MEDICAL ASPECTS OF NUCLEAR ACCIDENTS

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It is a privilege to speak before this distinguished group to review my experience after the nuclear reactor disaster in the Soviet Union.

The United States leads the world in the number of nuclear power stations and in the net generation of electricity from nuclear sources; it is followed by France and the Soviet Union. These power stations are located throughout the world and contribute a substantial percentage of the electricity generated. The United States obtains 16% of its electricity from nuclear power. Much of western Europe is heavily dependent on nuclear power. The Soviet Union generates 11% of its electricity from nuclear sources; this proportion is much higher in the Ukraine and represents a substantial proportion of the electricity export of the Soviet Union to eastern Europe.

These data clearly indicate that nuclear energy is a reality and the world is likely to require it for the next 50 to 100 years. Much of the world's population, about 70%, does not have adequate power. Many countries will rely on the development of nuclear energy in the next several decades. We in the United States are fortunate to have alternative energy sources or fiscal resources that much of the world does not. Because of this, we could probably avoid nuclear power if we chose to. However, recent events at Chernobyl indicate that nuclear energy-related emergencies are international or transcountry by nature. Even if the United States were to close its nuclear power stations tomorrow, it would not obviate the need to develop appropriate planning for nuclear emergencies.

THE CHERNOBYL ACCIDENT

Most people had not heard of Chernobyl before April 26, 1986. For orientation, the city of Kiev, with 2.6 million persons, is located 130 km southeast of Pripyat, the site of the Chernobyl nuclear power station. The Pripyat river adjacent to the power station flows into the Kiev reservoir, which supplies about one-third of the drinking water for the city of Kiev. The station has graphite-modulated reactors approximately 12 m in diameter and 7 m high.

The operating principles of RBMK reactors, such as those at Chernobyl, are straightforward. Cold water enters the reactor core and is boiled by the heat released by fission of uranium 235, steam and boiling water are separated, and the steam is then used to drive

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turbines and produce electricity. The steam is then condensed, cooled, and re-enters the cycle.

The Soviets were performing a safety test at the time of the Chernobyl accident. The objective was to determine whether residual kinetic energy in the turbines would generate sufficient electricity to run the water pumps if the external supply of electricity to the power station were terminated. Normally these pumps are run by electricity from the external electrical grid, but there are backup systems that use diesel fuel and come on-line in the event of a loss of electrical power. This occurs relatively rapidly with typical United States reactors but requires more time with RBMK reactors. One might wonder why there was interest in determining what happens if the external source of electricity is cut off. First, there can be technical failures that would isolate the reactor from the external power grid. There might also be terrorist attacks. Terrorists, for example, could try to isolate the power supply to a nuclear power station.

The Soviets did not immediately release the information about the Chernobyl disaster. However, increased levels of radioactivity were detected in Sweden on April 28 and shortly thereafter the Soviet Union made a brief public statement. I had the opportunity to enter the Soviet Union on May 2 when I offered assistance to the Soviet Union on behalf of the International Bone Marrow Transplant Registry.

The total release from Chernobyl excluding noble gases was about 50 million curies; about 25% was released on the first day. The release then gradually declined but increased again on day five or six. At this point the Soviets bombarded the reactor with boron, dolomite, sand, and lead. The bombardment was successful, the reaction was quenched by day 10, and the reactor was subsequently enclosed in a sarcophagus.

The radioactive plume released from the reactor was ejected to a height of up to 10 km. Initially, winds were blowing in a northwesterly direction. As a consequence, on April 28 the radioactive plume extended over the northern portions of the Soviet Union and into Finland. Within two days, a westerly wind drove the cloud over northern Sweden. Southerly winds then drove the radioactive plume over much of eastern and western Europe.

What went wrong at Chernobyl? The problem can be divided into two major elements: human factors and design aspects. First, the planned test procedures clearly violated Soviet safety regulations. Second, the operators did not follow the planned test. Third and perhaps most important, the operators lost a sense of vigilance towards safety.

These human factors would not have been enough to cause the accident had it not been for some design aspects. First, it was relatively simple for operators to override the safety systems of the reactor. Second, the control rods in this type of reactor have a slow insertion time and require almost maximum insertion to be effective; in fact, the accident occurred as the control rods were being reinserted. Finally, RBMK reactors have a positive rod reactivity coefficient. It was the combination of all these events, each very unlikely, that led to the Chernobyl emergency.

RESPONSE TO NUCLEAR EMERGENCY

What do physicians need to consider when such an event occurs? The key elements are assessment, containment, attempts to reduce exposure, estimation of dose to exposed individuals, and medical intervention.

