A Possible Approach to Large-Scale Laboratory Testing for Acute Radiation Sickness after a Nuclear Detonation

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After the detonation of an improvised nuclear device, several key actions will be necessary to save the greatest number of lives possible. Among these tasks, the identification of patients with impending acute radiation sickness is a critical problem that so far has lacked a clear solution in national planning. We present one possible solution: the formation of a public-private partnership to augment the capacity to identify those at risk for acute radiation sickness.

If a 10-kiloton nuclear device were to be detonated at ground level in a major U.S. city, U.S. government modeling suggests that tens of thousands of people within a radius of approximately 1 mile would be killed or severely injured. Beyond this radius, the number of serious acute injuries would rapidly decrease, but an even greater number of people would be at risk of exposure to dangerous levels of radioactive fallout. Most of these people would be outside of the immediate blast vicinity and would likely have few if any traumatic injuries, and most will be ambulatory. More important, as prodromal symptoms are likely to be non-specific, these people would probably not have acute symptoms in the first hours or days that could unquestionably be attributed to radiation.

The identification of patients with impending acute radiation sickness from the million or more people who might be in the general vicinity of the fallout plume is a critical problem that so far has lacked a clear solution in national planning, but which, if solved, could lead to more appropriate matching of patient medical needs and available medical capacity and thus potentially save thousands of lives. In this article, we formulate the proposition that a public-private partnership with national commercial clinical laboratory chains may be a key to solving this problem.

Radiation Exposure in the Fallout Zone

Fallout is pulverized material that is forced into the atmosphere as a result of surface level detonation. This fine-grained material becomes infused with radioactive particles from the nuclear detonation as it is carried miles into the air before falling back to earth. The plume of radioactive dust can travel miles downwind as it gradually settles. Modeling indicates that dangerous levels of fallout could extend as far as 20 miles from ground zero. In a densely populated urban environment, this would translate to well over 100,000 people being exposed to levels of radiation from fallout sufficient to cause acute illness.

If people in the area of the fallout know to immediately seek adequate shelter and stay there for several hours, deaths from fallout could be dramatically reduced. It is, however, reasonable to assume that many people would not be willing, able, or aware of the need to shelter. Even in the best case, it is likely that thousands of people would be at risk for radiation sickness from fallout. Some victims in the path of the radioactive fallout would be exposed to supralethal levels of radiation and would not survive regardless of medical intervention, and some would receive lower levels of exposure, which would not require immediate medical attention. But many thousands of people would fall in a
middle range of radiation exposure, in which medical intervention could make the difference between life and death—if they could be rapidly identified, triaged, and transported to locations where they could receive appropriate medical care. This group could number in the tens of thousands, but possibly a million individuals or more would need to be screened to identify this subgroup.

**Acute Radiation Sickness (ARS)**

Acute radiation sickness, or ARS, is a systemic illness caused by exposure to a level of whole body ionizing radiation sufficient to damage the hematopoietic, gastrointestinal, cardiovascular, or central nervous system. The threshold level of whole body radiation needed to develop initial signs and symptoms of ARS is approximately 1 Sievert (Sv) in a healthy adult. Below this level, radiation exposure can have long-term health effects, such as an increase in the lifetime risk of cancer, but is unlikely to cause serious acute problems. In humans, the dose of radiation expected to kill 50% of those exposed within 60 days, or the LD50/60, is 3.5 Sv. With adequate medical treatment, the LD50/60 may double to about 7 Sv.

Some bodily tissues are more sensitive to the effects of radiation than others. In general, tissue sensitivity to radiation is proportional to the rate of its cell proliferation and inversely proportional to the degree of cell differentiation. For example, bone marrow, where blood cells are made, is among the most sensitive. Relatively low doses of radiation may suppress the bone marrow and yet cause little damage to other organ systems. The effects of bone marrow cell suppression (ie, hematopoietic syndrome), characterized by increased risk of opportunistic infection and uncontrolled hemorrhage due to gradual pancytopenia, may take days or weeks to become clinically manifest. With good medical care, most patients with only bone marrow suppression will probably survive.

In contrast, patients with higher doses of radiation exposure will experience acute gastrointestinal, cardiovascular, and/or neurological effects well before the effects of bone marrow cell suppression are clinically evident. In most cases, patients presenting with these symptoms cannot survive even with good medical care. Therefore, it is the cohort of patients with impending, but not yet fully manifest, hematopoietic syndrome that are most likely to be saved by medical intervention. Table 1 summarizes the various syndromes that comprise ARS and the corresponding radiation doses needed to cause them.

