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February 5, 1971 707566

A technician at the Atomic Energy Commission's Agricultural Research Laboratory is in an Oak Ridge hospital today for observation and tests following an incident yesterday after which he showed symptoms of exposure to radiation.

The technician was admitted to the Medical Division of Oak Ridge Associated Universities. He is an employee of the University of Tennessee, which operates the Agricultural Research Laboratory for the AEC.

The technician is believed to have been exposed to a cobalt-60 radiation source shortly before noon yesterday (February 4) when he and another technician were irradiating seeds for use in the Laboratory's experimental programs.

Preliminary investigation of the incident indicates that the man inadvertently entered a room where the irradiation was being carried out while the radioactive source was still outside its shielded container. The door through which he passed to enter the room has two interlock systems designed to prevent inadvertent exposure.

An investigating committee has been named to look into the causes of the accident.

(MORE)

[redacted]

Dose 260R

REPOSITORY OAK RIDGE OPERATIONS OFFICE
COLLECTION PUBLIC INFORMATION (M-4)
BOX No. ACTIVE RECORDS CATALOGED FOR HUMAN RADIATION EXPERIMENTS PROJECT
FOLDER

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[redacted]

The facility in which the incident occurred is known as the Variable Dose Rate Irradiation Facility and is used routinely for irradiations involving research programs with both plants and animals.

It is heavily shielded with a separate control room to permit remote operation of the radiation sources after specimens for irradiation have been placed within the room.

# # #

February 5, 1971



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*Reprinted from E: ıta Medica International Congress Series No.*
PROCEEDINGS OF THE XIth INTERNATIONAL CONGRESS OF RADIOLOGY
*Rome, September 1965*

# TOTAL-BODY IRRADIATION IN THE HUMAN BEING*

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Each year there are increasing hazards of radiation to human beings. These risks are associated with increased medical and industrial uses of radioisotopes, with the exploration of outer space, and with reactors, many of which will be built to supply nuclear power. While we rightly emphasize the dangers of radiation, we should also keep them in proper perspective. Other dangers in the modern world may be much more important; for example, automobiles and synthetic chemicals. The sciences and industries using atomic energy have promoted safe practices to a truly remarkable extent, and many such laboratories and factories provide an environment of great safety.

Although we do not wish to exaggerate the dangers of radiation, we should deal in a direct and practical way with such dangers as do exist, and we should be prepared to treat radiation injury when it occurs. Much is known about responses to radiation; however, radiation injury is very complex because it can be experienced in many different ways – with variations in type and energy of the radiation, in dose rate, and in the part of the body exposed. Furthermore, the body's response to irradiation involves many complicated cellular and humoral mechanisms, some of which are still poorly understood.

We in Oak Ridge have had the opportunity to study eight healthy men exposed in a serious radiation accident (Brucer, 1959), and over a hundred patients given total-body radiation as therapy for malignant disease. From these experiences and from other published information we have developed some familiarity with the effects of such exposures.

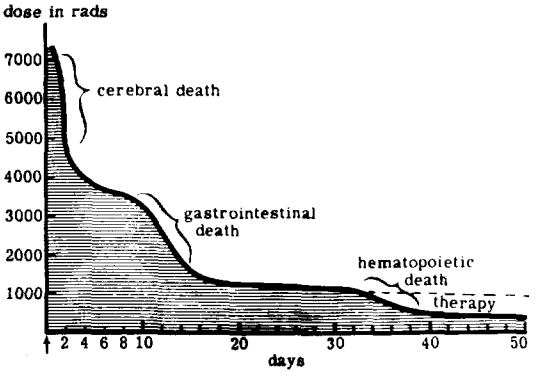


*Fig. 1.* Patterns of survival after various doses of total-body irradiation. The fine horizontal lines represent the length of survival after various doses.

* From the Medical Division, Oak Ridge Institute of Nuclear Studies, under contract with the U. S. Atomic Energy Commission.



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*Clinical features of total-body irradiation*

For purposes of discussion it is desirable to emphasize the effects of a single brief dose of penetrating gamma radiation absorbed uniformly by the whole body. The responses to this type of injury show distinct patterns that are quite predictable.

The clinical syndrome produced depends upon dose. Fig. 1 shows the three distinct patterns of injury that may occur. There has been little well-documented experience with extremely high doses in the human being; the neurological and gastrointestinal syndromes shown in the chart are assumed to occur, but this assumption is based partly on animal experiments. The *neurologic syndrome*, resulting from extremely high doses, would be characterized by convulsions, coma, and death within a few hours or, at most, two or three days. Human experience with two accident victims has suggested that cardiac damage and vascular collapse may be prominent with high doses in man (Shipman *et al.*, 1961; Karas and Stanbury, 1965).

At somewhat lower doses, *gastrointestinal* disturbance predominates, with persistent nausea, vomiting and diarrhea, and death within two weeks or less. The most important pathologic lesion is considered to be destruction of the epithelium of the small intestine, and the mechanism of death is believed to be loss of fluid and electrolytes along with bacterial invasion via the intestinal route.

At lower doses the *hematologic* disorder predominates. Here a complex group of events unfolds in a predictable pattern over a period of weeks. Within a few hours anorexia, nausea, and vomiting usually occur. (These symptoms should not be confused with the "gastrointestinal syndrome" which implies much more than transient nausea and vomiting.) This phase of illness is often called the prodromal reaction and is associated with apathy and fatigue. Ordinarily these symptoms clear up within two or three days, and the patient is likely to feel well for two weeks or so. Then bone-marrow depression becomes severe and the patient suffers from hemorrhage and infection due mainly to a deficiency of thrombocytes and granulocytes. These complications may be fatal, but if they are not, spontaneous recovery begins about the sixth week and progresses rapidly.

*Hematologic changes*

Peripheral blood – The absolute *lymphocyte* count falls within a few hours after significant exposure, most of the decrease occurring during the first 48 hours. At 48 hours an absolute lymphocyte count of above 2,000 suggests that there has been no life-threatening dose; between 1,200 and 2,000 suggests a significant but probably nonlethal dose; less than 1,200, a serious dose; below 500, a possibly lethal dose; and below 100, an almost certainly lethal dose. After the initial decrease in numbers, the lymphocyte levels tend to remain rather stationary, and in nonlethal doses there is a slight increase toward normal after about 30 days.

The *neutrophil* count may rise transiently within a few hours, and very high values suggest severe injury. Little information is available on this early increase in neutrophils; however, stress-induced release of cells already formed must account for it. The more commonly described manifestation, leukopenia, begins to be prominent after a few days. At sublethal and low-lethal dose levels, there may be a plateau, or even a slight temporary rise, in neutrophil values at around ten days to two weeks; the most severe leukopenia then develops during the third and fourth weeks, to be followed by a fairly rapid return to normal. At higher radiation doses the leukocyte count may be very low by the second week, and when this happens the prognosis is extremely poor.

Changes in *thrombocyte* values tend to be very similar to those in the neutrophils, although an early thrombocytosis is not so well documented as early neutrophilia.

Early changes in the red cell values of the blood may be caused indirectly by dehydration. An anemia due to marrow damage takes some weeks to develop and reaches its greatest severity just as leukocyte and platelet values are beginning to recover.

