Chapter IV: Practical Applications: Radiation Countermeasures, Radiation Safety Hospital and Home, Diagnostic and Radiation Therapy

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There are some contingency plans in place for dealing with radiation accidents, and willful acts of radiation terrorism. Following the discovery of radium and x-rays, there has been recognition of the deleterious effects of radiation exposure. Physical dosimetry, film dosimetry, and the development of thermoluminescent dosimeters, as well as ionization chambers (Geiger counters) have been routinely in use in hospitals and nuclear power plants. The largest radiation accidents in the modern era led to analysis of how local populations could optimize management of such disasters (Chernobyl nuclear reactor accident, 1986, Fukushima nuclear reactor accident, 2011). Emergency management teams, and medical and environmental cleanup protocols have been designed and tested in most institutions (1-3) There does remain significant concern (4-6). Additional information on how to manage such potential problems is available on web-based emergency sites for first responders, and will be made available in real time.

Some hospitals have placed into their emergency management manuals separate sections for radiation emergencies. These protocols have included installation of shower facilities at emergency room entrance points, triage methods to separate radiation contaminated from uncontaminated patients, who are entering the facility, and within the hospital environment, as are other ways to effectively manage radiation casualties (5). Some hospital systems and hospital networks have implemented a local and regional management centralized control office for directing ambulances and first responder vehicles to the appropriate areas for each category of casualties. Some emergency management plans include a designated central "command post" that would communicate directly with ambulance and first responder vehicle drivers to direct patients to specific locations. These emergency management systems should work well with a "manageable" number of casualties (10 – 100). However, in a scenario of a massive radiological event: fission bomb, or large dirty bomb with significant cloud of radiation emitting isotopes, and the resultant 100's or 1000's of casualties, many of these management plans may fail (6). This section of our web-based Radiobiology/Radiobiology Methods Textbook will summarize available information, what plans are in place to increase readiness, and methods by which to deal with scenarios in which the "surge capacity" of a hospital or emergency response team might be exhausted by a large event.

<u>Current Situation:</u>

Hospital or institutional management plans for radiation accidents currently follow protocols, which include both policies and procedures. In hospitals and research institutions, a finding of spilled radioisotopes activates the local Radiation Safety Office response. All hospitals and research facilities have in place a clean-up management plan. In the case of radioisotope spills in a laboratory or a clinical setting, members of Radiation Safety Committee arrive on the scene, take measurements with Geiger counters and perform wipe tests, identify the isotope(s), remove or clean contaminated areas, and control the situation. Liquid spills are managed by appropriate cleanup methods including when necessary removing sections of carpeting, flooring, and wall areas, and after completion of a “wipe-down” and re-assess, then recertifying the area as restored to safe conditions.

The use of brachytherapy sources in Radiation Oncology departments including implantation into tissues of after loaded radioisotope emitting seeds, strands, or in some cases permanent implants requires vigorous safety procedures. These procedures are associated with safety protocols, specific policies, and clear directives for counting the number of seeds, taking inventories, and searching all areas in the environment along the “trail of use” in the case of absent (missing) seeds or sources until all are recovered and accounted. Radiation Safety policies within hospitals and research institutions include updated and detailed strict protocols and procedures.

All personnel working with radiation emitting sources must wear film badges, and regular film dosimetry is carried out followed with reports of monthly and quarterly levels of exposure are managed. Individuals, who have exceeded ALARA (as low as reasonably achievable) levels, may be counseled and/or removed from further work involving radioisotopes for months or the rest of the year. Radiation workers and hospital personnel, who are exposed to ionizing irradiation as a regular ongoing part of their work (such as those working with patients who receive PET (Positron Emission Tomography scans), isotope preparation laboratories, physicians involved in cardiac fluoroscopy for catheter placement, diagnostic radiologists, radiation oncologists, nuclear medicine workers, and workers using intraoperative scanning techniques) all may be required accept a higher ALARA level as a work condition, than the level associated with the general population. Hospital and research facilities are required to have radiation monitoring devices. Violation of specific State or Federal rules can lead to imposition of sanctions. These “peace-time” policies and procedures are designed to protect the public, as well as radiation workers. Such a “peace-time” manageable system will be challenged in the face of significant environmental nuclear contamination, or a radiation terrorist event.

