Ionizing Radiation Injuries and Illnesses

Doran M. Christensen, DO*, Carol J. Iddins, MD,
Stephen L. Sugarman, MS, CHP, CHCM

KEYWORDS

• Acute radiation syndrome • Hematopoietic syndrome • Cutaneous syndrome
• Cutaneous radiation syndrome • Acute local radiation injury • Radiological • Nuclear

KEY POINTS

- Ionizing radiation injuries and illnesses are usually delayed, with the exception of extremely high or fatal doses.
- Stabilize medical and surgical conditions before dealing with radiological issues.
- Remove victim from contaminated area and remove potentially contaminated clothing using radiation protection principles.
- Obtain medical history and physical examination to include pertinent negatives.
- Obtain incident history and summon physics expertise to assist with radiation dose estimations.

INTRODUCTION

The spectrum of information related to diagnosis and management of radiation injuries and illnesses is vast. It is assumed that most physicians in practice have little or no remembrance of materials taught in secondary school or college about physics and

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Radiation Emergency Assistance Center/Training Site (REAC/TS), Oak Ridge Institute for Science and Education (ORISE), U.S. Department of Energy (DOE), Oak Ridge Associated Universities (ORAU), PO Box 117, MS-39, Oak Ridge, TN 37831, USA
* Corresponding author.
E-mail address: doran.christensen@orau.org

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units of measurement. A very brief overview will be provided. Ionizing radiation injuries and illnesses are very rare, as are contamination incidents involving radioactive materials (REAC/TS Radiation Accident Registry). Most health care providers have had little to no experience with such cases, with perhaps the exception of those working in radiation oncology or nuclear medicine, where diagnostic and therapeutic application normally occur.[1] Furthermore, many medical school curricula do not include information about Disaster Medicine including radiological and nuclear hazards[2]; this is despite the fact that radiation sources (radioisotopes) enjoy widespread use in industry (eg, oil, gas, electrical power, and engineering); food, blood, and medical supply treatment; the military; research, and medicine. The US Nuclear Regulatory Commission and the States maintain approximately 22,000 radioactive materials licenses.[3] Exposures to ionizing radiation and internal contamination with radioactive materials can cause significant tissue damage and conditions. Emergency practitioners unaware of ionizing radiation as the cause of a condition, may miss the diagnosis of radiation-induced injury or illness. A review of the pathophysiology and medical management of radiation injuries and illnesses is thus important to fill this gap.

APPLICABLE PHYSICS

Radiation is generally defined as energy that is propagated through space.[4] A basic understanding of physics is necessary to fully apprehend the injuries that may result from radiological incidents. Radioactive materials are substances that emit ionizing radiation in an effort to reach nuclear stability. Ionizing radiations have sufficient energy to create charged particles, that is, ions, by the removal of a negatively charged electron from an atom. Electrons circle in orbits around central atomic nuclei made up of positively charged protons and electrically neutral neutrons.[5–9] Removal of an electron from such an atom would create 2 ions: the negatively charged electron and the positively charged atomic remnant. If ionization occurs in a biologically important molecule like a strand of DNA, the genome may not be able to function properly.[10]

Types of Ionizing Radiation

There are only a few ionizing radiations of concern for practical medical purposes: alpha particles, beta particles, positrons, and neutrons, plus the pure electromagnetic energy radiations gamma rays and X rays. All of these radiations, with the exception of X rays, are emitted from the nuclei of unstable radioactive atoms. X rays can be machine produced or can occur when electrons drop to lower energy orbital shells due to "self-ionization" of radioactive atoms.[5–9]

Alpha (α)

An alpha particle consists of 2 protons and 2 neutrons and has a +2 charge associated with it. It is very effective at ionizing other atoms and deposits its energy rapidly across its linear path. For medical purposes, this is important because an alpha particle can travel no more than a few centimeters in air and, as a general rule, cannot penetrate the outer layer of dead human skin. Alpha particles are therefore an internal hazard only. Materials that emit alpha particles pose a radiological hazard only if taken into the body via inhalation, ingestion, or if they enter the body via a contaminated wound. A sheet of paper is an effective shield for alpha particles (**Fig. 1**).[5]

Beta (β)

A beta particle is identical to an electron; however, because of some nuclear transformations it is emitted from the nuclei of some radioactive materials. Negatively charged beta particles, typically thought of as negatively charged, can penetrate further than

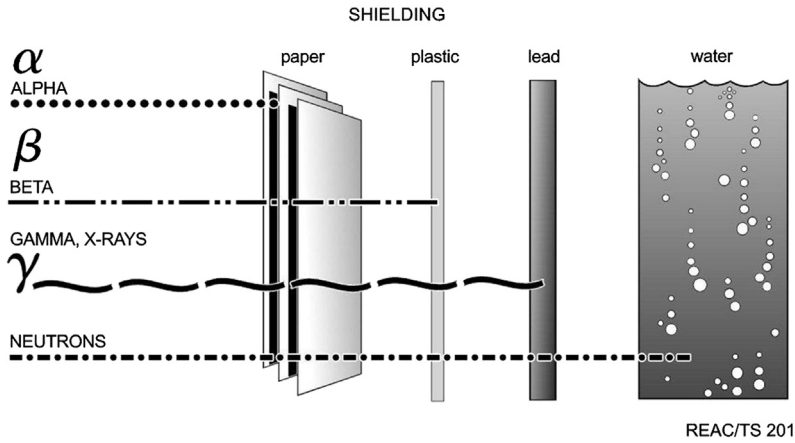

Fig. 1. Shielding requirements for various ionizing radiations.

alpha particles (several feet in air) and can penetrate human skin sometimes into subcutaneous tissues. Betas can therefore be an internal or an external hazard. A sheet of plastic, even plastic eyeglass lenses, can shield humans from most beta particles (see Fig. 1).[5]

Positron (β^+)

Positrons are positively charged beta particles emitted from the nuclei of some radioactive materials. They are essentially the antiparticles of electrons. When a positron interacts with an electron (its antiparticle), their masses are converted to energy (annihilation) resulting in the release of 2 "coincident" 511 keV photons at 180° from each other. Shielding from these photons requires dense materials like lead, steel, or concrete (see Fig. 1).[5] Positron-emitters are commonly used in some medical procedures.