Bone marrow – Since marrow changes develop rather slowly in the human, the bone marrow may appear almost normal as long as one or two days after an exposure



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in the near-lethal range. However, careful observation will show certain cellular alterations, particularly disturbances in morphology of red cell precursors (Fliedner *et al.*, 1964), that may indicate serious damage; these changes, if pronounced, will eventually be followed by profound hypoplasia. Reduction in the mitotic index of the marrow may be a dose indicator, and it appears that it may be best assessed about the fourth day after exposure (Fliedner *et al.*, 1960). Chromosome abnormalities are also

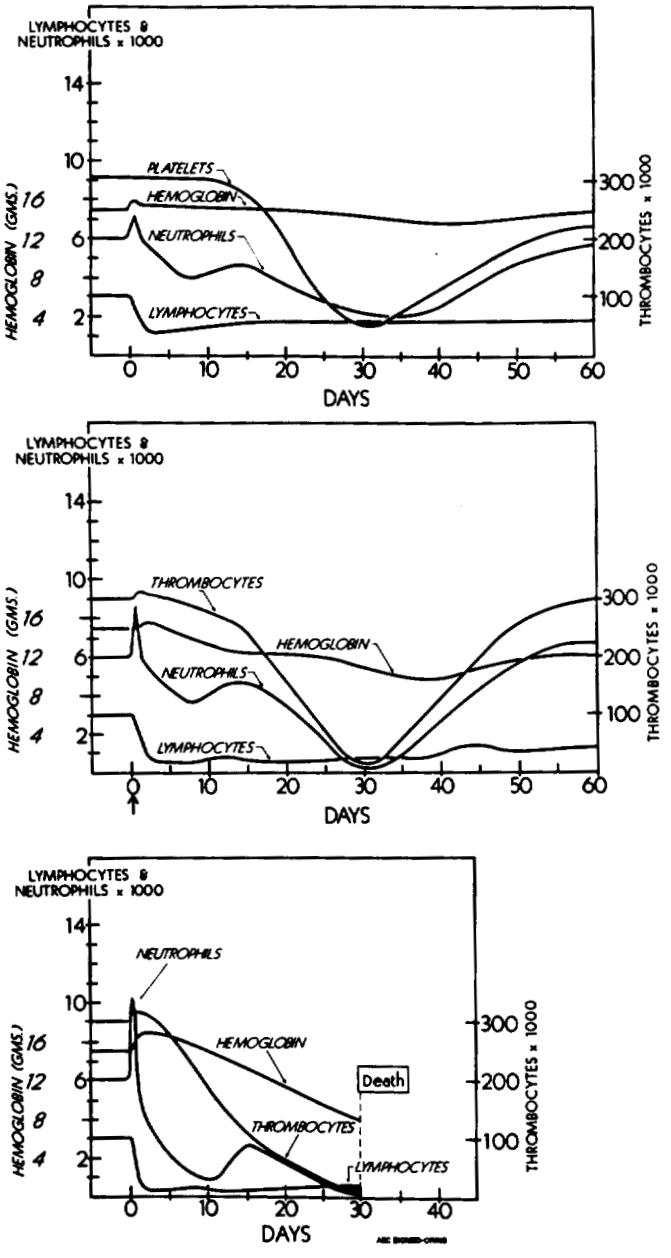


*Fig. 2.* Characteristic hematologic responses for 200, 300, and 450 rads in the human being.



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reported (Bender and Gooch, 1962). During the fourth and fifth weeks after exposure, the greatest depletion of the bone marrow is reached and the only persistent cells may be plasma cells and unidentifiable mononuclear forms. At six to eight weeks after exposure, recovery is associated with a hypercellular marrow.

*Comments on typical syndromes*

Now that we have described an orderly pattern of response dependent on dose, we must add some comments and reservations.

Variations in sensitivity – There are, of course, differences in sensitivity among various members of a population, but these are no more pronounced than one might expect for any type of injury.

Delay in development of manifestations – One of the most distinctive features of radiation injury is that a considerable period of time passes before the full extent of the injury is apparent. This is particularly true for the hematologic syndrome. The deficiency of blood cells reflects injury to the blood cell forming elements in the marrow and lymphatic tissues. Most of the injury is to very young cells, and, since there is a time lag for cell maturation, this explains part of the delay. However, this factor alone will not account for the three or four weeks' delay in appearance of greatest depression of blood cells, and it appears likely that some of the genetic injury manifests itself in later cell generations. Much is yet to be learned about this.

It is clear that the time pattern is very different for different species; the whole process takes place much more rapidly in the smaller mammals. The time course shown in the illustration is for the human being, with greatest marrow depression reached in the fourth or fifth week (Fig. 2). In the mouse this point would be reached before the eighteenth day.

With the larger doses of radiation, the duration of severe marrow depression is greater; it starts much earlier and (barring death) persists a few days longer before recovery begins. An exception to this pattern may occur in some persons who receive acute doses of about 100 rads and show only a mild marrow depression that persists for some months.

Spontaneous recovery – If the patient survives for five or six weeks after a single acute exposure, a dramatic, spontaneous recovery occurs. This recovery appears inherent in the sequential pattern of response to radiation. The recovery is surprising to persons who are accustomed to thinking in terms of more chronic exposure with its more persistent damage. This sudden recovery involves regression of most or all clinical manifestations but does not, of course, eliminate subtle remaining changes such as chromosome abnormalities. If the patient dies during the period of greatest marrow depression, autopsy may show an almost complete absence of hematopoietic cells in the bone marrow. One may be tempted to assume that the damage was "irreversible" but this physiologic evaluation is not justified on morphologic grounds. We know that marrows with a remarkable degree of hypoplasia can recover if supportive care succeeds in tiding the patient over the critical period. It would be more accurate to say that the patient failed to survive the marrow damage, without trying to judge the reversibility of the process in the marrow.

*Factors that alter the response*

All the preceding statements must be modified when we consider radiation experienced under different conditions.

A lower *dose rate* greatly increases the total dose that can be accepted. However, if irradiation is protracted over many weeks, or longer, and the dose is high enough to produce clinical damage, then the rapid spontaneous recovery cannot be expected; a much more chronic and less reversible disease is produced.

Partial-body irradiation, of course, has special features, with relatively high doses being tolerated if some bone marrow is protected, and local manifestations at the site of exposure assuming greater importance.



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*Therapy*

For acute X- or gamma-irradiation of the whole body, we have good therapy which will greatly improve the survival in patients with the hematologic syndrome. Although we can do little to alter the gastrointestinal, cardiovascular, and neurological damage that is fatal at very high doses, experience has shown that most accidental exposures are at the lower doses, for which treatment is feasible.

Treatment is sometimes referred to as "supportive" but this may be too weak a word to describe the measures available. While for chronic radiation damage we have little to offer that is decisive, for the effects of a single exposure there are measures that sometimes save life by controlling hemorrhage and infection until recovery can occur. The major weapons are infusion of fresh thrombocytes, protection of the patient from infection, and the administration of antibiotics. At certain dose levels, where recovery seems otherwise unlikely, an attempt to produce a temporary marrow graft may be made.

*Bone marrow grafts*

The clinical experience with grafts of bone marrow has been very different from that in experimental animals. In mice, grafts are produced with great reliability and much research is directed toward understanding the immunologic complications that develop when the donor and recipient are of different genetic strains (Congdon, 1959). In patients treated for leukemia with large doses of radiation and homologous marrow, the common outcome is failure at the first stage; that is, absence of any evidence of a take. After many attempts, only a few successful grafts have occurred. The immunologic problems of persisting foreign bone-marrow grafts have thus been encountered only rarely in the human being. It is believed likely, however, that in severe radiation accidents a temporary graft might be obtained and might carry the patient until his own marrow could recover. The temporary nature of the graft would, perhaps, be insurance against severe immunologic complications (Mathé and Amiel, 1964).