Radiation Level Monitoring Outside the Hospital/Research Institution:

Requirements for measuring radiation levels in commercial and private buildings have been part of the Private and Commercial Real Estate industry for decades. Frequent ongoing radon gas measurement and detection may be required, principally in basements, and in buildings constructed over geographic regions rich in radium deposits or over prior mining sites such as previous coal mining facilities. The radon testing industry has become a routine part of the process of sales and construction processes in the Real Estate market. People are aware of the hazards of continuous low levels of radon gas irradiation. There are published reports of an increase in lung cancer in smokers, who also are also exposed to radon, and there is a significant published literature on late effects of prolonged radiation exposure for Uranium miners, as well as working in nuclear power plant and nuclear weapons industry environments. These data were collected both within and outside the United States. The average citizen’s concern about radiation exposure is ameliorated by knowledge that hospitals and research institutions are required to have radiation safety monitoring. Women, who may be pregnant, are cautioned against having diagnostic or therapeutic radiation exposure due to the hazards of radiation exposure to a developing fetus. This safety program is a well-organized system for “peace-time," but it also breaks down in the event of a large radiation contamination or willful radiation terrorist event.

<u>Managing a Radiation Disaster:</u>

Local disasters within the United States, as well as worldwide, will be managed by activating a specific set of procedures (5). The most experience in disaster management has been gained from outcomes analysis of the EMS (Emergency Management System) responses to weather related disasters (flood, tornado damage, volcanic eruption, hurricane/wind damage, and earthquake) or physical disasters (freight car derailment and chemical spill, airline crash, industrial building explosion, and endemic biological/infection agent spread such as the recent events with: SARS (2007), Influenza (2010), Ebola (2015) and Zika virus (2016)). In some of these scenarios, identification of the source of the "disaster" may be obvious (in the case of a volcano). However, the cause may be more subtle in the case of a localized infectious agent (Legionnaire's disease, SARS, and influenza outbreak). With irradiation related disasters the same range of response procedures and the speed of diagnosis and magnitude of the event would also apply.

In the case of a nuclear reactor explosion or meltdown, the physical site of the contamination will be immediately obvious. In the case of a fission bomb or dirty bomb (radiological dispersion device), the potential for radiation contamination related to a geographic site will also be determined by the speed of detection of radiation by Geiger counter or film dosimetry badge with color change related to dose. However, in the case of a clandestine dispersal of radioisotopes, or in other situations in which a conventional blast may not be associated immediately with radiation contamination, the diagnosis of the situation will have different dynamics. For example, in the case of the Boston marathon bombings (2014), the first explosion and cloud of dust and debris was visible by all television and visual media reporting. This was followed by a second blast with further dispersal of dust and a large cloud. If there had been radioisotopes in the pressure cooker bombs, the time from the 1st. explosion to detection of radiation emitting isotopes in the dust cloud (were this a radiation emitting device) would have certainly involved a lag, perhaps long enough for hundreds or thousands of individuals to inhale radiation contaminated dust. Depending on the isotope and magnitude of dispersal, hundreds or thousands of individuals would subsequently be diagnosed as having internalization of radioisotope (respiratory contamination), a larger number might have radioactive dust on their clothing, and there would be environmental contamination that could cover a significant area in areas without immediate human exposure.

The characteristics of an aerially dispersed isotope, (half-life) biological effect <u>in</u> <u>vivo</u>, and magnitude of the clean-up will dictate the medical requirements for managing potential casualties, and the scope of the event could be significant. The disaster plan by which to manage an event, the scope of the Boston marathon bombings (were radioisotopes involved), would be potentially containable. In contrast, if radiation emitting isotopes were involved in an event the scope of the 9/11 world trade center plane crashes and subsequent explosions, the area of the aerial dispersal would be far greater, a larger number of individuals would have been contaminated, and the physical/geographic area requiring cleanup would be significantly greater.

Preparedness drills for the spectrum of potential radiation contamination events encourage reliance on several basic principles of radiation biology; however, depending on the magnitude of the event, radiation management plans will rapidly be overwhelmed by the casualties with combined injuries: thermal burn, concussion, penetrating wounds, fractures, and hemorrhage.