Neutron

Neutrons are emitted from some radioactive materials. Those materials, however, are rare. More commonly, neutrons are associated with a criticality, a term used for nuclear fission or "the splitting of the atom." Neutrons can occur across a wide range of energies and can travel very long distances in air. They are not very interactive, but depending on their energy, can cause much damage to tissues when they finally interact because of their mass. Hydrogen is an excellent material for neutron shielding because its nucleus is approximately the same mass as the neutron. Water and paraffin are excellent shields for neutrons because they contain a large number of hydrogen atoms (see Fig. 1).[5] Neutrons are the only kind of ionizing radiation that can make other matter radioactive by adding neutrons to other atomic nuclei called "neutron activation."

Gamma rays and X rays

Gamma rays and X rays are photons or pure electromagnetic energy that have no mass. For that reason, they are not very efficient at creating ionization in matter and are much more penetrating than alpha and beta particles. Generally, gamma rays are more energetic than X rays and are more penetrating. Shielding from gamma or X rays requires high atomic weight materials such as lead, steel, or concrete (see Fig. 1).[5]

Units of Measurement

Radioactive materials are quantified by their decay rate. This is referred to as activity and defined as the number of disintegrations occurring per unit time. One disintegration per second (dps) is a becquerel (Bq) in SI units (International System of Units of Measurement). This unit is so small that it is much more common to see units of millions of Bq (megabecquerels or MBq) or trillions of Bq (gigabecquerels or GBq) or even larger.

More commonly used in the United States is the conventional unit called the curie (Ci) which is equivalent to 3.7×10^{10} dps (or Bq). Common subdivisions of the curie include the millicurie (mCi, thousandth of a curie) and the microcurie (μCi, millionths of a Ci). Disintegrations per minute (dpm) are also commonly used. A simple conversion factor is 1 μCi = 2.22 million dpm = 37,000 dps = 37 kBq.[5] Specific activity is a concept that describes activity per unit mass. Common units include Ci/g and Bq/g.

Radiation Dose

When ionizing radiation deposits its energy in the human body, it is referred to as absorbed dose or simply dose. The unit of measure for dose used in the United States is the rad. The unit for radiation dose in the SI system is the gray (Gy). A gray is equivalent to 100 rad or 0.01 Gy is equivalent to 1 rad. Use of the SI units is recommended.[5]

Equivalent Dose

Some radiations are more effective at causing long-term effects than others. The method for equating the biologic effect and longer-term risk from exposure to the various kinds of ionizing radiation is called equivalent dose. Equivalent dose is calculated by multiplying the radiation dose in rads or Gy by a radiation weighting factor (W_R). The radiation weighting factor is different for each radiation based primarily on their abilities to interact with other materials, and it relates the amount of biologic damage, and thus resulting risk, caused by any type of radiation to that caused by the same absorbed dose of X rays or gamma rays. Equivalent dose is measured in the United States with a unit called the rem. The SI unit is the sievert (Sv). The relationship between rem and Sv is the same as the relationship between the radiation absorbed dose units rad and gray: 100 rem = 1 Sv and 0.01 Sv = 1 rem[5–9]

As an example, simply put alpha particle irradiation (by internalization) is 20 times more effective than gamma rays or X rays at causing long-term tissue damage (**Table 1**).

RADIOBIOLOGY

Radiobiology is the study of effects of ionizing radiation on living creatures. The very basics assist in understanding ionizing radiation injuries and illnesses. Elements in this

Table 1
Radiation types and their weighting factors

Radiation Type	W_R (Weighting Factor)
Gamma- and X-rays	1
Alpha	20
Beta	1
Neutron	5–20

section are derived from a Hall and Giaccia text entitled "Radiobiology for the Radiologist,"[10] which is recommended reading for background in managing radiation-induced injuries and illnesses. A few of the major concepts follow.

Deterministic Effects of Ionizing Radiation

The short-term or relatively early effects of exposure to ionizing radiation are called deterministic effects because, essentially, the radiation dose "determines" the effect. There are also other factors that help determine radiation effects: total dose, dose rate, volume of tissue irradiated, type and quality of the radiation, presence of other disease conditions, concomitant physical trauma and/or thermal burns, and individual susceptibility.[10] Each of these factors contributes to worsening of the effects of radiation exposure. For deterministic effects, there is a "threshold" dose at which an effect is seen. As the dose is increased above that threshold, the effect worsens.

Stochastic Effects of Ionizing Radiation

Stochastic effects of radiation exposure are effects that occur by chance. An example of a stochastic effect is carcinogenesis. As the dose is increased, the likelihood that cancer will develop increases.[10] Counseling patients on the longer-term risk of radiation exposure is difficult and complex. In reality, several delayed effects need to be explained to exposed persons or families to help relieve anxiety. A few are mentioned in **Box 1**.

There are several information sources regarding the topics in **Box 1**. These include documents on the atomic bomb data and effects on survivors, hereditary effects in children of atomic bomb survivors, effects on children who were *in utero* at the time of the Japanese atomic detonations, cancer risk following low doses of ionizing radiation,[11–14] effects on personnel after the Chernobyl disaster such as thyroid cancer in children,[15] exposure of children to computed tomographic scans, and relationship to carcinogenesis.[16] Good sources of information about these matters are available in the Biologic Effects of Ionization Reports V–VII from the National Academy of Sciences and Sources and Effects of Ionizing Radiation from United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), a 2-volume set most recently published in 2008. These sources should be accessed by anyone who might reasonably be expected to counsel patients and their families on the effects of ionizing radiation.

Exposure or Irradiation Versus Contamination

If one is in the presence of a source of ionizing radiation, one is being exposed or irradiated. There is *no transfer* of radioactive materials required for an exposure or

Box 1
Delayed effects of ionizing radiation

- Radiation carcinogenesis
- Genetic hazards
- Late organ effects from therapeutic doses of radiation
- Vascular changes, fibroatrophy
- Cataracts
- Infertility
- Thyroid dysfunction

irradiation. As a reminder, an exposed or irradiated patient cannot contaminate others, equipment, or facilities. On the other hand, if something or someone has radioactive materials physically in them (internally contaminated) or on them (external contamination) they could cause contamination of others.[5,10] It is important to recognize that contamination with different materials results in differing risks. External contamination with an alpha-emitter will not pose a hazard unless that material is internalized, but contamination with a beta-emitter may be of concern because beta particles can penetrate beyond the outer, dead layer of skin, resulting in a potential risk for skin injury. Conversely, the level of concern is much higher for much smaller *amounts* of an internalized alpha emitter as compared to an internalized beta/gamma emitter because of the alpha's ability to create greater ionization/damage within cells as compared to that of a beta or gamma emitter.