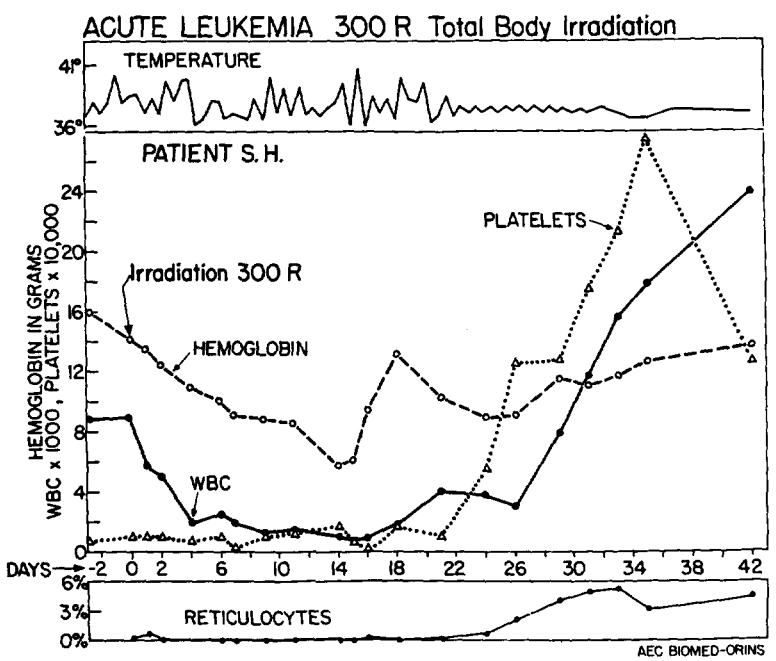


*Fig. 3.* Temperature curve and hematologic course in patient who developed a remission in acute leukemia after a single large dose of total-body irradiation.



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In our own program we have repeatedly attempted to treat patients with acute leukemia by means of large doses of total-body irradiation, followed by intravenous injection of homologous marrow from several different donors. We have seen no clear evidence of a graft, but in a few instances remissions have been produced. We subsequently found that such remissions could sometimes be produced by the large dose of radiation alone (Andrews *et al.*, 1961). Fig. 3 shows the course of events in a severely ill patient with acute leukemia who developed a complete but temporary remission after total-body irradiation without marrow administration.

Although clinical efforts to use homologous marrow grafts have been discouraging, the need for such a therapeutic measure is so great that vigorous efforts to achieve this end should be continued.

*AEC-NASA retrospective study of radiation effects*

Because of the obvious need for more information on irradiation effects in the human being, our laboratory has launched a major effort to compile data on this subject. This project is supported by the U. S. Atomic Energy Commission and the National Aeronautics and Space Administration. Our major subject of study is the large group of patients who have been given therapeutic total-body irradiation and the small group of persons who have been exposed in radiation accidents. Dr. Clarence C. Lushbaugh is in charge of the study at our institution. The project involves the copying of hospital records from all exposed patients, particularly those data indicating the state of the patient just before exposure and for six weeks after exposure. The records are sent to Oak Ridge where they are extracted and coded in an elaborate data-retrieval system using a computer. Information collected is not limited to that expected to be relevant to the changes produced by radiation, since it is anticipated that some unexpected radiation effects may be shown to occur.

The objective of this study is to learn more about the radiobiology of man: specifically to determine the dose-response relationships for a whole group of clinical and laboratory changes. This information should provide a better basis for health protection and for the therapeutic use of radiation.

The patients treated clinically with total-body radiation will total at least 1,200. These can be divided into three main groups: A large number were given radiation as a treatment for polycythemia, chronic leukemia, lymphosarcoma, and Hodgkin's disease; patients with acute leukemia treated with radiation in preparation for marrow graft attempts; and patients with renal failure who were irradiated in preparation for kidney grafts. For purposes of study, the observations are handicapped by the underlying diseases present; on the other hand, these clinical studies have the advantage of fairly good determinations of radiation dose. The group of radiation accident cases carries much less satisfactory dosimetry, but it has the advantage that the victims were normal at the time of injury.

This study has been set up in an "open-ended" fashion so that additional patients can be added indefinitely and current statistical assessments can be made conveniently by computer at any time during the study. We believe that this study will contribute effectively to the growing need for information on the radiobiology of man.

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Reprint from

"HANDLING OF RADIATION ACCIDENTS"

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 1969

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# POSSIBILITIES FOR IMPROVED TREATMENT OF PERSONS EXPOSED IN RADIATION ACCIDENTS*

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**Abstract**

POSSIBILITIES FOR IMPROVED TREATMENT OF PERSONS EXPOSED IN RADIATION ACCIDENTS. The number of persons exposed to acute radiation accidents continues to be small and the clinical experience in handling them is thus obviously limited. The great increase in use of radioactive materials and the growing number of power reactors constitute greatly augmented potential sites for accidents, but fortunately the number of accidents is not increasing. There appears to be some shift in the type of accidents, with a relative increase in those in which excessive dose to a small part of the body is the predominant feature.

There has been little progress in treating local radiation injury but methods for handling the hematopoietic syndrome are definitely improved. With platelet transfusions we have a powerful aid in managing hemorrhage; the more difficult problem in persons with severe marrow depression is infection. The development of sterile environment facilities and the availability of better antibiotic therapy are important advances. Where these measures are not adequate, more experimental procedures give some promise: the injection of concentrated leukemic or normal leukocytes, the use of cross circulation, or the injection of allogeneic bone marrow.

Classification of the injury and estimation of its severity are more effectively done now than a few years ago, and contribute to better treatment.

Even though the use of nuclear energy has greatly increased, serious radiation accidents continue to be infrequent. This good record can be attributed to the work of radiation safety experts and the competent performance at all levels in industry and research. Because of the knowledge derived from earlier accidents, and because of medical progress in managing patients with severe disorders or repression of the immunohematopoietic function, we now have fresh possibilities for saving the lives of lethally irradiated persons.

## Classification of Accidents

When we attempt to compile a list of accidents we find no good definition of the minimal incident that should be included. The reporting of total-body exposures below 25 R is very inconsistent as is that of minor local exposures. Although these unreported episodes may become the subject of law suits and may conceivably contribute to late effects such as leukemia and neoplasms, they do not account for any serious early morbidity or mortality.

Even without a rigid definition, it is possible to make a list of obviously significant accidents; Lushbaugh and Castañeda [1] list 25 separate ones that occurred between 1945 and 1968 including the exposures of the

* From the Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tenn., under contract with the United States Atomic Energy Commission.



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Marshallese and Japanese fishermen in 1954. Aside from the last two mentioned groups, who were exposed to fallout from an atomic bomb test, we have the following: 23 accidents, 94 persons exposed, 32 with serious injuries, and 12 fatalities (excluding one radiation suicide), Fig. 1. This experience allows us to establish medically meaningful groups, classifying accidents according to source and kind of radiation. There are two main types: (1) uncontrolled criticality excursions with the victims exposed to fission neutrons mixed with gamma and particulate radiations, and (2) photon and electron exposures from high-energy accelerators, from electronic components that produce X rays, from radioisotopes that have been freed accidentally into the environment, or from encapsulated but unrecognized radiation sources. The details of management of radioactively contaminated wounds in persons not otherwise exposed to high doses of radiation will not be covered in this paper; earlier reports deal with this problem [2, 3, 4, 5].