**Table 1. Radiation Dose and ARS Syndrome**

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>Syndrome</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-8 Sv</td>
<td>Hematopoietic</td>
<td>Potentially survivable</td>
</tr>
<tr>
<td>8-30 Sv</td>
<td>Gastrointestinal</td>
<td>Fatal</td>
</tr>
<tr>
<td>&gt;30 Sv</td>
<td>Cardiovascular</td>
<td>Fatal</td>
</tr>
<tr>
<td>&gt;30 Sv</td>
<td>Central nervous system</td>
<td>Fatal</td>
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</table>

**Treatment of ARS Patients**

There is no antidote to the effects of external radiation; however, supportive treatments exist that can partially mitigate the consequences of the hematopoietic effects. These consist primarily of bone marrow stimulating agents (colony-stimulating factors), blood products, and antimicrobial agents. Bone marrow stimulants such as filgrastim (G-CSF), pegfilgrastim (pegylated G-CSF), and sargramostim (GM-CSF), which are widely available and commonly used to treat cancer patients, stimulate undamaged bone marrow cells to produce more blood cells in order to compensate for the damaged bone marrow. These medications are more effective the earlier they are administered after radiation exposure—ideally within 1 or 2 days.

Blood products—especially platelets, which control bleeding—will be needed several weeks into the illness as the patient’s blood counts fall to dangerous levels. During this same time, antimicrobial drugs will be needed to fight infections that are likely to occur due to low white blood cell counts. These patients may need protective isolation to prevent infection during the time that their blood counts are the lowest. This kind of care is the same that is used for some cancer patients who develop neutropenic fevers or profound thrombocytopenia while undergoing intense chemotherapy. This kind of care is provided frequently in many U.S. hospitals. Although some of this treatment can be conducted on an outpatient basis, it is likely that most patients with a significant degree of hematopoietic ARS would benefit from hospitalization, if resources are available.

**No Operational Plan Exists**

There are likely to be enough hospital beds in the U.S. to treat all the patients with ARS. The Radiation Injury Treatment Network (RITN), a voluntary collaboration of bone marrow transplant centers, has been created to facilitate the hospital care of patients with ARS. The network provides the capacity to treat thousands of ARS patients. Furthermore, it provides the backbone of a system in which these specialty centers can help guide care at nearby general hospitals. But because regional medical resources would likely be limited, especially in the first few days following a detonation, and because time is of the essence in initiating

*A Sievert is a measure of the biological effect of radiation. By contrast, Grays, another common unit of measure of radiation, measures the energy imparted to a material by radiation. For gamma and beta radiation, 1 Sv equals 1 Gy. Gy and Sv have replaced the old units of radiation measure, rads and rems. 1 Sv equals 100 rems.
some treatments, and resources for transporting patients to where they can receive adequate care may be limited, it is crucial that those most likely to benefit from treatment be identified as quickly as possible.

In the event of a nuclear detonation, many times more people will likely present for medical triage than actually have early ARS. As always happens in disasters, victims present for medical evaluation for many diverse reasons. Because the transient initial symptoms of radiation sickness are often mild and nonspecific, symptoms alone are not enough to discriminate between those with or without radiation sickness. And geographic information, while useful, is not likely to be a sufficient screening tool. This is because even if this were known, an individual’s exposure will be affected by the adequacy of shelter. Therefore, it will be impossible to know with certainty who has been exposed to significant levels of radiation based solely on where they were after the detonation.

In a major metropolitan area, 1 million or more people might reasonably be concerned about dangerous radiation exposure and may need to be screened for radiation treatment. To date, there has been no operational plan developed to identify ARS victims on this scale.

**Time-to-Vomiting**

Some have advocated the use of the time from the detonation to the onset of vomiting as a crude screening tool with good negative predictive value. Most people exposed to doses of 2 Sv or more would be expected to vomit within 4 hours. Therefore, it has been suggested that this time-to-vomiting criteria could be used to separate those with doses higher or lower than 2 Sv. However, such a methodology, though easy to perform, may not be reliable. The 4-hour rule assumes a point-in-time exposure; it is not clear how time-to-vomiting would be useful if exposure occurs over many hours. Furthermore, vomiting in the midst of such an event may occur for a number of reasons other than ARS, including psychological stress, eardrum rupture, and head injury. Conversely, vomiting may be suppressed in some patients taking certain medications. Of note, a more comprehensive clinical assessment, the Medical Treatment Protocols for Radiation Accident (METREPOL), which assesses the effects of radiation on 4 organ systems and incorporates complete blood count testing (CBCs), has been developed and advocated by the European Group for Blood and Marrow Transplantation (EBMT).