Radiation Protection and ALARA

Protecting oneself, equipment, facilities, and the environment from exposure to ionizing radiation and/or contamination with radioactive materials is relatively easy when compared to chemical and biologic agents. This is because the energy from an ionizing radiation can easily be detected and identified with special instrumentation. Instrumentation that can give instantaneous levels of radiation or instantaneous identification of a radioactive material is readily available from several manufacturers.[5] There is also instrumentation available that will give accumulated dose to personnel or an area.

Health care providers should know that they can protect themselves from radioactive contamination relatively easily by using the same personal protective equipment (PPE) that is used as protection against biologic agents. The only difference between radioactive contamination and contamination with any other substance is that in the case of the former, some of the atoms emit radiation. A set of surgical scrubs, surgical mask, protective eyewear or face shield, head cover, shoe covers, and 2 pairs of nitrile gloves will generally meet protective needs. Be aware of protective clothing that does not "breathe" well, which may create a heat stress hazard during routine emergency activities. If the situation allows, PPE requirements can be lessened, thereby increasing responder comfort. On the rare occasion where respiratory protection will be required, an N95 mask or negative pressure HEPA-filtered respirator should suffice. Beware of interference of some of these PPE with ability to palpate, auscultate, and communicate with coworkers.[17]

The methods for minimizing the potential for exposure fall under the principles of ALARA, which is an acronym for "as low as reasonably achievable." These principles include the following: minimize *time* spent in the presence of a radiation source, maximize *distance* from a radiation source, maximize *shielding* between a source and persons, and minimize the *quantity* of radioactive materials in the area.[5]

Radiosensitivity and Radioresistance

Key to understanding the radiobiology of radiation injury is the concept of "radiosensitivity" and "radioresistance." These terms are the basis for an explanation of one of the oldest tenets of radiation medicine called the Law of Bergonié and Tribondeau (1906). This "law" simply states that cells that are actively dividing (are mitotically active or have a high mitotic index) and cells that are immature (or are not well-differentiated) are much more radiosensitive than other cells. The obverse is generally true: cells that are not actively dividing and those cells that are more differentiated are more radioresistant than others, with one major exception being mature lymphocytes (see the section "Hematopoietic Syndrome"). Radiosensitive cells of major clinical significance are hematopoietic stem cells, epidermal stem cells, endothelial cells, gastrointestinal

stem cells, and cells of the neurovascular system (see the section "Acute Radiation Syndrome").

Median Lethal Dose 50/60 ($LD_{50/60}$)

The $LD_{50/60}$ is the acute dose of ionizing radiation that will cause the death of 50% of a human population within 60 days without medical treatment. This radiation dose is on the order of 3.5 to 4.5 Gy (350–450 rad).[10]

Chromatid Breakage and Mitotic Death

As has been mentioned previously, any atom or molecule can be ionized by radiation. If the molecule happens to be a biologically important molecule, for example, chromosomal DNA, the end results could be highly varied. The good news for damage to chromosomal DNA is that there are repair enzymes called endonucleases, that can repair a DNA single-strand break (SSB). If there is a break in only 1 strand of DNA and it is repaired properly, the chromosome may be able to function normally, although it is possible that its function could remain impaired.

If there is a break in both strands of chromosomes or sister chromatids, there is a double-strand break (DSB). The likelihood that repair would be accurate is much smaller than repair of an SSB. If DNA is transferred between sister chromatids and the sequences are not exactly the same, that is, the exchange is "asymmetrical", improper repair may result in the chromosomes not being able to function at all or may be impaired. Centromeres are important to mitosis because those sites are where microtubules attach to help pull sister chromatids apart at mitosis. If the asymmetrical exchange results in more than 1 centromere in a sister chromatid (a dicentric), the chromosomes will not be able to divide at mitosis and will die a "mitotic death" (Fig. 2).

Apoptosis

Another important method of cell killing is called apoptosis. Apoptosis is a term that is sometimes called "programed cell death." It is a normal physiologic process that allows an organism to rid itself of senescent cells, cells that are functioning abnormally, cancerous cells, or cells that are predestined to be eliminated. Apoptosis is a process

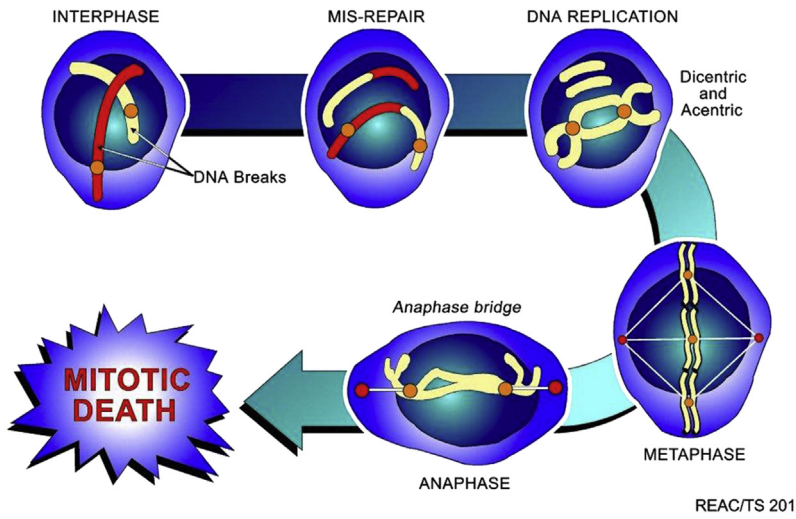

Fig. 2. Mitotic death.

of cellular death that is not accompanied by an inflammatory response, as opposed to necrosis. If a cell is damaged by a noxious agent such as ionizing radiation, it may initiate the apoptosis cascade and die. This is an abnormal physiological process that is sometimes called "cellular suicide." The genome is activated to produce the enzymatic sequence that will result in production of an executioner caspase enzyme that will result in cell death.[10]

