ACUTE EFFECTS OF EXTERNAL RADIATION

Eugene L. Saenger, M.D.

External radiation exposure produces the greatest number of overt nonstochastic injuries. Although this type of injury is of greatest interest to the clinician, radiation accidents are so rare that most physicians and public health authorities never encounter exposed patients. Fortunately the ionizing radiation dose and its distribution in the body can be measured with great accuracy and precision. Thus, the following statements are interpretable far more easily for radiation injury than for chemical, heat, light, blast, and burn injuries.

Several radiobiological principles are important to the understanding of the clinical and laboratory findings: The greater the percentage of the body exposed, the greater the effect. Accidental radiation exposure usually is irregularly distributed, which may moderate the clinical course. Shielding of a relatively small portion of the body (eg, the spleen) will give significant degrees of protection; the shielding of an extremity will help to protect bone marrow.

Other important factors determining the effects of exposure are the total dose and the dose rate. Dose is that amount of radiation or drug delivered. Inasmuch as response is proportional to dose, the larger the dose, the greater the response or the more rapid the onset of symptoms. Dose rate is somewhat more difficult to relate to the injury. A dose that might be lethal if delivered within minutes or hours is tolerable when delivered over days or weeks. In most external radiation injuries, exposures are acute; however, if exposure occurs over days or weeks, the effects often are initially attributed to causes other than radiation. Fractionated doses used in radiation therapy often produce minimal clinical changes until the total dose reaches 30 to 60 Gy (3,000 to 6,000 rad). Thus, the lower the dose rate, the greater the degree of racovery and the less the effect.

For the purpose of emergency planning, the $LD_{50/60}$ (the estimated median radiation dose leading to death in 60 days) is a useful guide in determining the need for supportive or aggressive therapy. If only first aid or minimal supportive therapy is available, the $LD_{50/60}$ is 2.5 to 3.5 Gy (250 to 350 rad); when hospital care and more supportive therapy (antibiotics, blood derivatives, reverse isolation) are available, the $LD_{50/60}$ is about 4.5 Gy (450 rad). With provision for intensive treatment, the $LD_{50/60}$ can be 6 Gy (600 rad) or more.[1]

Professor of Radiology and Director, E.L. Saenger Radioisotope Laboratory, University of Cincinnati Medical Center, Cincinnati, Ohio.

Not all irradiated individuals react exactly the same, but the differences are not clinically important in cases of acute irradiation, and there may be other explanations for the differences.

EXTERNAL RADIATION

The effect of external radiation may be considered in two ways. The acute radiation syndrome (ARS) is identified as a characteristic set of clinical changes that occurs when most (total body radiation, TBR) or large segments of the body are exposed relatively uniformly. The ARS also develops as a result of radiation therapy that involves total nodal irradiation.

Partial body exposure (PBR) produces a response that is less severe than with TBR, since much less (50% or less) of the body is involved. The prodromata may be similar but the remainder of the clinical course is far more benign.

A more frequent and often serious form of radiation damage is localized radiation injury (LRI). In this form there may be immediate onset of severe radiation burns, but clinical manifestations usually develop more slowly than after a thermal burn. There is often a latent period of days to one or two weeks before tissue injury is observed that may lead to painful ulceration and necrosis. An important finding distinguishing LRI from ARS is the absence of characteristic prodromal symptoms and signs and minimal or absent hematologic changes. LRI is really a subset of PBR and is not life threatening (Tables 1 and 2). Severe localized injury also may occur with whole body or partial body exposure. Ulceration and necrosis are greatly complicated in the presence of secondary infection.

Occasionally, radiation injury may develop concomitantly with trauma from other physical and chemical agents, in which case it is termed "combined injury" (CI). On the basis of extensive studies in laboratory animals, it is thought that these forms of injury potentiate each other's effects. Undoubtedly CI was quite common in Japan after the atom bombs were dropped, and it probably contributed to the high death rates experienced at Hiroshima and Nagasaki during the first several days. According to Soviet physicians, CI did not appear to be significant in the workers or nearby inhabitants at Chernobyl.

Finally, a radiation field may be small enough to affect one or more adjacent organs (eg, thyroid, lens, gonads), and acute and late effects would be restricted to those organs.