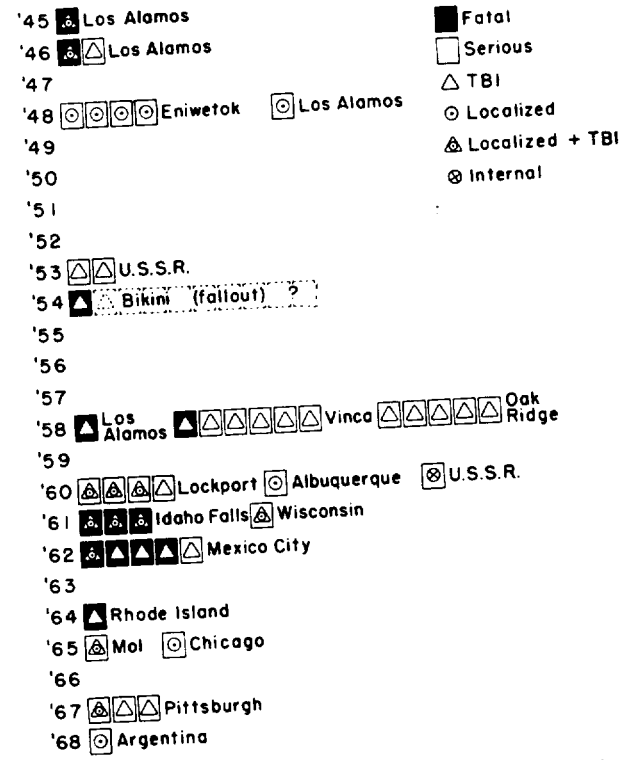


FIG.1. Major injuries in radiation accidents 1945-1968. Each box represents one person.

The lessons learned seem to preclude that any one type of accident would ever be repeated; indeed, most recent accidents involve new and unexpected combinations of circumstances that have eluded safety measures. There were 12 criticality accidents (Table 1) in which a total of eight men died, 12 were seriously harmed, and 23 others were exposed to smaller radiation levels not requiring direct, immediate medical help. Remote control systems have since been devised for testing critical assemblies and for operating reactors so as to prevent this type

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TABLE I

A CLASSIFICATION OF RADIATION ACCIDENTS

| | No. Accs. | Total Exp. | Total Hosp. | TBI Rx | Local Burns | Surg. | Fatal |
|---|---|---|---|---|---|---|---|
| Criticality | | | | | | | |
| Assemblies (γ, n) | 4 | 17 | 7 | 3 | 2 | 0 | 2 |
| Reactors (γ, n) | 3 | 11 | 8 | 8 | 0 | 0 | 4[a] |
| Fuel recovery (γ, n) | 5 | 17 | 11 | 8 | 1 | 1 | 2 |
| Totals | 12 | 45 | 26 | 19 | 3 | 1 | 8 |
| Radiation Sources | | | | | | | |
| Sealed (γ) | 4 | 31 | 7 | 5 | 3 | 2 | 4 |
| Free (γ + β) | | | | | | | |
| Weapon tests[b] | 2 | 294 | 91 | 23 | 18 | 4 | 1[c] |
| Spills | 2 | 2 | 2 | 1 | 1 | 1 | 0 |
| Radar (X ray) | 1 | 9 | 7 | 4 | 1 | 0 | 0 |
| Accel. (e, X ray) | 3 | 6 | 5 | 2 | 3 | 3 | 0 |
| Totals | (12) | (342) | (112) | (35) | (26) | (10) | (5) |
| Total without fallout victims | 11 | 52 | 25 | 12 | 12 | 10 | 4 |

a - 3 instantaneously from blast.
b - fallout field exposure of 290 persons from Bikini test.
c - death from hepatitis 6 months later.

of accident, but in the last 10 years five more criticality accidents of another kind have occurred during extraction and "clean-up" operations with fissionable fuels in solutions. This change in type of criticality accidents has not altered the needs of such victims for medical help but has reduced the incidence of severely damaged extremities.

Most of the victims in the second main type of radiation accidents (photon and electron exposure not involving fissionable material) have not known they were irradiated until either dermal burns or systemic signs of radiation sickness led to the diagnosis hours, days, or months after their unknown exposure at varying but sometimes relatively low dose rates. Except for one boy (in the Mexican accident) who was exposed to a cobalt-60 radiography source, and two men in the recent accelerator accident near Pittsburgh, the victims either had predominantly severe local irradiation damage with insignificant amounts of total-body irradiation, or clinically significant total-body irradiation without severe, accentuated local damage. In other words, either local or systemic damage usually clearly predominated; in rare instances in which both were severe, treatment was exceedingly difficult. Although gangrenous extremities occurred in three of the earlier criticality accident victims, two of them died early, 30 and 9 days after exposure, and no definitive management for the local injury could be undertaken. When exposure to the high radiation fluxes of criticality resulted in supralethal exposures to the operator and his early death, locally damaged extremities were treated only symptomatically, by cooling. Other workers in the room where the criticality occurred have usually received much smaller, easily treated exposures. In the more recent criticality exposures, which occurred in chemical processing of fissionable materials,

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survival was possible with conservative medical management; in only one instance did a damaged extremity require amputation (the accident at Mol, Belgium, in which the victim was irradiated by a criticality that occurred under his feet).

The limits of medical support in the high-dose criticality accident syndrome were demonstrated well in the two most recent American criticality accidents (in Los Alamos and Rhode Island). Profound hypotensive shock was temporarily stayed by vasopressor drugs and intravenous fluids for 33 and 49 hours before extravascular edema interfered with cardiac function. At these relatively early intervals the anticipated ravages of gastrointestinal damage had not yet occurred. Only one man (Los Alamos, 1945) has died with clinical signs that resemble gastrointestinal syndrome in animals. His death on the ninth day with agranulocytosis, thrombocytopenia, and septicemia, as well as a denuded intestinal tract, makes it possible to argue that his death was due to a fulminant form of the hematopoietic syndrome instead of the gastrointestinal syndrome.

In contrast to this experience with accidents during handling of fissionable material, morbidity after accidental exposure to photon-emitting devices has been complicated frequently (9 instances) by severe local radiation injury. The incidence of this type of accident could be considered much higher if we included here the beta burns to the hands of four workers at Eniwetok, and the Bikini accident in which 23 Japanese fishermen and 110 Marshall Island residents developed numerous beta burns from exposure to radioisotopes in a fallout field.

Without the complication of radiation necrosis of the skin or a large portion of an extremity, the acute radiation (hematopoietic) syndrome and its medical requirements do not differ in the two classes of radiation victims. The rapidly lethal, high-dose syndromes, however, have not been seen in the persons irradiated in noncriticality accidents and can usually be excluded from medical consideration where only photon irradiation is involved. Thus early shock, unconsciousness, or coma in a photon radiation accident victim would not be explained by the radiation exposure unless he received a greater dose than has so far been encountered, but shock could, of course, occur days or weeks later when cerebral hemorrhage, massive intestinal hemorrhage, and septicemia might develop as sequelae to agranulocytosis and thrombocytopenia.

## General Priorities and Early Management of Accidents

Classification and management of radiation accidents has been extensively discussed in previous publications [6, 7, 8, 9, 10, 11]. Immediately after an accident prompt action and decisions may be needed. A simplified order of priorities might be useful in those situations where time is not available for prolonged reflection:

(1) Remove patient from high-dose radiation field, or turn off or shield source.

(2) Deal with any traumatic hemorrhage and respiratory obstruction.

(3) Measure patients' radioactivity — decontaminate if necessary.

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(4) Establish radiation dose by biological and physical means — estimate degree of injury and modify management accordingly.