Direct Ionization and Indirect Cellular Interactions

Direct ionization occurs when a radiation directly strikes a DNA sequence causing a break in the strand. The energy resulting from ionization, 33 eV, is more than enough to break a C=C bond with its bonding energy of 4.9 eV.[10] Direct ionization is more common with what are called "high linear energy transfer" (high LET) radiations like alpha particles. Indirect ionization occurs primarily when a "low linear energy transfer" (low LET) photon strikes a molecule of water generating a "free radical." A free radical is an atom or molecule that has an unpaired electron in its outer orbital. Free radicals are chemically very reactive, and they can cause DNA strand breaks. Their ionization is called indirect because it is not the original ionizing event that results in DNA damage, but rather the interaction of the free radical with the target molecule. Orbitals or suborbitals contain 2 electrons in each. Each electron has a spin on its own axis that is in the opposite direction of the other electron: one spins in a clockwise direction and the other in a counterclockwise direction. Lack of a paired electron in that orbital makes the atom more chemically reactive.[10]

INITIAL MANAGEMENT OF RADIATION CASUALTIES

There are some general rules for management of radiation casualties. Most importantly, the morbidity and mortality from ionizing radiation injuries increase dramatically in the face of physical trauma, thermal burns, and other significant medical conditions. Therefore, unstable medical and surgical conditions should be stabilized before radiological issues increase to any level of significance (**Box 2**).[17]

OVERALL MEDICAL MANAGEMENT OF RADIOLOGICAL EXPOSURES

The prime consideration for the radiation-injured or ill is to stabilize unstable medical or surgical conditions first. Then, and only then, do issues related to exposure or contamination rise to a level of priority. After emergent stabilization of any immediate life-threatening emergencies, the focus can turn to treatment of acute symptoms and the anticipation of later complications. Acute pain may be severe and may be managed with acetaminophen and opioids. It is generally advised to avoid nonsteroidal antiinflammatory agents, as the patient may be at risk of gastrointestinal bleeding due to mucosal damage if the estimated dose is >5-6 Gy. It is important to obtain a clear history of the timing of symptoms and a complete blood count as soon as possible to help approximate dose of radiation received by the patient (discussed in detail in the later discussion). Type and screen/crossmatch is also indicated for the possible administration of blood products. HLA typing should be done as soon as possible if the dose is expected to be >2 Gy in preparation for bone marrow or stem cell transplantation for pancytopenia. Those who survive the acute phase following a large exposure will be at risk for severe infectious (i.e. sepsis), gastrointestinal, and metabolic complications.

Acute Radiation Syndrome

There is a spectrum of predictable processes that occur in the organ systems of the body after a radiological exposure (irradiation) and/or contamination. These are often

Box 2
Sequence for managing contaminated injured/ill patients

In the field, ensure that the scene is safe for entry of responders

Attend to unstable medical and surgical conditions if the area is safe to conduct such activities

Remove a casualty from any source of further potentially dangerous radiation exposure or contamination with radioactive materials: remove the victim from the radiation area, remove contaminated clothing, and leave clothing at the scene if possible

Obtain a standard medical history as for all injuries and illnesses

Obtain a history of the radiation incident and call for health physics support to assist with incident recreation and dose estimation

Obtain vital signs, including temperature and weight

Complete physical examination, including documentation of pertinent negatives

Survey radiological contamination of open wounds, the face, and intact skin

Obtain nasal swab of each naris and count with radiation detector as soon as possible (if alpha emitter is suspected let swabs dry and resurvey)

Diagnostic imaging as indicated

Laboratory: routine trauma and medical laboratory analyses

Laboratories: initial CBC with WBCs and differential, then serially every 8 hours until decrease is stable, then daily; initial serum amylase (if head and neck region are involved) then daily for 3 days; initial CRP then daily for 3 days

Urinalysis

Begin collection of excreta for radioassay

Treat other significant medical conditions as appropriate

Call REAC/TS for assistance (865-576-1005)

Abbreviations: CBC, complete blood count; CRP, C reactive protein; WBC, white blood cell.

grouped into subsyndromes based on the affected organ system and have some fairly predictable dose thresholds at which the "classic" subsyndrome presents. It must be understood that all tissues/organs involved in the injury may have some degree of pathophysiologic process of damage occurring during this time.[17–20]

Fig. 3 shows recommended sequence of treatment priorities for a radiation incident patient. The top red box indicates that medical/surgical stabilization is the absolute top priority. After stabilization, radiological issues can rise to a level of priority. The lower left-hand 2 columns shows the sequence of activities required for the patient who might be internally contaminated. The lower right-hand column shows the sequence of activities for someone who might have been exposed or irradiated. In some cases, all 3 columns will need to be followed because a patient could well be contaminated and irradiated.

Hematopoietic Syndrome

The bone marrow produces billions of cells per day making this tissue one of the most prolific in the human body; it is highly metabolically active. Also, most of the cells in the bone marrow are relatively immature. These 2 features make the bone marrow one of the most radiosensitive organs in the human body, damage to which can result in a multitude of symptoms and signs, some of which can be lethal.