Several basic principles would apply to all casualty situations, which involve ionizing irradiation:

1. In the case of aerial dispersal sheltering in place, indoors will be communicated widely and rapidly and will be a clear first principle.
2. First responders (police, emergency medical teams, fire departments) must utilize specific protective clothing to avoid their own contamination of skin, inhalation, or ingestion of isotopes.

Triage of casualties would include specific plans for management of those individuals with combined injury (burn, fracture, concussion, blood loss), but also guidelines for limiting, managing, and handling movement outside the area of ambulatory potential casualties, and 1st responder personnel within the immediate blast or aerial dispersal area (5). These plans would include: roadway and walkway management (potentially closing bridges, specific highway exits, and placing management teams at specific sites to avoid people leaving the area with isotopes in or on their person, and contamination of a wider environmental area. Radioactive materials on the clothing of exposed individuals) would be a problem. This latter situation would be complicated by the inevitable possible hysteria of populations, particularly once it was clear that there was radiation contamination in the areas of the initial explosion event.

Triage of casualties after an irradiation dispersal event would also range in magnitude from the Boston Marathon bomb type “contained event” to a large explosion event (fission bomb, massive dirty bomb/airline crash) containing radioisotopes. Casualty evacuation would follow the first principles of triage by physical injury. A high level of measured or estimated irradiation contamination would not necessarily influence the initial priority for evacuation of one person over another with lower radiation estimated doses, but with massive thermal burn, penetrating wound, fracture, or concussion. Once it was known that the explosion event contained radiation emitting isotopes, triage priorities might change. “Just in Time” instructions will be communicated to triage personnel.

The radiation dosimetry for triage management is the subject of a separate chapter within this web-based textbook. However, in the case of an explosion, the site/epicenter, would be known and thus calculation of radiation exposure from the blast emitting center of radiation, and/or isotope dispersal, could be rapidly calculated. These plans breakdown in the case of a clandestine exposure where the epicenter or multiple epicenter(s) are not known.

<u>Management of Casualties:</u>

The severity of blast, burn, and penetrating wound injury will determine the initial triage procedures. Triage of casualties whether in a battlefield situation (military), or domestic (civilian) situation will rely upon first principles of primary field triage, transportation to 1st. site of medical care, and then secondary triage from that facility (6).

The severity and number of injuries will also determine how casualties are managed at secondary hospital facilities. Once radiation is detected in the environment of the disaster, evacuation vehicles including ambulances and emergency room, ambulance bay facilities, as well as the rest of the hospital will be advised of the situation involving ionizing irradiation. Contamination of clothing and skin of patients and 1st responders will be a first priority. Removal of clothing and initial "wash down" of patients as best as possible can be carried out in the ambulance and certainly in the ambulance bay. Triage of "hot" radioactive patients separate from those, who do not have detectable radiation on their person should be part of the hospital's radiation management program. Some ambulance evacuation systems carry the Thermo Fisher Radiation Detection equipment, which can identify the type and variation of isotopes within the ambulance bay (1-3). This system of detection may also be important for identifying those isotopes with potential for short half-life (potentially providing an acute medical emergency) compared to those with long half-life (more risk for late effects, such as organ failure or carcinogenesis), as well as the spectrum of energy from gamma and beta emission (4).

Once casualties are cleaned, "wiped-down" either in the ambulance or in the hospital, further scanning of patients will be required to determine whether there was inhalation and/or ingestion of irradiation emitting isotopes. Casualty management in the hospital will follow principles applied as best as possible given the number of casualties and the surge capacity of each hospital (5).

Civilian populations will be managed by triage to hospitals based upon the types of casualty. For example, patients, who have penetrating chest wounds may require thoracic surgery, and may be triaged to one hospital with this capacity. Patients with severe thermal burns may be triaged to a hospital with a "burn unit" with that specialty capacity. Irradiation emitting isotopes on clothing or skin or internally identified in the casualties will be considered as an important, but secondary factor in the initial triage.