One of the early mistakes that can occur after all personnel have left the site of the accident is for someone to make an ill-advised return to turn off a machine, investigate the dose, or check for contamination. Unless there is immediate danger of an explosion or other imminent emergency, all should stay away until a safe, carefully planned procedure can be put into action.

If the patient is radioactive, this may be due to either contamination or induced activity. Induced radioactivity from neutron exposure has never presented any hazard to those caring for the patient and it adds little to the patient's dose. Its main value is as a help in estimating dose. It is absolutely essential to quantitate the radioactivity and to avoid excessive concern over low levels. Radioactivity from contamination can be a serious hazard to patient and personnel and must be dealt with rapidly.

To decontaminate, the following steps, with continuous monitoring, are indicated:

(1) Remove patient's clothing.

(2) Wash patient with detergent and water.

(3) Clip hair and shave contaminated areas.

(4) Debride wounds surgically. Resect implanted deposits of radioactive material.

(5) Deal with internal contamination by injecting:

a. stable element for dilution effect, or
b. suitable agent to increase excretion such as a chelating drug. In some instances it may be possible to alter metabolic balances so as to enhance excretion of unwanted material, i.e., to produce a phosphorus diuresis.

We establish radiation dose and degree of injury on the basis of:

(1) Clinical responses.

(2) Changes in hematologic values and other abnormalities in laboratory tests.

(3) Data from film badges and monitors.

(4) Estimation of source size, location of patient, and duration of exposure. Use of mock-up of accident in some cases.

(5) Measurement of induced activity (neutron accidents) and neutron-gamma ratio.

a. Radioassay of blood.
b. Whole-body counting.
c. Assay of hair and nails.
d. Assay of jewelry, clothing, etc.

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(6) Where internal contamination is present:

a. Measurements of activity with local probes and external counters as well as whole-body counters.

b. Assays of blood and urine.

It is important to gather and record all information that might be helpful in estimating patient's dose and in managing other accidents. The patient's clothing may contain valuable clues and should be set aside for carefully planned observation. Similarly, vomitus, hair, urine, and feces of the patient should be saved for radioassay and other possible measurements (such as content of stable sodium to be related to induced radiosodium). Data accumulated from such studies in previous accidents become a major resource in managing new accidents.

Review of previous accidents suggests that some patients have suffered because relatively uninformed personnel were too concerned about small amounts of induced radioactivity. There is no record that anyone ever received an intolerable dose of radiation by caring for a radiation accident victim in a first-aid station or hospital. The possibility of a doctor or paramedical person receiving a dangerous radiation dose in a radiation accident arises only if they must enter the radiation field in rescue attempts.

Management of the Hematopoietic Syndrome

Only a few radiation accident victims have received doses inevitably lethal, and the hematopoietic syndrome and local high-dose tissue damage have been the prominent clinical problems in managing accidents. The hematopoietic syndrome, as is well known, develops gradually, reaching its greatest severity about 30 days after exposure, and poses only two main clinical problems, infection and hemorrhage. The time course is remarkably uniform and the hematologic nadir occurs at the expected time even when the dose distribution is quite nonuniform. Methods of treatment have been improved significantly and a variety of measures are available; their choice must be carefully related to the severity of injury and the time course of the developing manifestations of thrombocyte and granulocyte deficiency. The procedures include various methods of preventing infection and supplying donor thrombocytes and blood cells.

Table II outlines steps in management. It is a suggested basis for decision making in therapy rather than a rigid guide. Although lymphocyte levels are listed as a valuable index of injury, other indices are also important; estimates of damage go on concomitantly by a variety of methods listed earlier but not in Table II. The table shows the essentials of clinical care and does not include procedures for obtaining additional research data.

Sterile Facilities

One way to prevent infection is by housing irradiated persons in ultraclean environments. Several groups are investigating these units [12, 13, 14, 15, 16]; they have been useful in treating burn patients, for example. For the 1967 accident near Pittsburgh, a "clean room" was improvised on short notice by putting portable laminar flow benches in a regular but isolated hospital room. The procedure was combined with the extensive use of antibiotics and no serious infectious complications occurred in the patients during the leukopenic phase.

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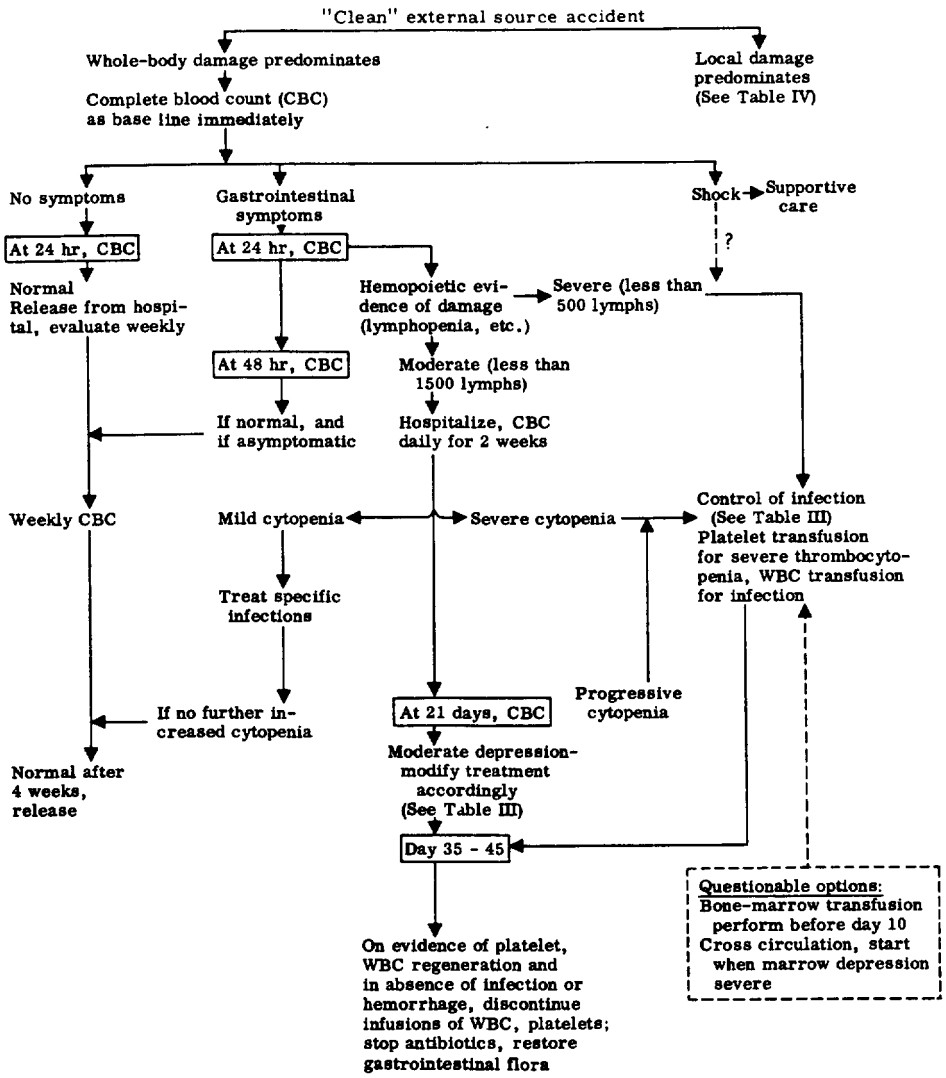
TABLE II

MANAGEMENT OF THE HEMATOPOIETIC SYNDROME

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Although we are not yet certain about the relative importance of endogenous and exogenous microorganisms in postirradiation infections, the threat of the latter warrants the use of some type of isolation system. Infections in patients immunologically suppressed by chemotherapeutic agents have been prevented with the "life-island" isolator systems. These devices isolate the patient in a plastic tent larger than the patient's bed, and provide sterile ports for the entrance of air, food, water, medications, and clothing, and the exit of wastes. There are, however, inherent difficulties with these isolators. It is difficult to do all that is needed to care for a patient in one of them, and if the inside of the unit becomes contaminated while the patient is in it, decontamination is difficult; operating costs have been found to be high; and there have been reports of untoward psychological reactions in patients isolated for long periods of time.