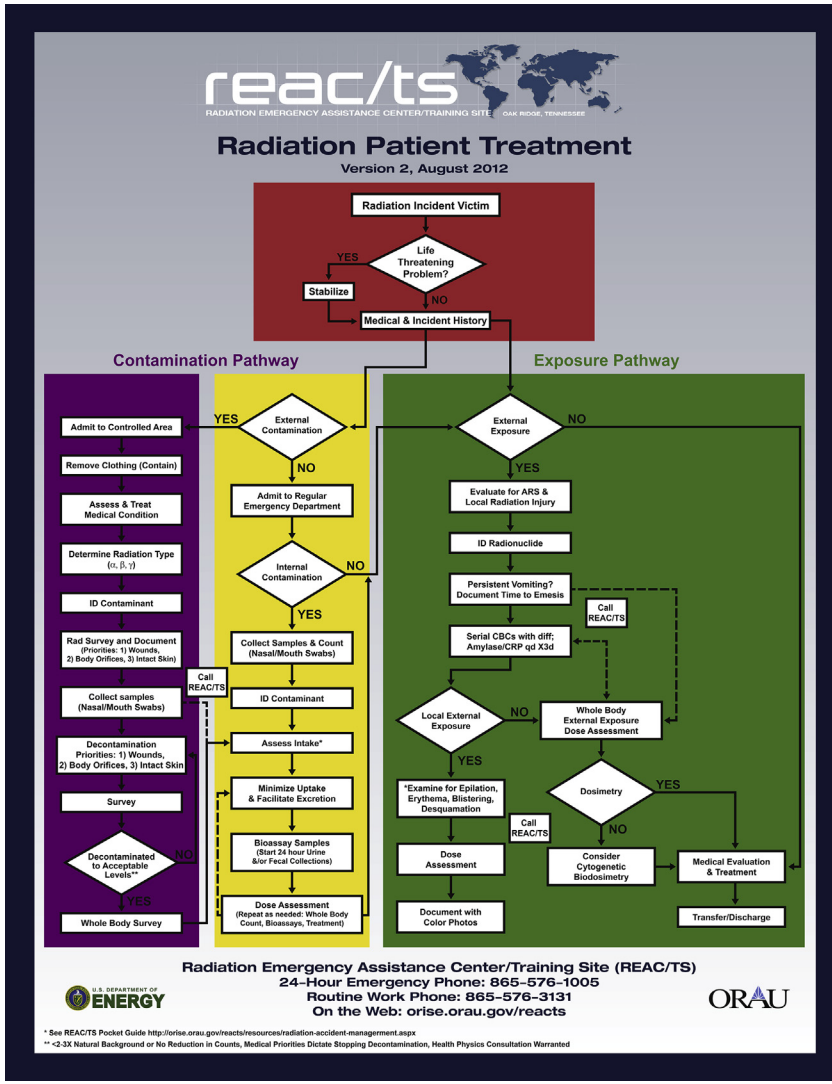

Fig. 3. REAC/TS Radiation Patient Treatment algorithm chart. (*Courtesy of* Oak Ridge Institute for Science and Education, Oak Ridge, TN.)

The lowest radiation dose that can produce changes in the bone marrow is about 0.20 Gy; however, clinical findings are not apparent until an absorbed dose of 0.75 to 1.00 Gy has been reached. The effects of ionizing radiation on the hematopoietic systems are deterministic, that is, as the dose increases, the hematopoietic acute radiation syndrome (H-ARS) becomes worse. The "classic" presentation will begin at doses greater than 2 Gy, but patients may be symptomatic at doses greater than 1 Gy.

Each type of blood cell has its own relative radiosensitivity. Of greatest concern initially following a radiation exposure is the damage that results to lymphocytes. The radiosensitivity of lymphocytes is the exception to the Law of Bergonié and Tribondeau mentioned earlier. Lymphocytes are terminally differentiated, and they are not

mitotically active, yet they are exquisitely radiosensitive. The radiosensitivity of lymphocytes is also dose dependent, which is the basis for dose-response curves that have been developed to allow health care practitioners to use reductions in the absolute lymphocyte count (ALC) (lymphocyte depletion kinetics) to estimate how much of a whole-body exposure a casualty experienced. As the dose of ionizing radiation exposure increases, the faster the lymphocyte count drops and the lower its nadir (Fig. 4).

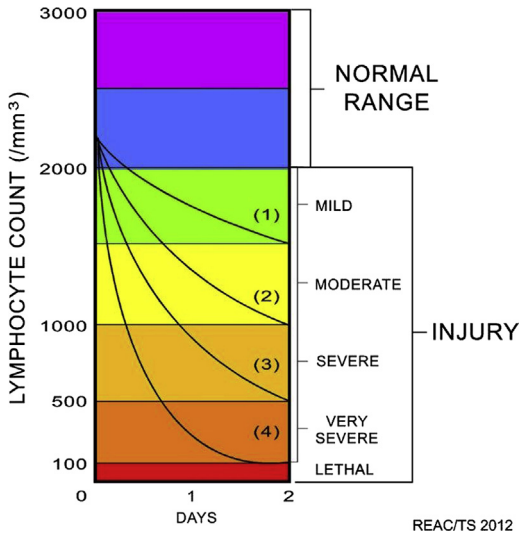

Fig. 4. Lymphocyte depletion kinetics. These lymphocyte depletion curves are called the "Andrews' curves" and are named after an early radiation medicine pioneer, Gould Andrews MD. (*Adapted from* Andrews GA, Auxier Jr, Lushbaugh CC. The importance of dosimetry to the medical management of persons accidentally exposed to high levels of radiation. In: Personnel Dosimetry for Radiation Accidents. Vienna: International Atomic Energy Agency; 1965.)

Absolute neutrophil count

The dose estimate from evaluating lymphocyte depletion kinetics can be used to predict another very important parameter, the drop in the "absolute neutrophil count (ANC)". As the immunocompetence of the casualty is degraded with the loss of lymphocytes, the loss of neutrophils can even further reduce the victim's immunologic competence. Infections will therefore become one of the greatest causes of morbidity and mortality in ionizing radiation incident victims.[18] The reduction of neutrophils usually occurs during a so-called critical period approximately 1 to 2 weeks after the exposure.

Enucleated cells

Mature red blood cells (RBC) and platelets are radioresistant. In keeping with the Law of Bergonié and Tribondeau, they are not mitotically active because they have no nuclei. They are also terminally differentiated. Their mitotically active and immature precursor cells, megakaryocytes and erythroblasts, are, however, sensitive to ionizing radiation. The time of appearance of significantly low levels of RBCs and platelets is also largely dependent on that cell's life cycle. For example, the developmental life cycle of RBCs is on the order of 4 months; therefore, an anemia caused by ionizing

radiation does not usually appear for weeks at survivable doses, whereas a thrombocytopenia appears much earlier.

Medical management of the H-ARS

Management of the H-ARS depends on 2 major considerations: bridging cytopenic gaps and management of infections. Therefore, a hematologist and an infectious disease specialist should be consulted on these cases.

Bridging cytopenic gaps

Bridging the cytopenic gaps can be tackled currently in 3 ways: provision of cytokines or colony stimulating factors; administration of bone marrow cells from a closely matched relative; or stem cell transplants.