Assessment: The first consideration is assessment of source term parameters. What is the nature of the accident? Does it involve a nuclear submarine, a power station, a nuclear warhead? What is the radionuclide inventory of the source and what is the fractional release? In the case of Chernobyl, the fractional release was about 4% of the fuel inventory. Another important consideration is the physical-chemical form. What proportion of radioactivity is released as noble gases? The particle size distribution will determine the biomedical consequences of the release. For example, large particles are more likely to fall close to the reactor than small particles. It is important to know the answer to these questions in planning an emergency response.

Containment: The next factor to consider is containment. There is a notion that the Chernobyl reactor was uncontained, but this is not correct. The Soviet term that applies to the type of containment around reactors of this type is localization. The type of containment for reactor Number Four at Chernobyl would not have met U.S. standards. Another major difference is that in the United States a structure usually encloses the entire reactor. There are five lines of defense in the U.S. reactors: ceramic fuel pellets, zirconium fuel rods, the pressure vessel, a steel containment structure, and a concrete and steel containment building. This is referred to as defense in depth and was not present in the Chernobyl reactor.

Release of radioactivity (excluding noble gases) from Chernobyl was about 50 million curies. In comparison, about 17 million curies were released from Three Mile Island. Thus, Chernobyl released three times as much radioactivity as Three Mile Island. The major difference between these accidents was in containment. Only an infinitesimal fraction of the 17 million curies released from Three Mile Island entered the environment, an efficiency in containment of almost 1 million-fold. At Chernobyl, all 50 million curies released from the reactor core entered the environment.

Reducing Exposure: What steps can be taken to reduce exposures and prevent serious injuries? These are divided into immediate and long-term interventions. First, it is necessary to consider individual versus population protection. Guidelines have been established by several international organizations regarding evacuation. When should people be evacuated? The initial decision at Chernobyl was to keep people at home. Eventually it was decided to evacuate a zone of approximately 30 km around the power station encompassing 2,700 km^2. Several thousand people received iodine tablets to prevent uptake of radioactive iodine. Iodine should be given relatively promptly after a release, within 4 to 24 hours.

Long-term methods to reduce exposure include decontamination and exposure modification. For example, it might be necessary to change the lifestyle of people, to modify their dietary habits, or to restrict their consumption of certain foods; relocation may be necessary. At Chernobyl, the evacuation of a 30-km zone around the reactor affected 135,000 persons.

Gamma field distributions several days after the Chernobyl accident have been published by the Soviets. Levels reached about 100 mR per hour in certain areas. The city of Chernobyl is 10 km southwest of the power station. The radioactive plume was driven to the northwest. Based on these types of data, the Soviets made the initial decision not to evacuate the population of Pripyat. It was perceived that the risk to individuals would be greater if the population were outside awaiting evacuation than if they remained in their concrete homes until appropriate plans could be made. Approximately 36 hours later, when the exact extent of the accident was clear and buses were available to transport people, the evacuation was effected.

Pripyat is a high-rise city with concrete buildings. Because of this it may have been reasonable to keep people indoors for the first several hours where they were relatively well shielded. The city is now uninhabited, and it is unlikely that it will be habitable for a prolonged period. Plans have begun to construct a new city outside the evacuation zone to house the staff of the power station. Soviet power stations, unlike those in the United States, are typically self-sufficient. In the United States, it is unusual to have a city of 50,000 people 2 km from a nuclear power station. So there are certain social and economic differences between siting of nuclear power stations in the Soviet Union and the United States.

The Chernobyl reactor is located next to the Kiev reservoir, which flows into the city of Kiev via the Dnieper River. Ships positioned in the reservoir were used to monitor levels of radioactivity in the water. About 30 artesian wells were dug around the city of Kiev to provide an alternative water supply. Despite the fact that the water in the Dnieper River never reached action levels (of radioactivity), use of the river water was discontinued as soon as the artesian wells were functional.

One important observation made at Chernobyl is that the radial distance from the reactor was not always correlated with the dose of radiation. That is, radiation exposure is influenced by condition of the release as well as atmospheric conditions such as wind direction and precipitation. It is necessary to be prepared to respond to the very complex patterns of radionuclide exposure as a consequence of reactor accidents.

Estimation of Exposure Dose: The next factor is to estimate the dose of radiation of exposed individuals. Exposure to radiation can be internal or external, and each of these pathways is complex. There is internal exposure from inhalation and ingestion and, as the radioactive plume passes, there is external whole body exposure. Ground deposition also contributes to external exposure.