ACUTE RADIATION SYNDROME

ARS has been divided into hematologic, gastroenteric, and central nervous system (CNS) phases. Classification of the changes that occur at acute dose levels is shown in Table 3. The dose values may vary as much as 50% depending on the factors mentioned above. This classification, developed by Thoma and Wald,[2] has been modified

TABLE 1

CARDINAL CLINICAL MANIFESTATION OF RADIATION INJURY

Procedure	Finding	Time of Onset	Minimum Exposure (Gy)
History	Nausea, vomiting	Within 48 hrs	∿1 (∿100 rad)
Physical	Erythema	Within hrs to days	∿3 (∿300 rad)
examination	Epilation	Within 2-3 wks	∿3 (∿300 rad)
Blood count	Absolute lymphocyte count[1] <1000 mm^3	Within 24-48 hrs	∿1 (∿100 rad)
Chromosome	Dicentrics, Rings Fragments	Within hrs[2]	∿0.1 (∿10 rad)
Sperm	>20 mil/ml	After 7 wks	∿0.15 (∿15 rad)

[1] Lymphocytes may decrease within hours. Obtain the baseline count as soon as possible and repeat the count.

[2] Requires 48-72 hours for analysis.

TABLE 2

CLINICAL MANIFESTATION OF LOCAL RADIATION INJURY*

Finding	Time of Onset
Irritation, Tenderness, Itching	Within 1-2 wks
Restriction of motion, Stiffness	Within 1-2 wks
Erythema, Edema, Decreased sensation	Within 1-3 wks
Bullae, Ulceration	Within 1-4 wks

*These findings and times of onset may vary.

TABLE 3

CLINICAL RADIATION INJURY GROUPS

Group	Clinical Manifestations (Without Treatment)	Approximate Dose (Gy/rad)	Clinical Classification
I	Mostly asymptomatic. Occasional minimal prodromal symptoms and subtle laboratory changes.	1.5 Gy (150 rad)	-----
II	Mild form of acute radiation syndrome. Transient prodromal nausea and vomiting. Mild laboratory and clinical evidence of hematopoietic derangement.	4 Gy (400 rad)	Hematopoietic
III	A serious course. Hematopoietic complications severe, and some evidence of gastroenteric damage present in upper portion of group.	4-6 Gy (400-600 rad)	Hematopoietic
IV	An accelerated version of acute radiation syndrome. Gastroenteric complications dominate the clinical picture. Severity of hematopoietic complications is related to survival time after exposure.	6-15 Gy (600-1,500 rad)	Gastrointestinal
V	A fulminating course with marked cardiovascular and/or CNS impairment.	50 Gy (5,000+ rad)	Neurovascular Cardiovascular Cerebral

somewhat over the years, particularly for those in Group V; deaths in this group now are attributed to cardiovascular rather than CNS injury.

The clinical course of ARS is shown in Table 4, which compares the progression of symptoms to that in a typical viral disease. In ARS, the time between exposure and development of prodromal changes is relatively short (hours to days). The severity is related to how rapidly the prodromata begin; the higher the dose, the longer the symptoms and signs persist and the greater the body involvement. Because accurate estimates of dose and dose distribution usually are not available early, careful clinical observation may serve as a guide for the level of care needed. The prodromal syndrome is a parasympathetic neurogenic response and is not secondary to gastrointestinal damage. In animals, it may be prevented by ablation of the CNS vomiting center.

In injury groups I, II, and III (Table 3), the prodromata usually persist no longer than 48 hours and are followed by a latent period of 18 to 21 days. However, the length of this latent period varies from one to two weeks with very high doses (6 to 10 Gy [600 to 1,000 rad]) up to three weeks with lower doses (1 to 6 Gy [100 to 600 rad]). During this period, the patient essentially is asymptomatic, although changes may be significant in various organ systems. A possible explanation for the absence of clinical findings during this period is that cellular division is in abeyance. When injured cells attempt to undergo division normally, the next phase of the ARS suddenly begins. Another explanation is that the latent period ends when a threshold of deficiency of cells develops. The critical phase, or the period of manifest illness, may last for three to five weeks and is followed by gradual recovery or death, depending on the severity of the exposure.

The onset of manifest illness in group IV patients is sooner, perhaps 7 to 14 days after exposure, and death may occur in two to four weeks. Individuals in group V have survived no more than two days in a few carefully studied cases.

Most of the clinical findings during the manifest illness phase induced by total body irradiation are from injury to a specific organ.[1] The predominant sign after very high doses (greater than 20 Gy or 2,000 rad) delivered in a short period is hypotensive shock; this is followed by anoxic convulsion, coma, and death, which typically occurs in less than eight hours without antishock therapy and within 30 to 48 hours with antishock therapy.