Cytokines or colony-stimulating factors

Granulocyte colony-stimulating factor (G-CSF) and granulocyte monocyte colony-stimulating factor stimulate immature granulocytes to proliferate, differentiate, and mature in the bone marrow. The Radiation Injury Treatment Network (RITN) is supported by the US Navy and managed by the National Marrow Donor Program. They recommend consideration of administration in healthy patients without other injuries at doses from 3 to 10 Gy (perhaps 2 Gy for children or the elderly). If multiple trauma or burns are present, lower doses may be more ideal thresholds for treatment, which ranges from 2 to 6 Gy. The World Health Organization (WHO) consultancy recommends consideration of initiating cytokine therapy for exposures of greater than or equal to 2 Gy within 24 hours of exposure, if possible: granulocyte CSF (filgrastim), 5 mcg/kg/d; granulocyte-macrophage (monocyte) CSF (sargramostim), 250 mcg/m^2/d; pegylated G-CSF (pegfilgrastim), in a 6 mg single subcutaneous dose. They extend this recommendation to include a decrease of ALC less than 500 that will persist for more than or equal to 7 days.[21]

The administration of CSFs must be timely, that is, preferably within several days of exposure. Administration will, of course, depend on having reasonable documentation that the acute whole body dose is 2 Gy or greater. The RITN website (www.ritn.net/) provides a more extensive discussion of managing cytopenias.

Bone marrow or stem cell transplants

Bone marrow transplants might be an acceptable treatment modality if there is an available allogeneic histocompatible donor. Patients with significant marrow injury estimated to be on the order of 2 to 9 Gy who become neutropenic within 5 to 7 days may need stem cell transplants (RITN). To be successful, these patients' other injuries such as physical trauma and/or thermal burns must be quite limited. The RITN website can be consulted for valuable information concerning the centers available for such transplants and other more detailed management guidelines. The WHO consultancy recommends consideration of stem/progenitor cell replacement (allogeneic hematopoietic stem cells from marrow, peripheral blood, or cord blood) if there is a lack of bone marrow recovery after 2 to 3 weeks of cytokine treatment and when that patient does not have other organ injuries.[21]

Prophylactic antimicrobials

Before the critical period of neutropenia, patients may need prophylactic antimicrobials to avoid reemergence of dormant viruses and other commensal organisms, for example, herpes simplex viruses, cytomegalovirus, *Candida spp*. These patients will need antimicrobials, antivirals, antifungals, and occasionally, antiparasitic agents if certain parasites are endemic.

Treatment of other infections

There are no guidelines *specifically* directed to management of infections related to the immunologic incompetence of *irradiated* patients. Therefore, most experts recommend the use of guidelines that have been developed by the Infectious Diseases Society of America for neutropenias from other causes.[22]

Cutaneous Radiation Syndrome or Local Radiation Injury

There are many terms to describe radiation injury to one of the body's largest organ systems, the skin. The terms cutaneous radiation syndrome (CRS), local radiation injury (LRI), radiodermatitis are all used in describing skin injury from radiation exposure. These injuries may be concurrent with total body irradiation or partial body irradiation (CRS), may be extensive enough in an area with other organs to cause a partial body irradiation, may be isolated to an area without major damage to other organ systems (eg, an extremity) (LRI), or may result from radiotherapy-induced erythema and edema. Radiodermatitis usually only describes skin effects of radiotherapy. These injuries may result in extensive disability, morbidity, and mortality. About 16 of the 28 acute deaths in Chernobyl were attributed to CRS.[23]

The inability to repopulate cell lines secondary to damage to epidermal stem cells in the basal layer of the epidermis occurs. The endothelial cells are also damaged and result in damage to the microvasculature as well as the extravasation of cytokines, neutrophils, macrophages, and other mediators into the surrounding tissues. The proinflammatory response seems to occur in successive waves. These injuries are best described as evolving. There is continued inflammation, tissue destruction, and often necrosis. The effects seen with time are excessive fibrosis into the affected tissues and even into the vasculature, poor wound healing, reinjury with the slightest of insult, and atrophy.

The threshold dose for deterministic effects in the skin is greater than 3 Gy (300 rad) for epilation or temporary loss of hair. The erythema dose for skin is about 6 Gy (600 rad). As the dose increases, skin effects worsen: dry desquamation at about 10–15 Gy (1000–1500 rad): moist desquamation at about 15–20 Gy (1500–2000 rad) ulcer formation and radionecrosis greater than 25 Gy (2500 rad).[17]

The clinical course of CRS is rather variable in that there may be a prodrome of erythema, pruritus, or burning/tingling sensation that can appear within the first 48 hours. There may be a latent phase in which the symptoms lessen or abate. Then, classically, the manifest illness phase occurs. Part of the variability with these injuries is that the patient may progress to manifest illness, skipping other phases. As a rule, the higher the dose, the faster this progression and worse the prognosis of the injury.

Medical management of CRS

Traditional treatment techniques for thermal burns are used in managing these patients. However, there are some differences for these injuries. The burn treatment modalities of dressing constructs such as Biobrane (UDL Laboratories Inc., Sugar Land, TX) and Integra (Integra LifeSciences Corporation, Plainsboro, NJ), surgical debridement, and grafting absolutely have a role in these injuries. The differences lie in the difficulty of demarcating the extent of the radiation injury. As the injury is evolving and ongoing, the naked eye cannot distinguish this line of demarcation. Various imaging techniques for evaluating extent of injury to the tissues and microvasculature should be considered before surgical treatment of these injuries. Another technique for demarcating the extent of injury is to do dose mapping. This technique along with another treatment modality was used by Lataillade and colleagues.[24] They combined dose mapping of extent of injury with injection of mesenchymal stem cells into the area

of injury with good results. There are other countries doing small case studies of mesenchymal-derived or adipose-derived stem cell injections into injuries.

Other treatment modalities may be helpful in these injuries. The World Health consultancy (WHO) gave a strong recommendation for use of Class II and Class III steroids used topically, topical antibiotics, and topical antihistamines.[25] Other techniques include hyperbaric oxygen therapy, use of pentoxifylline/vitamin E, aloe vera, and other topicals used in radiation oncology.

Gastrointestinal Subsyndrome

The small intestine is uniquely designed and has increased its surface area for absorption of material many-fold by a design of elevations of intestinal villi and deep crypts. The most sensitive cells in the gastrointestinal system are the stem cells in the crypts of Leiberkühn between small intestinal villi.[10] These stem cells are the precursors of both enterocytes and goblet cells. These cells proliferate and mature in 3 to 5 days and then they will slough off with the passing fecal material. The higher the radiation dose, the greater the destruction and damage to the villi such that the tissues may become totally disorganized, thus disrupting the absorptive ability of the small intestine afforded by the crypts and villi. Damage to the epithelial lining is a primary defect in gastrointestinal subsyndrome (G-ARS) that allows translocation of bacteria with resultant infections.