Administration of Radiation Countermeasures (FEMA/CDC):

A key component of casualty management will be the administration of radiation countermeasures. The Communicable Disease Center (CDC) has the push-packs (both general disaster and specialized for radiation) that will be delivered by Federal Emergency Management Administration (FEMA) (Appendix 1). In the absence of any new approved drugs at the present time, casualty management will follow basic principles of application of countermeasures following the historical events of nuclear reactor accidents or nuclear weapons facilities accidents. In the assessment of radiation effects, differentiating thermal from radiation burns may not be possible. However, calculation of the routes of transport of individuals from the site of the blast, and estimates of radiation dose will be applied to determine whether individuals will require Intensive Care Unit (ICU) care, bone marrow transplantation, regular hospitalization, or can be treated for non-radiation trauma and potentially sent home. Appendix 1 lists the current radiation countermeasures in the RAD-NUC push-pack.

The Radiation Injury Treatment Network (RITN) (See the web-based book chapter XXIX by Nelson Chao, M.D.) has established a consortium of hospitals ready and willing to take radiation casualties and place them in bone marrow transplant facilities with positive pressure rooms, and in many cases delay scheduled bone marrow transplant to facilitate management of these casualties.

Administration of antibiotics, antifungal agents, and granulocyte-colony stimulating factor (G-CSF) (which are currently in the National stockpile) will be delivered based on assessment of radiation dose and availability of resources.

There will be rigorous procedures applied to estimate the level of radiation exposure of individuals in the area of the event. Measuring devices for biodosimetry (RABIT-Columbia CMCR (4)), measurement of peripheral blood and urine markers of metabolomics following radiation injury (Columbia CMCR) will be applied if available to determine radiation level sustained. The basic principles of radiation dose sustained will be followed, and these include:

1. Location (distance) from the epicenter if known, and whether each victim was indoors or outdoors or partially shielded by concrete or steel is all important data. This data can be used to estimate dose sustained.
2. Measuring peripheral blood lymphocyte count at two different time points (if practical – in the case of 10 – 100 casualties), and assessing the slope of the decrease in that curve compared to a standard curve can help determine an individual's radiation dose sustained.
3. The two by two rule (if the person has shown nausea and vomiting within 2 hours of the event, suggests a total body radiation dose of over 2 Gy sustained).
4. Peripheral blood assessment of chromosome breaks, ring forms, and other chromosome abnormalities of lymphocytes as a radiation dosimeter (if practical in 10 – 100 casualties).

Radiation countermeasures available at the present time are limited to those agents described above. Once available and FDA approved, new radiation countermeasures that are being developed by the Center for Medical Countermeasures Against Radiation (4) may be available.

Currently Available Radiation Countermeasures:

Patients entering a triage process at a hospital after a radiation event will be managed as one would manage a bone marrow transplant recipient, who has gone through a conditioning regimen. Available countermeasures will include bone marrow transplant beds with positive laminar flow rooms, antibiotics and antifungal agents, and administration of G-CSF (Neupogen) to push the bone marrow for faster recovery if available and if the surge capacity of individual hospitals has not been exceeded. (See Appendix 1 for recently described list of agents.)

Antibiotics, Antifungal Agents, Bone Marrow Stimulatory Drugs, Bone Marrow Transplantation:

Several publications available "Just in Time" by web, or audio communication devices have listed current protocols at National Bone Marrow Transplant Centers for application of antibiotics and antifungal agents (6). Modification of these recommendations will, of course, require the availability of individual patient information to the electronic medical record by the RITN.

Application of standard hospital protocols for marrow transplant recipients may not apply in emergencies. The use of associated countermeasure therapies may not be possible if there are more casualties than available transplant beds. It will not be possible to give all patients a single treatment regimen. For example, individuals, who have a recoverable and accessible history (if electronic medical records are quickly available) of allergy to specific elements of a regimen will not receive those drugs. For example, a medical history of an individual patient may preclude application of antibiotic or antifungal agents. The use of steroids to prevent swelling may not be possible in some patients, who are being managed for other medical conditions. A "one-size fits all" approach to casualties may be necessary, but might go against the concept for "personalized medicine" currently being developed in our "peace-time" environment. Personalized medicine in management of radiation casualties may not be optimal or even feasible. In the setting of combined injury, which may be the overwhelming majority of patients coming in following a fission bomb or dirty bomb, patients will be managed according to severity of their non-radiation related injuries (thermal burn, concussion, fracture, penetrating wound, flash blindness, and other general medical conditions).