The CNS syndrome has been subdivided into the cardiovascular phase and the CNS phase. The true CNS syndrome is characterized by the immediate onset of severe neurologic symptoms; convulsions and death occur within minutes to a few hours following massive exposures (1,000 Gy or 100,000 rad); it has been produced in animals but has not been observed in humans.

TABLE 4

CLINICAL COURSE OF THE ACUTE RADIATION SYNDROME
AS COMPARED TO CLINICAL PATTERN OF VIRAL DISEASE

Viral Infection	Acute Radiation Syndrome	Approximate Duration (for Hematopoietic syndrome)
Inoculation or exposure	Exposure	
↓	↓	
Delay	Delay	Minutes/hours
↓	↓	
Prodromal stage (nonspecific systemic reaction)	Prodromal stage (similar to motion sickness)	1-4 d
↓	↓	
Incubation period	Latent stage	2-3 wk
↓	↓	
Manifest illness (typical clinical picture)	Manifest illness (specific)	Week 2 or 3 to 6
	↓	
Convalescence	Recovery or death	8-15 wk

With doses of 6 to 20 Gy (600 to 2,000 rad), the predominant symptoms are overwhelming sepsis and toxemia. Nausea, vomiting, diarrhea, dehydration, and death also occur. At doses of 2 to 6 Gy (200 to 600 rad), signs of infection and anemia may develop due to bone marrow depression with decreased blood cell formation. When the scalp or other hairy body parts are exposed, epilation can occur after 14 to 21 days and it suggests a skin dose higher than 3 Gy (300 rad). Epilation also may indicate the direction and distribution of the radiation. There is considerable overlap in the symptoms and causes of death in these three dose ranges. The median lethal dose for total body irradiation, however, is within the range that causes death from bone marrow depression. Death due to infection and toxemia is secondary to agranulocytosis and immune suppression.

In our laboratory, patients with metastatic cancer are being treated with total body radiation (TBR) and partial body radiation (PBR).[3] Although the prodromal symptoms of TBR and PBR are dose dependent, they are independent of volume of tissue exposed; however, the degree of hematologic changes is quite different. TBR typically decreases formed elements with a nadir at 25 to 30 days and gradual recovery occurs in three to four weeks. With the same dose for PBR, hematologic changes are minimal.

The dose rate affects the severity of the ARS. A single midline dose at rates greater than 0.05 to 0.10 Gy (5 to 10 rad) per minute caused a high incidence of radiation pneumonitis. Only when the exposures were fractionated to 1.65 to 2 Gy (165 to 200 rad) twice daily for three days or more was this complication minimized. The success of transplants also was improved. Acute radiation pneumonitis also has been observed following exposure of the lungs to single doses of about 9 Gy (900 rad) or more. With protraction, the changes may occur in weeks or a month at dose levels of about 4 Gy (400 rad).[4]

LABORATORY TESTS

The classification given in Table 1 allows establishment of the clinical injury group on the basis of the clinical manifestations and a routine blood count. These observations make it possible to estimate radiation doses in the absence of physical measurements at the time of the injury or afterward. Thus, it is possible to manage patients successfully in the absence of physical data.

At Chernobyl, Soviet physicians employed triage successfully on more than 500 persons at the accident site using only clinical manifestations (especially nausea and vomiting), daily absolute lymphocyte count, granulocyte counts, and results of chromosome culture of peripheral lymphocytes.

In immediate triage, the simplest and most valuable laboratory test is the absolute lymphocyte count. This set of curves is widely employed (Figure 1) and permits estimation of biological damage within hours and up to two days, after which a combination of clinical

