques must be used. *Table 2* shows the effects of γ-ray dose on dicentric chromosome frequency.

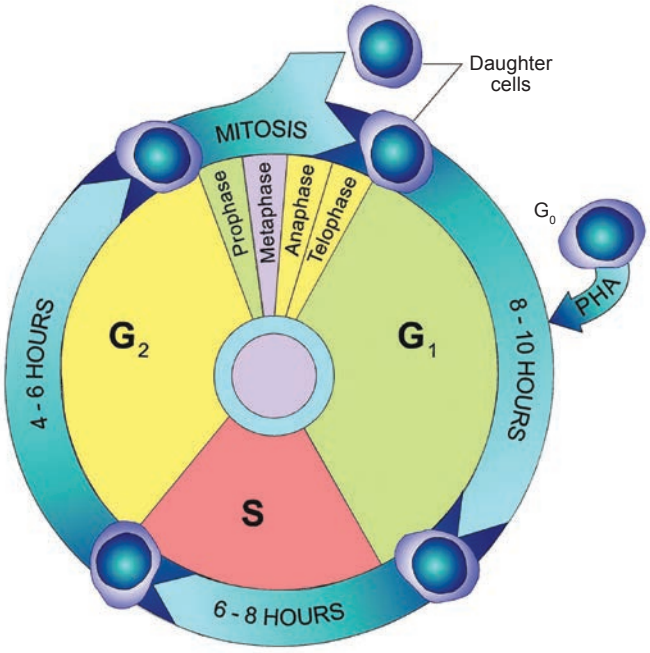

Figure 6.
The mammalian cell cycle, which consists of 4 mitotic stages—prophase, metaphase, anaphase, and telophase—the subsequent interphase stage, and 3 subsequent phases: gap 1, synthesis, and gap 2.

Scenario

A radiographer performs industrial radiography, or nondestructive testing, on a component at a factory. Whereas relatively low-energy x-rays are used for diagnostic human radiography (eg, 120 kVp), high-energy γ-rays at high dose rates from very active sources are used for industrial radiography (eg, 1.17 and 1.33 MeV gammas from cobalt-60, with activities of tens to hundreds of curie [Ci]), which are used to penetrate metallic objects to reveal potential defects.

After performing the procedure, he packs his equipment and leaves. He does not know that the radioactive source has become disconnected from the drive-cable used to guide the radioactive source through the guide-tube. The source is a 2.6-terabecquerel (2.6 TBq or 70 Ci) iridium-192 source. Before the radiographer discovers that the source has become dislodged and returns to retrieve it, a factory worker performs maintenance on a piece of equipment in close proximity to the unsecured source. Because of the nature of the repairs, the worker spends approximately 6 hours in the area. The source is on the floor, approximately 1 m from where the worker performs his duties. A quick calculation using standard dose factors results in a potential dose to the worker on the order of 2 Gy, or 200 rad. Later that night, 4 to 5 hours after his shift, the worker begins to feel nauseated.

Acute whole-body irradiation at the estimated dose of about 2 Gy in this worker would be expected to cause a mild and survivable ARS.[24,25] The effects seen at this dose are primarily systemic effects that are not specific to ionizing radiation exposure (eg, nausea) and damage

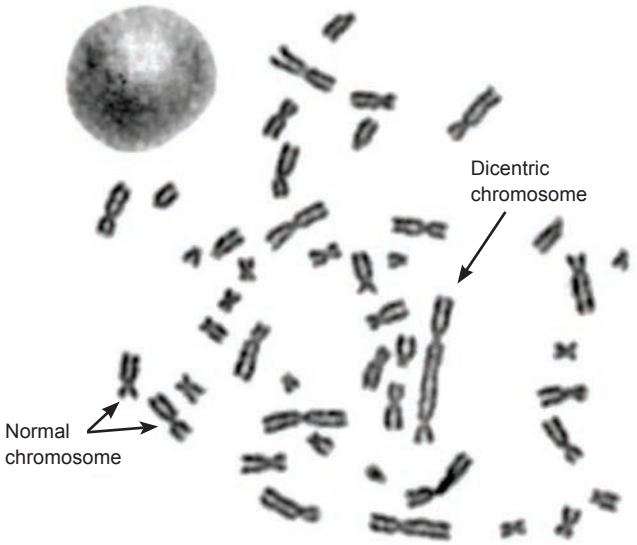

Figure 7.
Photomicrograph of a metaphase spread used for the dicentric chromosome assay.

to the hematopoietic system called *mild hematopoietic subsyndrome* of ARS, which will be discussed in part 5 of this series.[9] His ALC would be expected to drop in a dose-responsive manner. This trait was demonstrated on serial complete blood cell counts (with white blood cell differential every 6 hours times 4 for the ALC).

The number of dicentric chromosomes cultured from his peripheral blood cell count would also be expected to rise in a dose-responsive manner. This trait was demonstrated with the DCA that showed 200 dicentric chromosomes in 488 cells analyzed. Assuming no medical treatment is given, the median lethal dose 50/60 (LD50/60) for acute whole-body irradiation or irradiation of a significant part of the human body is on the order of 3.5 to 4 Gy (350-400 rad).[26] This worker, if young and healthy, would be expected to survive ARS at a radiation-absorbed dose of 2 Gy (200 rad) with only supportive care. The use of growth factors or cytokines such as granulocyte colony–stimulating factor might still be considered for this patient to stimulate production, differentiation, and maturation of other white blood cells.

Conclusion

Radiation's effects on biological systems can be quite complex but are in many ways predictable. Many factors have to be considered—not only those of radiation physics—including the results of energy deposition and the resulting effects on various biological systems. The physician may not consider the underlying pathophysiologic process of ionizing radiation exposure at the time of medical management of a case, but as the radiation dose becomes higher, medical management becomes more complex. As the process becomes more complex, the physician will need to explore more deeply the underlying pathologic process as she or he considers alternatives for intervention. The next article in the series[27] will focus on the management of the cutaneous manifestations of exposure to ionizing radiation.

Author Contributions

Dr Christensen and Mr Sugarman provided substantial contributions to conception and design; Drs Livingston, Christensen, and Parrillo and Mr Glassman drafted the article or revised it critically for important intellectual content; and Dr Christensen and Mr Glassman gave final approval of the version of the article to be published.

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