Management of Individuals with Inhaled, Ingested Isotopes:

A clear strategy for handling patients, who are still found to have radiation emitting sources either in the intestine/GI tract, the lung, or both will require identification of the types of isotopes and dose sustained, as well as availability of facilities for removing such contaminants.

For thoracic/inhaled radioisotopes, bronchopulmonary lavage may be a way to rapidly decrease the isotopic load; however, time from the initiation of inhalation till therapy may make it very difficult to remove a significant amount of isotopes, particularly if these have been attached to respirable particles "weaponized particles". These particles would be sequestered in lymph nodes and macrophages and lymphatics, and the situation will be worse if there has been significant smoke inhalation. Depending on the types of isotopes and the dose rate, those patients with significant radiation burdens may be triaged to be managed further at a hospital facility. Ingested isotopes, as well as inhalation isotopes, will be managed by assessing the dose, dose rate, and quality of isotopes through external measurements including Geiger counter measures or in some cases utilizing total body scanning techniques. These management tools will be available only if the number of casualties is manageable (10 – 100). In the absence of a viable and large medical care system to handle hundreds or thousands of casualties, patients will be managed by severity of the combined injuries and kept in areas where, depending upon the isotope and dose release by their body, they are unlikely to be in contact with individuals, who were outside the irradiated zone.

Management of Radiation Burns from Fallout:

Those individuals who have been in exposed areas where fallout is likely based on distance from the blast, will be advised to shelter in place (indoors) until aerial measurements detect a dissipation of the fallout. Those individuals, who have had significant areas of skin covered with radiation (more likely in a willful dispersal event, not associated with blast, no dirty bomb, and no fission bomb) will have radiation burn management according to established principles. Areas of the skin will be cleaned, and radiation mitigating agents placed on the skin. Very similar to thermal burns, radiation burns will be managed by coating the area with topical agents designed to minimize bacterial infection and allow healing. An assessment of the surface area subjected to radiation burns will be critical in this evaluation. Radiation burns as an isolated incident, not associated with combined injury will be managed by principles known to apply to thermal or ionizing irradiation burns (See the web-based textbook chapter XI, section B by Larry Jones, M.D. on Burn Management).

Development of New Radiation Countermeasures (Basic Rules (Safe in Elderly, Men and Women, Pregnant Females, Children, Interaction with Other Likely Used Medications, Dose Response Curve of Potential Toxicities, Management of Late Effects):

The Consortium of Centers for Medical Countermeasures Against Radiation (CMCRs), as well as other nationally funded research programs have understood the importance of safety in delivering a radiation countermeasure (4). Since the majority of exposed individuals in a general civilian population will be those over a wide age range, males and females, the possibility of pregnant females at various stages of gestation, the elderly, children, as well as a very large number of individuals taking other medications for pre-existing medical conditions, a radiation mitigator agent must be “safe” above all. A safe radiation mitigator must be one likely to produce no deleterious effects in individuals, who have not sustained a significant radiation dose to produce bone marrow failure, and in the absence of appropriate dosimetry and triage procedures, individuals may request a radiation mitigator, whereas, in fact they do not need one, and would be best served by going home, staying out of the hospital environment, and sheltering in place. Therefore, a radiation mitigator must be safe in the non-irradiated individuals. The toxic dose for a practical mitigator must be very high and such a dose response curve should be established well in advance of its administration to any and all individuals. The issue of polypharmacy will be critical. A radiation mitigator must be safe to administer to those casualties, who have other medical conditions and are taking other medicines.