The G-ARS like the CRS has the "classic" clinical presentation of prodrome, latent period, and manifest illness phase and like CRS is highly variable. The prodrome is characterized by nausea, emesis, occasionally diarrhea, and abdominal cramping. As the dose increases, the presentation of the prodrome may be more severe. Similar to the CRS, the higher the dose, the shorter the latent period. At higher doses there may be no latent period at all. As the dose increases, the effects become worse with severe nausea, emesis, hematemesis, hematochezia, fluid/electrolyte shifts, hypovolemia, obstruction, renal failure, and eventually cardiovascular collapse.[26]

Management of G-ARS

Emesis in the prodrome or the manifest illness phase of G-ARS is treated with 5-HT_3 receptor antagonists such as ondansetron 2 to 4 mg intravenously (IV) every 8 hours as needed for nausea or emesis.[25] Decontamination of the gut may be accomplished with the use of antibiotics, essentially to reduce the number of pathogenic bacteria that may become displaced to other parts of the body to cause infection. Nutritional support is absolutely essential if the patient is to survive, which may require total parenteral elemental nutrition (TPN) including the amino acid L-glutamine.[20] Despite being classified as "weak" recommendation by the recent WHO consultancy, antiemetics, antibiotics, and aggressive alimentary supplementation with TPN are reasonable efforts to initiate.[21,25]

Neurovascular Syndrome

The neurovascular syndrome (N-ARS) certainly occurs with total body irradiation greater than 20 Gy (>2000 rad).[17] Other authors say N-ARS can start at greater than 10 Gy (1000 rad).[25] Still others say N-ARS requires a higher than even 20 Gy (2000 rad). Significant cognitive, balance, and other neurologic signs and symptoms can be expected. The syndrome is universally fatal, so supportive, palliative care is indicated. A key point is that ionizing radiation does not cause neurologic signs and symptoms such as convulsions, coma, or extreme neurologic signs and symptoms at *survivable* doses. If neurologic findings are present and the dose of ionizing radiation is known to be less than 10 Gy (1000 rad), other causes should be sought.

Internal Contamination with Radioactive Materials

Internal contamination with radioactive materials is essentially a medical toxicology issue or the treatment of poisonings. This issue is very complicated and will require the assistance of REAC/TS, medical toxicologists, or health physicists, and physicians with experience with these injuries. Additionally, NCRP Report No. 161, Management of Persons Contaminated with Radionuclides: Handbook – Recommendations of the National Council on Radiation Protection and Measurements[27] should be available in emergency departments, radiation safety office, and/or occupational medicine clinic. Additionally, each of these facilities should have a copy of the REAC/TS Pocket Guide: Medical Aspects of Radiation Incidents,[17] which provides guidance on internal contamination, radiation protection, contamination control, and other valuable topics; this may be obtained by downloading in PDF or e-Pub form from the REAC/TS web page (https://orise.orau.gov/reacts/radiation-accident-management.aspx) or by attending a REAC/TS training course. The REAC/TS 24/7 emergency contact phone number is 865-576-1005.

Management of internal contamination with radioactive materials

A foreign material can enter the body in 4 ways, including inhalation, ingestion, absorption through a puncture or injection wound, or percutaneous absorption across normal skin. Because of the scope of this work, only management of more common radionuclides will be covered. General principles of management of internal contamination include the following: reduce absorption and internal deposition; enhance elimination or excretion; and begin treatment as soon as a credible and significant dose has been determined (**Box 3**).

Specific treatment methods

Intakes can be minimized by controlling contamination, removal of victims from contaminated environments, and removal of contaminated clothing.[27] Absorption may be reduced or inhibited by using some standard toxicologic therapies some of which have fallen or are falling from favor: gastric placement of activated charcoal, gastric

Box 3
Specific treatment methods for internal contamination

Minimize intake

Reduce and/or inhibit absorption

Block uptake

Isotopic dilution

Promote excretion

Alter chemistry of the substance

Displace isotope from receptors

Chelate

Bronchoalveolar lavage

Surgical removal

From International Atomic Energy Agency. Dosimetric and medical aspects of the radiological accident in Goiania in 1987. Vienna (Austria): International Atomic Energy Agency; 1998. IAEA-TECDOC-1009. Available at: http://www-pub.iaea.org/MTCD/publications/PDF/te_1009_prn.pdf. Accessed May 29, 2013.

lavage, the use of emetics, and the use of purgatives and laxatives. The use of oral stable iodine to saturate the metabolic processes of radioiodine incorporation into the thyroid hormone is an example of a blocking agent. Forced diuresis with IV fluids for ^{3}H (or tritium, the radioactive isotope of hydrogen) demonstrates the dilution technique.

Reduction or inhibition of absorption of some radionuclides can be accomplished using ion exchange resins orally (eg, Prussian blue or ferric [III] hexacyanoferrate [II] for internalization of radiocesium, radio thallium, or nonradioactive thallium). The chemistry of some substances can be changed, for example, barium sulfate or aluminum-containing antacids orally for ingested radiostrontium to result in strontium sulfate, which will be eliminated in the feces.

Chelation in the United States is generally accomplished with diethylene triamine pentaacetic acid (DTPA) of which there are 2 salts: Ca-DTPA and Zn-DTPA. Ca-DTPA is about 10 times as effective at chelation as the zinc salt; therefore, the first dose of DTPA is given 1 g IV and later doses are given 1 g IV as the zinc salt. DTPA is approved by Food and Drug Administration only for internal contaminations with plutonium, americium, and curium. Although DTPA may be effective for other heavy radioactive metals, its use in those cases would be off-label. Other chelators are available such as deferoxamine and penicillamine. There is no specific antidote for uranium. Depending on the amount of internalized uranium, alkalinization of the urine to 8 to 8.5 may be helpful. At larger internal burdens, uranium is dialyzable. Bronchoalveolar lavage used in experienced hands could be used for larger pulmonary intakes of various radionuclides. Amputations may be the last result for injuries that are not amenable to other therapies because of massive radiation tissue damage and/or complications.

Potassium iodide

After the Fukushima Japan 2011 nuclear power plant accident, many people sought out potassium iodide for "post-exposure" prophylaxis, even as far as on the US west coast. Radioactive I-131 can be suspended in the air or contaminated food and water supplies, so exposure occurs through inhalation and ingestion.