A relatively new type of patient isolation unit cleans air by forcing it through high-efficiency particulate air filters (HEPA), and it provides a laminar flow of the clean air across the patient's bed. The room is arranged so that all personnel remain down-wind from the patient. The filters remove 99.99% of airborne particles above three-tenths of a micron in diameter. The laminar-flow technique reduces levels of environmental contamination as effectively as does the plastic tent isolator but without the restrictions on activity of patient and medical personnel.

We have installed such a laminar-flow patient isolation facility at the Medical Division of Oak Ridge Associated Universities (Fig. 2). It consists of two ultraclean rooms separated by a preparation room and an anteroom. Air is forced into the rooms by blowers located in a plenum chamber behind the filters at a velocity of approximately 90 feet per minute. Positive pressure is maintained in the rooms by the addition of outside air to the filter supply. Room temperature and relative humidity can be maintained at 72 °F and 60%. Conventional bathroom facilities are located at the downstream end of the room. The adjoining preparation room contains work benches, a sink, range, and refrigerator, and has pass-through interlocks into the isolation rooms. Two double-door sterilizers, one steam and one

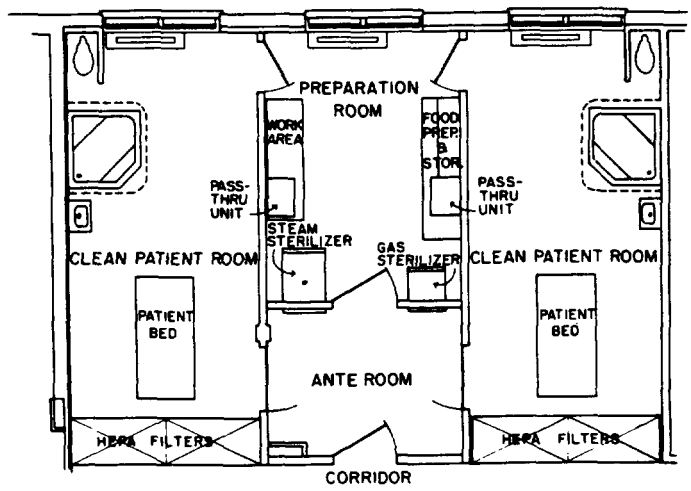


FIG. 2. Floor plan of laminar-flow sterile patient facility at Oak Ridge Associated Universities.

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gas, are located between the anteroom and the preparation room. The anteroom is equipped with large windows into the isolation areas and has a two-way communication system so that patients can see and talk with visitors.

Although some patients with marrow depression die from organisms that have apparently been part of their normal flora, the patient can presumably more readily resist invasion by these organisms, to which he has already developed defense mechanisms, than by unfamiliar species. Secondary antibody responses probably are more radioresistant than primary ones [17]. Preventing contact with exogenous microorganisms by means of laminar-flow rooms may prove very useful in the treatment of persons injured in radiation accidents.

Antimicrobial Agents

Antibiotics and other antimicrobial agents play a large part in carrying heavily irradiated patients through the period of severe marrow depression. These drugs can be used in several ways, and their best application is not yet known. A few years ago we believed that they should be given only to treat infection, not prophylactically, except for nystatin to prevent certain fungus infections. The availability of controlled-environment procedures to prevent exogenous infection, and the demonstrated effectiveness of some of the newer antibiotics have recently changed this view.

Since the period of increased susceptibility to infection does not develop until two or three weeks after exposure, there is time for fitting the course of treatment to the patient's need. During the early period after exposure, attempts should be made to clear up any local infections — of the skin, for example — even minor ones; drugs should be carefully chosen for this on the basis of sensitivity studies. The mouth and teeth should have expert attention to correct any lesions that provide likely sites of invasion.

As the period of severe leukopenia approaches, antibiotics should be given to reduce the flora of the respiratory and gastrointestinal tracts as much as possible. The justification for this has several bases:

(1) Organisms normally nonpathogenic can cause fatal infections.

(2) Infections tend to develop with great rapidity; the usual local clinical responses to infection — redness and pus formation — are likely to be entirely absent and systemic features difficult to interpret. Thus even if effective drug therapy is available, we may fail to apply it in time.

(3) It has been demonstrated in other types of patients with severe marrow depression that reduction of the bacterial flora helps to control clinical infections.

(4) Since the worst phase of marrow depression will last only 3 or 4 weeks, we are not faced with all the problems of long-term antibiotic therapy.

Irradiated patients are likely to have clinical infections with the same types of organisms that prevail in patients with hematologic disorders — Candida, staphylococci and gram-negative bacteria. Most of the patients with leukemia, "aplastic anemia," and other pancytopenic blood disorders, however, have a more prolonged period of enhanced susceptibility and may

also be much more debilitated. Chronic fungus infections other than candidiasis, which are frequent in blood disorders, have not been a problem in radiation accident victims.

We now believe that radiation accident patients with severe marrow depression, who are in a sterile environment facility, should be given antimicrobial drug therapy before there are clinical signs of infection. The patients exposed in the recent accident near Pittsburgh had extensive serial studies of bacterial flora and were managed on an antibiotic regimen that appeared highly effective. It was given under the direction of Dr. Abraham Braude and Dr. Kenneth Brown of the University of Pittsburgh Medical School. Antibiotic therapy was started in the absence of clinical evidence of infection when the total leukocyte count fell below $1000/cm^3$ and was continued until it rose to $2000/cm^3$. Neomycin 4 g/day, oxacillin 2 g/day, and nystatin 500,000 units t.i.d., were given. Starting about 3 weeks after exposure and continuing until the major hazard of infection was past, a preparation of neomycin, bacitracin, and oxacillin was used in the nasal cavities. During this program of treatment some organisms could be isolated from the upper respiratory tract, while the feces became sterile to culture. One patient developed a urinary tract infection believed due to organisms acquired earlier, and this was treated effectively with streptomycin and lincomycin.

Table III offers a plan for management of infections to be used in conjunction with a sterile environment.

Platelet Infusions

Thrombocytopenia is the main mechanism of bleeding in the hematopoietic radiation syndrome and infusions of platelets have provided an important advance in the treatment of patients with marrow depression. Bleeding and infection often develop simultaneously in patients with depressed bone marrow. When infection develops first it damages capillaries and enhances the likelihood of hemorrhage, and when hemorrhage develops first the interstitial and mucosal collections of blood provide media for bacteria. Thus prevention of bleeding is an important part of avoidance of infection. We would recommend the infusion of fresh donor platelets, at least 2 units/day, in any irradiated patient with a platelet count below $10,000/mm^3$, even without clinical bleeding, and if evidence of important clinical bleeding is present, we would give platelets, even if the count is as high as $60,000/mm^3$. In cases of clinically serious bleeding, fresh whole blood plus very large amounts of platelets may be needed, and platelet donors with thrombocytosis (as in polycythemia vera) may offer special advantages.