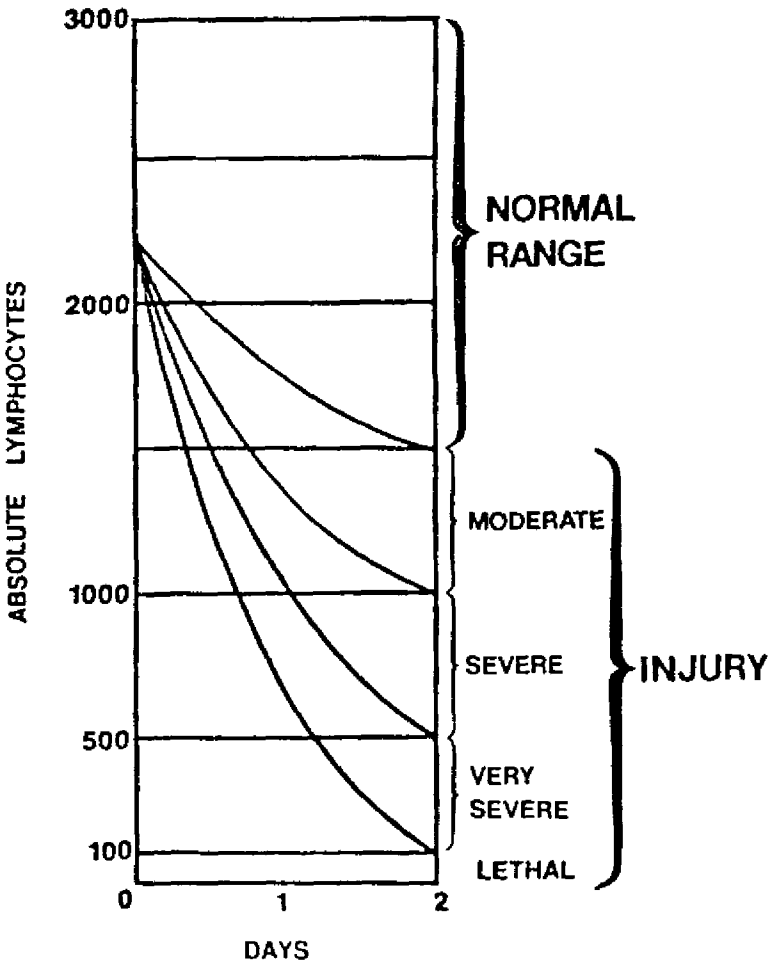

Figure 1. Schematic relationships between absolute lymphocyte level and clinical injury as estimated in the first 2 days after exposure. (From Andrews GA, Auxier JA, Lushbaugh CC: The importance of dosimetry to the medical management of persons accidentally exposed to high levels of radiation. In Personnel Dosimetry for Radiation Accidents. Vienna: International Atomic Energy Agency, 1965.)

manifestations and additional laboratory tests will dictate the type of medical care and facilities needed.

The changes in granulocyte and platlet counts are also important during the entire clinical course. Because of their longer life span, the erythrocytes decrease more gradually than granulocytes and platelets as a function of dose and other associated factors. The typical granulocyte changes in patients in Groups II and III are shown in Figure 2. Low doses result in an increase in granulocytes during the first few days, but this is not a favorable sign, particularly when associated with a decrease in lymphocytes; granulocyte count falls rapidly in the next seven to ten days. At doses of 2 to 5 Gy (200 to 500 rad), there is often a paradoxical rise ("abortive rise") in granulocytes, peaking at about 15 days. Various explanations have been advanced; the concept of a population of injured cells entering the circulation briefly and then dying seems reasonable. The abortive rise may have some dosimetric value in that it suggests that the dose equivalent to the "whole" body is less than 5 Gy (500 rad).

Recovery begins when the nadir of the granulocytes is reached at 20 to 30 days, assuming adequate control of secondary infections and other complications. A more rapid fall in granulocyte count to a nadir of a few hundred cells before 20 days requires intensive therapy. Platelets follow a course similar to that of granulocytes but delayed by two to three days. A detailed analysis of the blood changes is found in reference 5.

Other Tests

Other valuable laboratory tests are chromosome analysis of peripheral lymphocytes and sperm analysis. The assay of chromosome changes in peripheral lymphocytes due to ionizing radiation is an excellent biological dosimeter. Although the characteristic changes, especially of dicentrics and rings, are not specific for ionizing radiation, this technique gives an excellent indication of the level of biological insult. Early sampling is important because of the radiosensitivity of the lymphocyte. This technique also is useful in evaluating whether the distribution of radiation is uniform TBR or perdominantly PBR. If there is a disproportionate number of dicentrics per cell from the predicted Poisson distribution of the in vitro standard curves for uniform irradiation, then an uneven distribution of radiation is suspected. Sperm analysis is especially useful for determining low dose exposure and the direction of the beam, as an aid in the determination of uniformity, and for rehabilitation and family counseling. Specimens must be obtained before 40 days after exposure and again after 60 days.