A question in the use of radiation mitigators, which has arisen has been the concept of a consequence of its use bringing on a potential “delayed second public health crisis”. In other words, if individuals are administered a radiation mitigator, which increases survival of a large population, there will be a need to minimize the risk of delayed radiation side effects in survivors, which otherwise would not have been as great a problem. There is concern over the potential for a surge of individuals with late deleterious effects. The history of survivors of Hiroshima and Nagasaki A-bomb survivors has raised concern for the possibility of large secondary burden of survivors at risk for radiation induced late organ failure, as well as leukemogenesis and carcinogenesis. Thus, a radiation countermeasure itself should not add to the risk of late effects specifically induction of cancer. There is currently no answer to these questions; however, the safe development of radiation mitigators must take into account all organ systems and all late effects.

Just-in-Time Information Distribution:

The concept outlined in this section of our web-based textbook are obvious to some first responders and medical personnel, but very difficult to understand in the setting of a true disaster. Therefore, "just-in-time information" transferred to large civilian populations through the media (television, radio, web-based transfer of information, cellular telephones, I-phone) will be managed by local disaster management cities. Presentation of clear information is extremely important. All emergency room hospital personnel are not trained in managing radiation casualties, nor are all first responders, ambulance personnel, policemen, and firemen skilled in managing radiation casualties. Therefore, just-in-time information transmitted to all of these sources has been a focus of the disaster management and preparedness sources in the United States and in other countries.

Disaster-Management, Dynamics, and Management of Casualties Within a Large Population:

In the case of a fission bomb or dirty bomb, traffic management both vehicles and pedestrians will be critical (5). The unavailability of certain exit routes from an area may prohibit traffic movement, for emergency response vehicles, just-in-time information as to what hospitals are available, which are accessible, and which can be reached by conventional routes will be critical. In a city surrounded by rivers or water ways, the destruction of bridges will be a second issue in addition to highways. The management of large crowds will require police and first responder forces, and various traffic flow containment strategies. As was the case in the World Trade Center attacks on 9/11, the focal situation in Manhattan and New York led to exit strategies in all directions and at all different speeds. There was central destruction of specific buildings, but not a specific block of egress. In the case of a fission bomb or multiple dirty bombs, traffic control and management will be critical to provide for safe and sound evacuation.

Given the vast literature of radiobiology, and on existing dosimetry devices and existing countermeasures, as well as radiation safety rules and regulations, we sought rather to focus this virtual textbook on reporting current methodologies used by scientists in each of these various disciplines. It is hoped that these methodologies can bring new scientists into the field of Radiation Dosimetry and Radiation Countermeasures, by providing information of the most up-to-date methods and assay systems of use to move the field forward.

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Appendix 1: Ongoing effects by the RITN on the strategic National Stockpile. What components will be in the "push-pack" to arrive at a nuclear disaster site:

1. **Zinc-DTEA (Pentatate-Zinc) Chelator for Transuranium Compounds: One company may have at present all the business related government contracts.**

2. **Neupogen, Leukine: Neupogen 480 mg. vials. Leukine, 250 mg. per vial. If I.P., must be diluted, if S.C., is given 1 use vial, if I..V., there is a concern that there is a rubber stopper, and it may not be uniformly usable for people, who have a latex allergy. It is not stable. For individuals who receive 2 Gy or above to be used as indicated. It requires refrigeration at 2-8 C^0. It will be delivered in refrigerated trucks.**

   There is a potential concern in the use of Leukine, because of the use of bacteriosidal water, which may be a problem for its delivery to neonates.

   Amgen (Neupogen) had applied and was approved by the FDA for use of the drug as a radiation countermeasure according to the FDA animal rule. This event should help further stabilize the drug in the stockpile in the United States, even though this drug is FDA approved for use in the clinic is in existence.

3. **Potassium Iodide (60 mg): Individuals will be given 2 tablets. This drug was considered as unnecessary, but after the reactor accident in Fukushima, Japan, and radioiodine in that environment, it was put back in the stockpile. Has it been approved for pediatric patients?**

4. **Radiogarde-Prussian Blue, 500 mg. capsules: Individuals take 18 capsules a day. Manufacturer one company: For use to speed Cs^{137} clearance from the body.**

5. **Odansetron-Anti-Emetic, B.I.D., two times per day. Has Phenylalanine, so may not be used in some people with Phenylketonuria.**

6. **Intravenous fluids include: Normal saline, and half-normal 0.5 (1/2) saline.**

7. **Burn Treatments**

8. **Antimicrobials**