Leukocyte Infusion

Although multiple cellular and humoral factors are undoubtedly involved in the susceptibility of marrow-depressed patients to infection, granulocytopenia is by far the most important. If healthy neutrophils could be injected they would probably help greatly in combating infection. Clinical experience has been obtained in the treatment of other types of severe marrow depression with cells from donors with chronic granulocytic leukemia and has provided effective in the control of infection [18, 19]. In a small percentage of cases, transient leukemic marrow grafts were obtained and one group of investigators encountered some cases of secondary disease. The potential use of leukemic cells in radiation accident victims raises the question of permanent transmission of leukemia. This danger appears so remote, in view of expected immunologic responses, that it probably should not be a reason for withholding these cells when need is critical.

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Unlike marrow graft therapy, in which there is a wait of 10 to 14 days for the cells to proliferate, treatment with leukocytes gives immediate benefit. (Of course, very large amounts of infused marrow might also have some immediate effect, if enough granulocytes are included.) At present there is no adequate source of normal granulocytic cells; when such cells become available in adequate volume, they should constitute a valuable therapeutic agent.

TABLE III

CONTROL OF INFECTION

| | |
|---|---|
| Immediately after diagnosis of significant radiation exposure (100 R or more) | Search for occult and obvious infections.<br>Culture any suspicious lesion, especially carious teeth, gingivae, skin, and vagina.<br>Culture clean-caught urine.<br>Treat any infection with appropriate antibiotic as determined from sensitivity studies.<br>Include nystatin oral suspension 300,000 units q.i.d., with an antibiotic regimen. |
| If granulocyte count decreases to less than $1500/mm^3$ | Isolate patient in protected environment, such as "life island" or laminar-flow clean room.<br>Antiseptic bath and shampoo daily with full strength pHisoHex or Betadine to all of skin surface.<br>Trim finger and toenails carefully and scrub daily.<br>For female patients, daily Betadine douche and insert one nystatin vaginal tablet, b.i.d.<br>Culture nares, oral pharynx, sputum, urine, blood, stool, and skin folds (groins and axillae) 2 times a week. |
| If granulocyte count drops to less than $750/mm^3$ | In addition to the above, sterilize gut and give prophylactic antibiotics after a cathartic, unless patient has diarrhea or otherwise cannot tolerate it, neomycin 1.0 gram q 4-6 h; oxacillin* 0.5 gram q 4-6 h; nystatin 1,000,000 units q 4-6 h.<br>If *Pseudomonas aeruginosa* is present in stool culture add polymyxin B, 50 mg p.o. q 4 h.<br>Add appropriate antibiotic if cultures and sensitivity studies indicate persistence of resistant organism.<br>If patient develops diarrhea from the antibiotics, treat with paregoric and kaolin-pectin suspension. |
| If granulocyte count rises to over $1500/mm^3$ | Discontinue isolation and antiseptic baths.<br>Discontinue bowel sterilizing and prophylactic antibiotic regimen, except nystatin.<br>Continue oral nystatin 3 days after discontinuing other antibiotics. |

*For bowel sterilization alone, with nonabsorbable antibiotics, one could substitute, for neomycin and oxacillin, gentamicin 200 mg q 4 h plus vancomycin 250 mg q 4 h.

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Cross Circulation

At the time of the Pittsburgh accident, Dr. E. Donnall Thomas suggested cross circulation as a possible form of therapy for such patients. Although the procedure was not used then, it should be considered for serious radiation accidents. Intermittent cross circulation has been used for patients with diseases of the liver, kidney, and blood-forming tissues [20, 21]. One pair consisted of a patient with uremia who was cross circulated with a patient having severe marrow depression associated with acute leukemia. With this pairing the uremic patient provided leukocytes and platelets to the marrow-depressed patient and the latter's kidneys served to clear waste and adjust electrolytes for the blood of both. While this procedure appears to be fraught with risks of immunologic complications, it has been performed without prohibitive difficulties. Untoward reactions tend to develop after several days and may require discontinuation or a change of partner.

In using this procedure to treat a radiation accident victim, we would need to recognize that if a septicemia were already present the hazard of transmitting the infection would raise a serious ethical problem, even though the partner with a normal hematopoietic system could presumably control the bacteria for both. Nevertheless, cross circulation as a potential form of therapy deserves consideration in cases with temporarily severely depressed marrow and the threat of fatal infection.

Bone-Marrow Graft

Grafts of homologous bone marrow do not seem to be usable for therapy of radiation accidents at the present moment, but developments in this field are so rapid that their potential value should be considered.

In the management of the recent accident near Pittsburgh, one of the irradiated patients had, by remarkable coincidence, an identical twin and a successful marrow graft was accomplished [22]. Dr. Niel Wald and his associates, who were in charge of the patients, decided against attempting a homologous graft in the other heavily exposed patient who recovered without this measure.

It is widely believed that even if success with grafts could be obtained, immunologic incompatibilities would result in a high incidence of severe secondary disease reactions. The most common experience in man, however, based on attempts to treat acute leukemia rather than radiation injury, has been a failure of initial take. Certain factors should make radiation accident victims quite receptive to grafts — they have not been sensitized by previous transfusions, and the radiation is usually experienced at a high dose rate. Gengozian [23] has shown in animals that a high dose rate distinctly facilitates a "take" of the graft.

Furthermore, we believe that rapid advances in tissue typing will allow much improved selection of relatively compatible homologous donors. Thus the possibility of marrow-graft therapy is not to be dismissed if suitable circumstances arise.

Marrow grafts were tried in the Yugoslavian accident victims treated in Paris by Mathé and his associates. In those patients the grafts were given relatively late after the exposure, and the time course of the hematologic improvement of the grafted patients was not enough different from that of other similar accident victims to demonstrate a clear benefit [24].

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Quantitative measurement of red cell populations strongly suggested that a transient graft had taken place. There was no secondary or foreign bone-marrow disease.

An important consideration in the use of marrow-graft therapy is that a 10- to 14-day interval is required after the cells are given before hematologic benefit is apparent. Thus we would ordinarily give the graft by 10 days after exposure, or preferably even earlier, if the beneficial effect is to be available when it is needed.

Management of High-Dose Local Radiation Injury

The accidents characterized by pronounced damage to parts of the body, with or without severe signs of hematopoietic depression from total-body exposure, are especially difficult to manage. The radiation injury to local tissues is often more severe than it first appears and progression of the damage may continue over a period of many months. Early judgements on the amount of tissue that will undergo necrosis usually turn out to be underestimates.

Hematopoietic depression from irradiation of the marrow increases the risks from surgical procedures during the first 6 or 8 weeks after exposure and may constitute a valid reason for delaying definitive surgical treatment of gangrenous lesions. This is usually not, however, a justification for delays of many months, and these long periods of observation and waiting are usually due to uncertainty about the extent of damage and the nature of the surgical procedure that will be ultimately needed.

In the recent accident treated in Pittsburgh, one patient who also had severe total-body irradiation damage suffered pronounced local damage to the distal parts of all four extremities. Over a period of many months amputations of hands and lower legs were performed. The operations were delayed in the vain hope that revascularization would occur and that it might be possible to save more tissue than originally seemed likely. Dr. Michael Gilberti [25], who was responsible for the surgical management of these patients, has stated that in retrospect he believes that much earlier amputation would have been preferable, probably at 2 to 3 months after exposure. In this accident the early erythema and bleb formation gave a demarcation, which eventually proved to indicate the limits of viable tissue. Later, persistent discoloration of the skin and ulceration coincided with these limits. The amputated tissues showed such extensive endothelial proliferation and obliteration of vessels that the irreversible nature of the damage was confirmed.