MANAGEMENT

The levels of treatment should be considered in terms of current $LD_{50/60}$ estimates. At present, those who received from 1.5 Gy (150 rad) to less than 4 Gy (400 rad) need minimal postexposure therapy

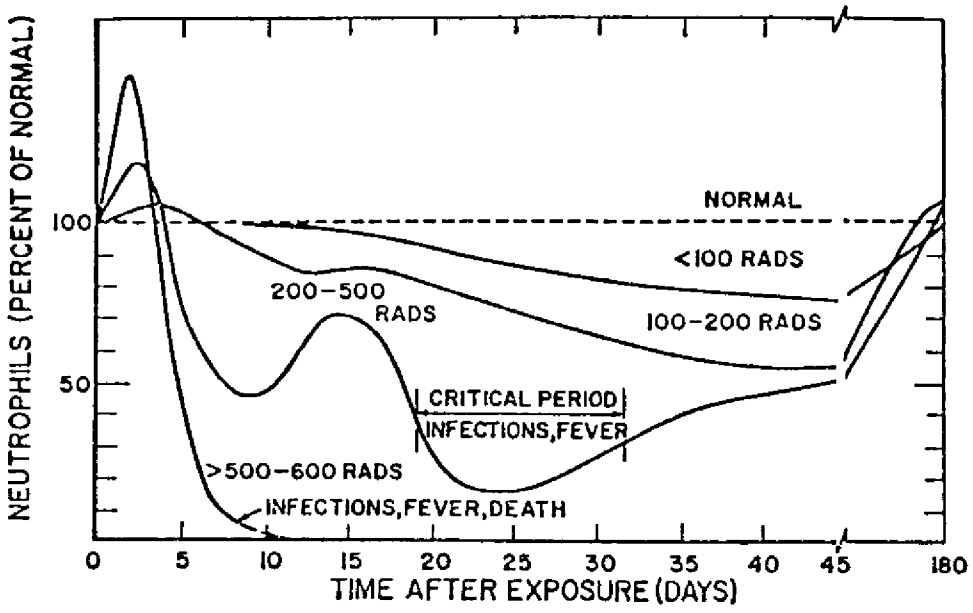

Figure 2. Smoothed average time-course of neutrophil changes in human cases from accidental radiation exposure as a function of dose (From Langham WL (ed): Radiobiological Factors in Manned Space Flight: Report of the Space Radiation Study Panel of the Life Sciences Committee, Space Science Board, National Academy of Sciences, National Research Council. Washington, NAS/NRC, 1967.)

such as adequate shelter from the elements, places to rest and sleep, good nutrition, and therapy for overt clinical infection. As the $LD_{50/60}$ approaches 4 Gy (400 rad), more rigorous supportive care becomes essential, and the level of care depends on the number of people affected and supporting personnel, the ability to prevent and treat infection and bleeding, and availability of appropriate hospital facilities.

The LD_{50} can be increased to 6 to 7 Gy (600 to 700 rad) after single high dose rate exposure and to 12 to 15 Gy (1,200 to 1,500 rad) with fractionated doses of 2 to 4 Gy (200 to 400 rad) per day. Most of the latter are patients who have had supralethal exposures prior to receiving bone marrow transplantation for pre-existing diseases. (Note: All dose estimates should be regarded as varying by at least ± 25%.)

Acute Radiation Syndrome (ARS) - Whole Body and Partial Body Irradiation

Group I (about 1.5 Gy [about 150 rad]): Only the simplest level of care (shelter, adequate clothing, adequate food and water intake, and careful clinical observation) should permit satisfactory recovery while limiting demands on therapeutic resources. Antiemetics and tranquilizers may be required.

Group II (1.5 to 4.0 Gy [150 to 400 rad]): More rigorous therapy is necessary, depending on the changes in clinical state and laboratory values.

In the prodromal phase, antiemetics and tranquilizers are helpful. Fluid and electrolyte balance may be affected by vomiting and diarrhea. Cultures of body orifices and skin should be taken to determine the most useful antibiotics. Stool softeners should be considered. Rectal and vaginal palpation and rectal thermometers should be avoided.

During the latent period, daily clinical and laboratory observation is essential (see Table 1). In the presence of elevated erythrocyte sedimentation rate (ESR) or fever, prophylactic antibiotic therapy may be considered.

As the patient enters the critical period, antibiotics should be administered if warranted by results of cultures of body fluids, body surfaces and orifices, and excreta. Blood and derivatives should be used only for specific indications.

Reverse isolation is useful if agranulocytosis and infection become apparent and the clinical picture worsens. All fluids, supplies, and personal articles should be sterilized. A separate kitchen using prepackaged foods and cooking preparation simplifies management. Cultures from attending personnel should be taken regularly to minimize contamination by saprophytes or pathogens.