If the level of radioactivity in the air, water, or various foods is known as well as the population's average intake, one can calculate the intake of radioactivity. This is then corrected for factors that relate to fraction of dose distributed and effect on various tissues to calculate an effective dose.

Dose Calculation of Acutely Affected Individuals: Physical measurement of dose in accidents is complex. Environmental dosimeters are potentially useful but may be destroyed or unrecoverable. They also cannot determine uniformity of dose. Radiation badges are useful. They may be off scale but special badges or thermoluminescent dosimeters are available that cover the scale of accidents. Unfortunately, badges may not accurately reflect distribution. It is considerably different if a person receives 8 Gray to the whole body versus 8 Gray to the whole body except for one leg, because hematopoietic stem cells in the shielded leg can reconstitute the bone marrow.

In this type of accident it may be necessary to rely on biological dosimetry to determine dose. Medical history, symptoms, and measurements of cells in the peripheral blood and bone marrow were used at Chernobyl. A careful medical history is useful. Questioning the firemen and determining how they entered the building, where they were in the building, and what their exposure to fire versus potential radiation allowed some estimation of dose.

The interval from exposure to the development of nausea is also important. There is a correlation between radiation dose and the incidence of nausea or vomiting. However, since there are many causes of nausea in a nuclear reactor accident besides radiation, including burning plastics and other materials, one cannot assume that nausea is a reliable indicator of radiation dose. The absence of nausea can be useful however. Unfortunately the perception of time in an emergency is imprecise. It is not only time on-site, but potential time of exposure that is important. If a person is in the building behind a concrete wall, his time to development of nausea is not the same as that of someone who is standing near the radioactive core. So one can only get a sense of the relationship between nausea and time, not an absolute dose.

Another approach is to measure circulating levels of granulocytes, lymphocytes, or platelets in the blood at intervals following exposure. Generally, these levels are correlated inversely with the dose of radiation.

A final approach in estimating the dose is cytogenetics. Ionizing radiation causes intrachromosomal and interchromosomal exchanges. Therefore, one can approximate the radiation dose by determining the proportion of aberrant metaphases or dicentric chromosomes in the blood or bone marrow.

Initially the Soviets screened approximately 2,000 individuals by external counting of radioactive iodine over the thyroid. Five hundred people were identified as being at highest risk. The 200 least severely affected individuals were hospitalized in Kiev, and 300 were flown to Moscow. It is estimated that 100 to 200 people received a dose in excess of 1 Gray.

What are the biologic effects of radiation exposure? At very high doses (greater than 50 Gray) there is instantaneous death, usually from central nervous system toxicity. No one at Chernobyl received this dose, except perhaps the operators, but they were killed instantly by the explosion. At doses between 10 and 15 Gray, death occurs from gastrointestinal toxicity over one or two weeks. There were several deaths in individuals who received doses in the lower end of this range at Chernobyl. At doses between 3 and 10 Gray, the major cause of death is damage to the bone marrow. This occurs over several weeks.

What are the effects of radiation on man? Alpha particles (composed of neutrons and protons) have a low penetrance. They can be extremely damaging to human tissues but do not play a major role in these kinds of reactor accidents. Beta particles (electrons) penetrate about 1 to 2 cm in human tissues. Gamma rays are not radioactive but cause ionizations in tissues and penetrate human tissues effectively. If one considers the effect of radiation on man, affected individuals might have beta burns and gamma effects as well as thermal burns from the fire. With regard to deep structures, the major effect would be from gamma radiation although ingested radioactive particles can radiate a person internally from beta transmission. Thus, the evaluation of toxicity from this type of accident is exceedingly complex.

Medical Interventions: The next issue is medical interventions. Most of the severely affected individuals were treated at Hospital Six in Moscow, which houses a hematology unit specifically but not exclusively dedicated to dealing with victims of radiation accidents and which has an experienced team of physicians including Drs. Angelina Guskova and Alexandr Baranov. The major medical interventions are indicated in Table 1 and the transfusion-related approaches in Table 2.

One approach to preventing infections was administering oral antibiotics that modify the gastrointestinal tract flora. The Soviets used trimethoprim and sulfamethoxazole. The value of this intervention is unproven. Another approach to preventing infections is to provide isolation either in single rooms utilizing masks, gowns, and hand washing or in laminar air flow rooms. The Soviets used these for some patients. There are such rooms in most major medical centers.