The EPA estimates that the risk of inhalational exposure is no more than a 10-mile radius surrounding a nuclear power plant, but ingestion can occur over a broader area (50 miles).[28] I-131 has a relatively short radioactive half-life of about 9 days, where nearly all of its radiation is dissipated within 3 months. Potassium iodide is used to block the uptake of I-131 into the thyroid tissue, decreasing the malignancy. But it is most effective when administered before I-131 exposure, and the benefits are significantly decreased after the exposure. The best evidence for the use of potassium iodide is in infants, children, and pregnant women. The risk of thyroid cancer is minimal in patients exposed to radioactive iodine after the age of 20 years and virtually no risk after 40 years of age.[29] Despite these facts, the sale and demand for potassium was very high after this nuclear incident and in most cases was not warranted. **Box 4** provides potassium iodide indications.

RADIOLOGICAL AND NUCLEAR INCIDENTS OF MEDICAL AND PUBLIC HEALTH CONCERN

There are several scenarios about which emergency planners, health care providers, and public health officials need to be aware. Some have the potential for massive destruction and multiple casualties, whereas some have the potential only for causing minor, although sometimes major injuries/illnesses in only a few persons.[30–35] Some scenarios present the challenges associated with managing mass casualties, many of whom will not be physically injured. Issues related to managing masses of persons

Box 4
Indications for potassium iodide administration

Predicted thyroid exposure

5 cGy in children, pregnant women, and breastfeeding women

10 cGy in adults between 18 and 40 years of age

500 cGy in those older than 40 years of age, solely to prevent radiation-induced hypothyroidism

From Center for Drug Evaluation and Research (CDER), U. S. Food and Drug Administration. Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies. Rockville (MD): U.S. Department of Health and Human Services; 2001. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080542.pdf. Accessed September 30, 2013.

who have anxiety, fear, and/or confusion may well interfere with the ability to practice medicine or recover from such an incident.[36,37]

Radiological Exposure Device

A radiological exposure device is conventionally thought of as surreptitious placement of a radiation source in an area that will expose unwary victims. Depending on the source activity and the time of exposure, several untoward consequences can occur. CRS and acute LRI might be expected. More significant exposures could result in H-ARS or even G-ARS depending on the circumstances. The numbers of affected persons would depend on how well the source was hidden and how wary public health and safety officials were about recognizing radiation injuries and illnesses. Several cases in the past couple of decades involving persons unwittingly handling dangerous radioactive sources have resulted in deaths of several people: 1996 Gilan, Iran, 1 seriously injured[38]; 1994 Tammiku, Estonia, 1 death, several seriously injured[39]; 2000 Samut Prakarn, Thailand, 3 deaths (7 seriously ill, hundreds significantly exposed),[40] among others.

Radiological Dispersal Device

A radiological dispersal device (RDD) is any device designed to spread radioactive materials. The 1987 Goiania, Brazil, cesium-137 accident in which 4 people died and 20 more became seriously ill can give an idea how a non-explosive RDD might cause havoc.[41,42] Many think of RDDs as explosive devices commonly called “dirty bombs” such as improvised explosive devices (IED) to which radioactive materials have been added. IEDs are relatively easy to make; all components can be purchased at farm supply stores. They are detonated daily around the world and cause untold injuries and deaths. RDDs do not need to explode; however, any device that could be used to spread radioactive materials is technically an RDD. The consequences from deployment of an RDD would depend on the amount and activity of the radioactive material and how widely the material is disseminated.

Nuclear Power Plant Incident

Nuclear reactors use a controlled fission process to generate electrical energy. The reactor core, where the fission process occurs, is the heat source that provides the elevated temperatures necessary for steam generation and electricity production. **Fig. 5** shows a pressurized water reactor, which can generate huge amounts of heat. If cooling of the reactor is interrupted, degradation of the components can occur

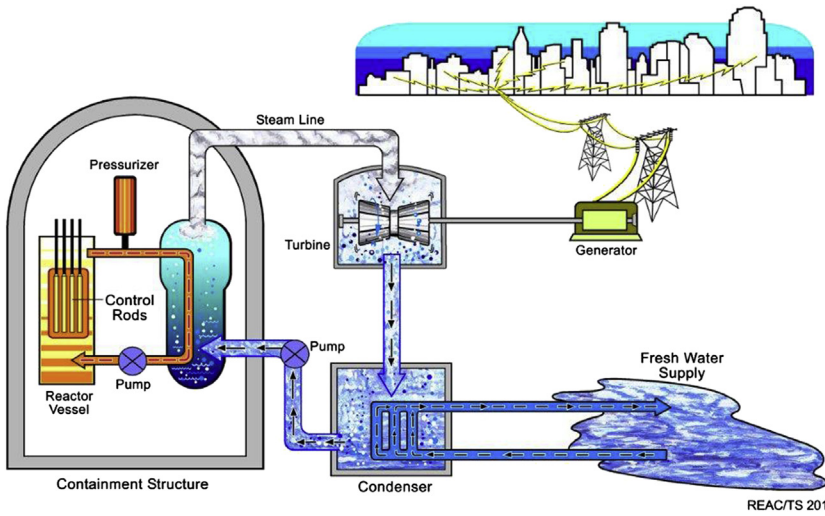

Fig. 5. Pressurized water reactor.

potentially, resulting in the release to the environment of radioactive materials such as radioiodines, ^{137}Cs, among others.

Improvised Nuclear Device/Nuclear Weapon

Nuclear reactors use heat generated to make electricity, but nuclear weapons use the criticality reaction to produce a detonation. Regardless of whether state-sponsored or as a result of a terrorist attack, a nuclear detonation would have catastrophic effects. If detonated in a populated urban area, even a small IND of less than 20 kT could be expected to cause tens of thousands of prompt deaths and many more within weeks. Wounds in survivors of the blast will likely be serious, including physical trauma, thermal burns, and eye injuries. Significant physical trauma including total blunt bodily trauma, ruptured tympanic membranes, and ruptured pleurae (pneumothoraces and pneumomediastinum) may be seen. Thermal burns can result from ignition of clothing or physical structures. Eye injuries can result from infrared exposure of the retina with temporary or permanent blindness. Many eye injuries could also result with foreign bodies from flying debris.

SUMMARY

Medical management of radiation exposure requires careful consideration of the route and type of exposure. Concomitant medical and surgical conditions require strict attention, as these increase morbidity and mortality. H-ARS, G-ARS, and CRS may be amenable to various therapies, although consultation is advised. N-ARS treatment is palliative.

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