Patients should be cleansed carefully, but irritation of mucosal surfaces that might promote bleeding should be avoided.

As agranulocytosis increases, consideration should be given to maintenance in a germ-free environment using laminar flow units if available. Air barriers (plastic rooms, bubbles) are efficient for nursing care. However, patients, except those who are only partially or less responsive, dislike these units as being restrictive and inducing claustrophobia.

Groups III and IV (4 to 6 Gy [400 to 600 rad]): Many therapeutic interventions become more important as the level of agranulocytosis increases. The prodromal period is more severe and prolonged. The latent period is shortened to 7 to 14 days. The maintenance of fluid and electolyte balance is especially important and should be guided by results of frequent laboratory testing.

Handling of ARS cases has benefitted from the experience gained with transplant patients. Vigorous treatment need not start immediately following exposure; in most cases, following the prodromal period, there is a latent period of at least one to three weeks. If there is no latent period, only symptomatic care is necessary because death is virtually inevitable.

In most accidents, the exposure of marrow is not uniform and return of function is likely depending on dose, dose rate, and volume. Advances in transplantation continue to suggest new directions in therapy.

When intensive treatment of ARS is considered after high doses of radiation (eg, multiples of the $LD_{50/60}$), bone marrow transplantation is a practical form of therapy. Except for the Yugoslavian[6] and Pittsburgh[7] incidents, this therapy has not been previously reported in human beings. There is some question of whether the mixed, nonmatched, marrow transplants performed in Yugoslavia functioned even briefly because they were administered late; however, the treatment apparently did no harm. The successful syngeneic transplant in Pittsburgh was between identical twins; this is the only recorded case of transplantation to an irradiated patient who was in prior good health, that is, one not suffering from a hematologic disease.

In the Chernobyl disaster, bone marrow transplantation in 13 patients resulted in 12 deaths and one spontaneous recovery. Unknown are the circumstances of the exposures, the severity of injury (eg, concomitant burns, other trauma), radiation doses, dose rates, interval between exposure and transplantation, and success or failure of bone marrow matching. One or more of these factors, as well as the availability of proper equipment and trained personnel, affect the outcome of transplant treatment, especially under emergency conditions.

Until these factors are analyzed carefully, bone marrow transplantation continues to be an investigational treatment for unplanned radiation exposure. It is intended to replace marrow that has been destroyed; however, if injury to the gastroenteric tract, heart, or central nervous system is extensive, it is doubtful that marrow transplantation will play a significant role, although it may be an important part of the life-support system under these extremely difficult circumstances.

The most distressing findings in the Chernobyl experience were severe and extensive beta burns to the skin and oropharynx from contact with radioactive particles. Some of this material was soluble and soaked through wet clothing to the skin. This material also was inhaled, which produced severe mucositis with copious secretions. Management was symptomatic. These changes were regarded as significant causal factors in patients who died.

Because there are few cases of accidental radiation exposure, the suggestions for management are primarily anecdotal or derived from experience in patients irradiated for cancer and other diseases. Nevertheless, it seems reasonable that the careful diagnostic and therapeutic methods summarized here and in the current medical literature will help to decrease morbidity and mortality following unintended radiation exposures.

References

1. Management of Persons Accidentally Contaminated with Radionuclides. NCRP Report No. 65. Bethesda, MD, National Council on Radiation Protection and Measurements, 1980.

2. Thoma GE, Wald N: The diagnosis and management of accidental radiation injury. J Occup Med 1959;1:421-447.

3. Saenger EL, Silberstein EB, Aron B, et al: Whole and partial body radiotherapy of advanced cancer. Am J Roentgen Rad Ther Nucl Med 1973;117:670-685.

4. Van Dyk J, Keane TM, Kau S, et al: Radiation pneumonitis following large single-dose irradiation: A re-evaluation based on absolute dose to lung. Int J Radiat Oncol Biol Phys 1981;7:461-467.

5. Hubner KF, Fry SA (eds): The Medical Basis for Radiation Accident Preparedness. New York, Elsevier/North Holland, 1980.

6. Jammet HP: Treatment of victims of the zero energy reactor at Vinca, in: Diagnosis and Treatment of Acute Radiation Injury. Geneva, World Health Organization, 1961, pp 83-103.

7. Gilberti MV: The 1967 radiation accident near Pittsburgh, PA and a follow-up report, in Hubner KF, Fry SA (eds): The Medical Basis for Radiation Accident Preparedness. New York, Elsevier/North Holland, 1980.