To treat infections, the Soviets used systemic antibiotics and antifungal agents. They had an adequate supply but felt that third-generation cephalosporins and newer semisynthetic penicillins might be advantageous. Some were flown into the Soviet Union with the help of Dr. Armand Hammer and Dr. Drew Winston.

Transfusions also are an important part of emergency measures. Exposure to radiation causes neutropenia and thrombocytopenia. Anemia develops late and is relatively easy to correct. Platelet transfusions are more complex. It is desirable to use single-donor platelet transfusion, which requires sophisticated leukapheresis devices. One unique thing done following the Chernobyl disaster was to use autologous frozen platelets. Granulocyte transfusions are a theoretical possibility, but since most data suggest they are not useful in patients with granulocytopenia, they were not used after the disaster.

The importance of irradiating blood products must be borne in mind in dealing with emergencies. If a person who has received a substantial dose of radiation is given blood products that have not been irradiated, there is a risk that lymphocytes in the blood products will cause graft-versus-host disease, which can be fatal. This can be prevented by radiation of the blood products with 15 Gray.

What is the role of bone marrow transplantation in nuclear accidents? There is a dose of radiation that irreversibly destroys the bone marrow, and the only way to rescue the life of such an individual is to perform a bone marrow transplant. This approach is used frequently in treating various hematologic disorders, such as aplastic anemia and leukemia. In this circumstance, very high doses of chemotherapy and radiation are given intentionally to eradicate the leukemia cells. As an unavoidable consequence, the normal bone marrow is destroyed. One must perform a bone marrow transplant from a suitable donor, usually an HLA-identical sibling or parent. After transplantation it is necessary to administer immunosuppressant drugs (methotrexate or cyclosporine) for three to six months to prevent graft-versus-host disease.

TABLE 1

SUPPORTIVE CARE AND ANTIBIOTICS

Oral Nonabsorbable Antibiotics (eg, Trimethoprim/Sulfamethoxazole [Bactrim, Septra])

Isolation

Laminar Air Flow

Systemic Antibiotics/Antifungals

Antivirals (eg, Acyclovir [Zovirax])

Intravenous Immune Globulin

TABLE 2

TRANSFUSIONS

Red Blood Cells (RBC)

Platelets - Single Donor

- Autologous Frozen

Granulocytes

Plasma Products

Plasmapheresis

Blood Products Irradiated >15 Gray

One can envision a radiation accident being similar somewhat to a treatment scheme. Unfortunately, in a reactor accident there is only an imprecise idea of the dose, dose rate, and dose distribution. Another difference is that the victims receive radiation under conditions in which damage to other tissues is considerable. Therefore, a substantial portion of patients die of toxicity unrelated to bone marrow damage.

A bone marrow transplant is only effective in preventing death from bone marrow failure. It cannot prevent death from skin burns. In accidents, the determination of who should have a bone marrow transplant is complex and is complicated by the fact that at the time one needs to decide whether to do a bone marrow transplant, it is not possible to know the full extent of nonhematopoietic damage. In the Chernobyl type of accident, one anticipates at least a 50% risk of death from skin burns or other nonbone marrow toxicity. The problem is that it may not be possible to identify those individuals. Different courses of action are possible. One can do no bone marrow transplants or perform bone marrow transplants on all potential candidates and accept the fact that 50% will die of other toxicities. In the 50 in whom transplants might succeed, one expects a success rate of approximately 50%. Thus, if one starts with 100 transplants, the expectation of success is approximately 25%. This expectation was fulfilled by the outcome at Chernobyl. Thirteen bone marrow transplants were done; two patients survive.

What principles underlie the use of bone marrow transplants in radiation accidents? First, high doses of radiation, 8 to 15 Gray, are associated with a high risk of death from bone marrow failure. Second, high-dose radiation is associated with a low risk of death from other causes. This notion depends very much on the specific accident. In the case of a U.S. nuclear reactor accident, this concept is probably true. In the context of the Chernobyl accident, this concept was not true because the ratio between beta and gamma radiation was very high and because there was a 2,000° C fire.

The third concept is that the risk of an adverse outcome of transplantation is low. This concept also proved to be not entirely correct since transplants can cause graft-versus-host disease. The final notion is that permanent engraftment may not be necessary for beneficial effect. This concept is probably correct. It may be adequate to have temporary engraftment to allow recovery of the patient's bone marrow. In an ideal situation, the bone marrow transplant would be rejected in a patient with sufficient hematopoietic stem cells to recover. This was the case at Chernobyl. The two survivors who received bone marrow transplants have recovery of autologous hematopoiesis. One question that cannot be answered is whether these individuals would have survived without a bone marrow transplant.