**Chromosomal Dicentrics**

The gold standard for determining radiation exposure is the measurement of chromosomal dicentricism—aberrant chromosomes created by exposure to radiation. This analysis, however, is labor-intensive and time-consuming and requires specially trained technicians. It is not performed in most clinical laboratories outside the Centers for Disease Control and Prevention (CDC). Therefore, its usefulness in screening thousands of people in a short period of time is limited. Newer approaches to cytogenetics are being developed that involve fewer steps and could potentially have a turnaround time of 2 days—the same time frame during which drawing an absolute lymphocyte count would be most useful. The U.S. government’s Biomedical Advanced Research and Development Agency (BARDA) has provided funding for the further development of new tests for chromosomal dicentrics. Additionally, there are efforts to develop capacity in routine laboratories for dicentrics biodosimetry capabilities to be used during a radiation emergency.

**Other Methods of Biodosimetry**

Other types of biodosimetry under development include analysis of tooth enamel using such techniques as electron paramagnetic resonance (EPR), also known as electron spin magnetic resonance (ESR); metabolomics; and stress gene signature analysis. EPR detects the quantity of radiation-induced free radicals in dental enamel, which are then correlated to an absorbed radiation dose. Ideally, EPR is performed on extracted teeth, but modifications have been made in order to perform EPR in situ; however, this decreases its reliability due to the presence of confounding substances (eg, dentin). A metabolomics-based biodosimetry would involve performing mass spectroscopic analysis on body fluid (eg, urine) to identify molecules characteristic of radiation exposure (radiation biomarkers). Stress gene signature analysis involves collecting lymphocytes from the blood and analyzing their gene expression profiles with particular attention to genes whose expression is augmented with radiation exposure. These tests are not readily available for use and are not currently scalable for a response to a nuclear detonation.

**Possible Solution: Absolute Lymphocyte Counts**

In contrast, a validated, simple, and inexpensive laboratory measurement that can determine radiation dose—albeit with somewhat less precision—is the absolute lymphocyte count (ALC). An ALC is one of the most common and straightforward clinical tests. Part of a complete blood count with differential white blood cell counts (“CBC with diff”), it is performed in nearly every clinical laboratory every day.

When lymphocytes (a type of white blood cell) are exposed to ionizing radiation, they undergo a predictable rate
of decline that correlates with the radiation dose. A 50% decline in absolute lymphocyte count in the initial 24 hours following exposure, followed by a further, severe depletion within 48 hours, indicates a potentially lethal dose exposure. Therefore, if the time from radiation exposure to the acquisition of the blood specimen is known, lymphocyte counts can be used to estimate the radiation dose. With this estimated dose, people can be sorted into 3 treatment categories: exposure level too low to require treatment, exposure level too high to benefit from treatment, and exposure level meriting treatment.

For ALCs to be most useful, measurement at 48 hours after exposure is ideal. Serial measurement of lymphocytes may provide a better estimate of radiation dose than a single test but logistically becomes more difficult. It is unclear what the capability is for laboratories to determine the rate of lymphocyte depletion (the rate constant), which may provide the best information about prognosis. Also, if there is a delay in running the test, which is likely during such a chaotic time, it is unclear to what extent lymphocyte numbers continue to fall after the blood sample has been drawn but prior to the sample’s being analyzed—an area in which further research is needed. Blood stored at room temperature for 2 days will yield a reliable result. But for lymphocyte counts to be useful for screening people for ARS, 2 significant challenges must be addressed:

1. There must be a way to draw the blood and run the tests quickly and on a massive scale. It is possible that a million people could be in the general area of the fallout, and it is likely that they would all have to be screened to identify the 100,000 or so with radiation sickness.

2. There must be a way to get the results to the clinicians who would be treating the patients.

While most hospitals can perform hundreds of lymphocyte counts in a day, it is expected that all hospitals and their respective laboratories within driving distance of the detonation site will be overwhelmed with caring for the tens of thousands of people with acute injuries. Some physician offices and clinics can also perform lymphocyte counts, but the desktop analyzers that they typically use are not capable of performing large volumes of tests.

**Information Needs**

In addition to being able to perform the test, it is just as important that the results of the test be efficiently made available to clinicians who would be treating the patients. After a nuclear detonation, a large portion of the local population, including those with impending ARS, will likely be on the move. Thus, patients in need of screening will probably not be in the stricken city 48 hours after the detonation. In fact, they may not remain in the same place where their blood is drawn long enough to get their results the next day or to receive treatment days later. Furthermore, some patients with borderline results may benefit from serial testing, which may need to be performed in different locations as patients continue to migrate away from the point of detonation. Therefore, an information system must exist to enable the patients’ treating clinicians, wherever they are, to access the results of the test irrespective of where the blood was drawn or the test performed. It is expected that, except in the attacked city, the internet and electrical grid will be functional following a single 10-kt detonation.