I would suggest that the decision-making process regarding transplants is similar to many clinical situations in which one tries to calculate the risk/benefit ratio of an intervention. Many factors determine the likelihood of success following a transplant. For example, if the dose of radiation is 12 Gray, the person is unlikely to recover without a transplant. If the person has a genetically identical twin as a potential donor, then the risk of transplantation is small. Therefore, one is likely to proceed with a transplant. If the dose of radiation is 5 Gray and the donor is HLA-mismatched, it is likely that the risk/benefit ratio is not advantageous and a transplant will not be done. Thus, each case must be evaluated individually; it is difficult to suggest general guidelines.

Most radiation victims will not have an HLA-matched donor; therefore, one must consider alternatives. One approach is to use an HLA-mismatched donor following removal of T-lymphocytes from the donor bone marrow. By removing the T-lymphocytes, graft-versus-host disease can be decreased or prevented but the likelihood of graft rejection is increased. The net effect is to increase the probability of a temporary graft followed by recovery of autologous hematopoiesis.

It can be demonstrated in mice that one can convert an LD_{90} of radiation into an LD_{10} by giving a T-cell depleted bone marrow transplant that is ultimately rejected. Another alternative for a radiation victim without an HLA-identical relative is to use an unrelated HLA-matched donor. This requires the use of an HLA-typed unrelated donor pool containing 50,000 to 100,000 potential donors. Such pools exist in Europe and the United States.

Bone marrow transplantation represents a relatively minor part of the total response to a radiation accident. At Chernobyl several hundred people were hospitalized; of these, 100 to 200 received a dose in excess of 1 Gray. Thirty-one people died; the rest are well and at home. Many lives were saved by the use of sophisticated antibiotics, antifungal agents, acyclovir to prevent herpes virus infection, and sophisticated transfusions.

Revised guidelines for bone marrow transplantation suggest that individuals who received less than 8 Gray probably do not require a transplant. Before Chernobyl, it was thought that a dose of 4.5 Gray was the LD_{50} in man. It now seems that most individuals can survive doses of 6 to 8 Gray if sophisticated supportive care is available. At doses between 8 and 12 Gray, a transplant should be considered in the context of the risk/benefit ratio in each patient. Above 12 Gray, transplants are probably not indicated because of the likelihood of death from nonhematopoietic toxicity.

PREPAREDNESS

Is the United States prepared for large radiation accidents? I would suggest that we are prepared to deal with small accidents involving fewer than ten individuals. We also are reasonably well prepared to deal with evacuation of large populations. I am less certain there are optimal plans to respond to the magnitude of the disaster that occurred at Chernobyl. I also am not certain that there are optimal plans whereby tertiary care medical facilities that have transplant, hematology, or plastic surgery units are linked with or have on-going relationships with nuclear power stations. For example, if suddenly, 100 people who needed bone marrow transplants arrived, how would they be dealt with? The International Bone Marrow Transplant Registry is working on this problem. For example, in the context of Chernobyl, Registry staff knew immediately how many beds were available in each of the 138 transplant centers worldwide. It is not difficult to fly victims to these centers if needed. We must have international preparedness, and I think we are learning lessons from Chernobyl and moving in this direction.

Another point worth considering is the need for an international registry of individuals and organizations experienced in dealing with radiation emergencies--physicians with expertise in radiation biology, sophisticated supportive care, and possibly transplantation. Unfortunately, these fields have diverged. People knowledgeable in radiation biology usually have inadequate knowledge of modern intensive care. People in supportive care and those doing marrow transplants often have limited knowledge of what can happen in a nuclear power station accident. These specialists need to work more closely.

Again, I want to thank you for inviting me to speak at this symposium. I hope that the lessons derived from Chernobyl will not go unheeded. They show that we live in a nuclear age, that the implications of nuclear energy are by definition international, and that there are no international boundaries when it comes to nuclear energy. The ultimate message from Chernobyl is that all of us must work together in the context of modern technologies, such as nuclear energy and space. We must not let political differences interfere with the peaceful uses of these technologies, because we live on a very small planet.

Acknowledgements

I would like to thank my Soviet and American colleagues for thoughtful discussion of several issues raised in this review. Special thanks are due to Drs. Angelina Guskova, Alexandr Baranov, Andrei Vorobiev, and Leonid Ilyan from the USSR; Richard Champlin, Richard Jacobs, Paul Terasaki, and Marvin Goldman from the US; and Yair Reisner from Israel.

My special thanks to Dr. Armand Hammer for his medical and humanitarian efforts.

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