Both Quest Diagnostics and LabCorp have existing internet portals that allow physicians as well as patients to view laboratory results. These portals have very large capacity and are routinely accessed millions of times per day by clinicians, patients, and healthcare facilities. Most hospitals, physicians, and clinics are already registered users of one or both of these systems. Both companies indicate that registering new users in a crisis, though daunting, is feasible. The release of laboratory results to exposed individuals has the potential to create confusion among lay persons, especially in a high-anxiety situation. It remains to be determined whether releasing information to the patient directly would be advisable. The fact...
that a large percentage of the U.S. population is already registered in one or both systems could save time, reduce misidentification, and in some cases give access to baseline lymphocyte counts.

**Radiation Treatment, Triage, and Transport Response System (RTR)**

The U.S. government has developed the concept of multiple treatment, triage, and transportation locations in and around the stricken city to provide initial care to victims of all kinds. These RTR sites would be established at large locations of opportunity such as gymnasiums, auditoriums, and similar locations. These RTR sites could potentially provide phlebotomy, patient registration, and brief clinical assessment 48 hours post-detonation. Because a large segment of the population may have relocated to another city in that 48 hours, blood drawing and patient registration sites would need to be established in nearby cities and towns as well. At these sites, phlebotomy could be performed by laboratory personnel, medical volunteers, and government personnel. Existing national laboratory chain draw stations in these cities could also serve these functions. There is a need to model the most likely relocation sites for major cities to quantify the resources available in the surrounding locales. In addition, the use of point-of-care, battery-operated analyzers, capable of providing the lymphocyte count within minutes (now undergoing FDA evaluation), might augment capacity, especially at RTR sites with limited electricity.

**Many Details Must Be Addressed**

Although the national laboratory chains provide enormous testing capacity and robust information infrastructure, many operational, logistical, and regulatory hurdles must be overcome to fully harness their capability, including, among others: patient identification, physician order requirements, reagent supply bottlenecks, packing of specimens, transportation from draw sites to processing facilities, payment for services, and integration of test results from the multitude of smaller laboratories that would also be testing patients.

**Accurate Patient Identification**

In order for information to be useful, and not potentially harmful, it has to be accurately associated with an individual patient. Following a nuclear detonation, members of the public may have little identification on hand, and some may not know, or have, or be willing to share their social security number. However, the need for a definitive way to match patient and specimen (with draw time clearly indicated) through a unique identifier is essential. An alphanumeric identifier using a combination of birth date, name, and street address—all things expected to be known by patients from memory—is one possibility. There would need to be agreement by all stakeholders on the specifics of the identifier and just-in-time instructions for personnel entering patient and specimen information.

**Physician Order Rules**

Many states regulate laboratory tests by requiring that a physician or other healthcare provider order the test. This will not be possible in the event of a nuclear detonation. In those states in which a healthcare order is needed for laboratory testing, state governments should develop provisions to suspend this need in an emergency situation, perhaps by including a blanket waiver of these requirements in an immediate emergency declaration by the governor or the secretary of health.

**Reagent Availability**

A third obstacle that must be addressed is the availability of reagents. While national laboratory chains have the capacity to do 1 million lymphocyte counts, the instruments on which these tests will be performed have a supply chain of reagents needed for their operation. Currently, the national laboratory chains adhere to “just-in-time” principles that leave them with only a few weeks’ supply of reagents on hand—not enough to accommodate testing for 1 million people. If national laboratory chains are to be employed in the medical response to a nuclear detonation, the suppliers of their reagents will also need to be engaged and the feasibility of reagent stockpiles and the ability to rapidly mobilize reagents evaluated. The cost of keeping large amounts of reagent on-site at all times might be prohibitive in normal circumstances. In addition to reagents, phlebotomy supplies (eg, EDTA tubes, needles, tubing, and tourniquets) may also need to be stockpiled.

**Other Laboratories**

Even if LabCorp and Quest were to provide the bulk of ALC testing after a nuclear detonation, a large number of tests would also be performed in hospitals (eg, on injured patients) and by other smaller laboratories. It would be important to take advantage of this testing capacity and to be able to access the results of these tests.

**An Untapped Resource**

In the event of a detonation of a nuclear weapon, quickly and accurately identifying those most likely to benefit from
LARGE-SCALE LABORATORY TESTING FOR ACUTE RADIATION SICKNESS

medical treatment for radiation sickness would be a daunting task, but one that could save tens of thousands of lives. Engaging the large clinical laboratory chains in national planning to provide access to their capacity in a clinically relevant timeframe could help to solve this tough challenge and strengthen U.S. resilience.

REFERENCES


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