Dr. Gilberti cites as advantages of early operation in such cases:

(1) A lessened danger of infection. (Late infection, mainly due to Pseudomonas, was a severe problem in this patient.)

(2) Reduction in the period of severe pain and requirements for narcotics.

(3) Reduction in hospital stay.

This accident involved high-energy X rays. Other accidents with less penetrating radiations may produce destruction of the skin with sparing of deep tissues. Where demarcation lines are not clear and the status of

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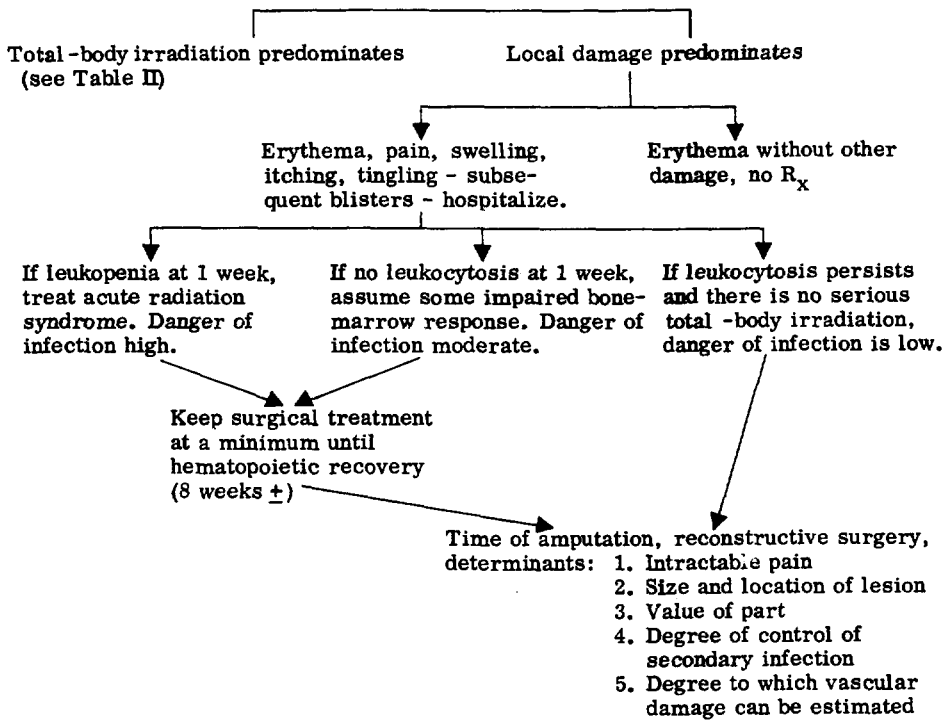
deep tissues is obscure, some period of delay in surgical treatment may be inevitable. When the impaired tissue is part of the torso or face, there are even fewer guidelines for the timing of resection of necrotic tissue and beginning of reconstructive procedures.

Table IV indicates the management sequence in patients with predominantly local injury.

TABLE IV

INJURY FROM EXTERNAL RADIATION

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## DISCUSSION

P.N. KRISHNAMOORTHY: A case was reported by Dr. Cowper during the Symposium on Personnel Dosimetry for Accidental High-Level Exposure to External and Internal Radiation held in Vienna in 1965[1]. In that particular case, some of the contractor's workmen who were in the general vicinity of an accident site, but who were not in any way subjected to any irradiation either internal or external, complained of nausea a few hours after the accident.

G.A. ANDREWS: I am aware of the general statement on that point by Dr. Cowper, but do not know any details. I hope that at some stage he will provide further information to indicate whether the symptoms encountered simulated closely those of true irradiation injury.

J.L. WEEKS: Perhaps I could just make a comment on this point. The contractor's personnel at Chalk River following the NRX accident in 1952, manifested some symptoms of disease, or perhaps one might say, unease, but there was no vomiting as far as I know. However, by their very number they illustrated the clear need for a facility which could handle a large number of people only a few of whom might be seriously affected.

H.T. DAW: Would you elaborate a little, Dr. Andrews, on the place of leukaemic cells in the therapy for radiation-injured individuals, and what assurances are there that in man no transfer of leukaemia would take place?

G.A. ANDREWS: The use of leukaemia cells is admittedly highly experimental and is suggested only for patients with severe marrow depression whose lives are threatened by infection. Although a transient graft of leukaemic cells might be obtained, there is no evidence yet that the disease could be permanently transplanted. There is every reason to believe, on the basis of animal and human data, that if the recipient regains his immune competence, he will reject the foreign leukaemic cells.

T.E. MEINDERSMA: Bacteriological decontamination is still considered to be a procedure entailing quite a few difficulties and risks. As part of the European co-operation programme, the Gnotobiology Project Group of the European Organization for Research on Treatment of Cancer is trying to find ways of achieving bacteriological decontamination. I should therefore be interested to know which method of this kind was used during

[1] Personnel Dosimetry for Radiation Accidents (Proc. Symp. Vienna, 1965), IAEA, Vienna (1965) 16.

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the Pittsburgh accident. When applying bacteriological decontamination it is advisable to ensure strict microbiological isolation. So far it has not been proved that laminar flow is strict enough for the purpose.

G.A. ANDREWS: In the 1958 accident at Oak Ridge, we did not try to sterilize the patients and, generally speaking, gave them no antibiotics. In the recent accident near Pittsburgh, the patients were in a laminar-flow type of facility and were given topical, non-absorbable and absorbable antibiotics on the basis of a leucopenia, even though clinical infections were not obvious. No cultures could be produced from the faeces so some form of sterilization was achieved at least as far as the gastro-intestinal tract was concerned.

As regards the relative merits of laminar flow and other methods of isolation, there seems reason to believe laminar flow facilities are more effective in controlling airborne contamination. The degree to which other types of contamination are controllable depends upon auxiliary methods, all of which can be used in a laminar flow facility; and in the facility we are now setting up in Oak Ridge, we are combining laminar flow with other techniques, e.g. use of masks and gowns, sterilization of all materials going to the patient, etc.

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RADIATION RESEARCH SUPPLEMENT 7, 390–397 (1967)

# Radiation Accidents and Their Management

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Radiation accidents have been a valuable source of information on radiation effects in man (*1–9*). As contrasted with studies of therapeutic radiation, the accidents usually involve normal people. Furthermore, the follow-up clinical and laboratory studies of accident victims are almost always carried out with great thoroughness. One disadvantage of the information derived from accidents is that the radiation exposure is usually nonuniform in distribution and penetration, and accurate dosimetry is often lacking.

Most radiation accidents involve a sudden, brief exposure to penetrating radiation. In contrast, the exposures that may occur in the exploration of space are likely to include a large component of less penetrating radiations, although this situation can, of course, be greatly altered by shielding (*10*). In addition, there are the problems of the unfamiliar types of radiation, with their high linear energy transfer (LET); but perhaps most strikingly different from our previous experience will be the degrees of protraction involved. The exposures lasting for days or weeks will be considerably longer than those in most radiation accidents. Data in man for exposures of this duration are very meager. If astronauts receive high exposures from solar flares, these will probably be relatively short and thus more nearly approximate our previous experience. However, they may be superimposed upon a more prolonged, lower-level radiation exposure.

Even though they are not directly applicable to the space problem, it may be helpful to consider what we know of previous radiation accidents. The most important information has to do with the responses to doses in the near-lethal and sublethal ranges. Higher, supralethal doses are rare and are unlikely to be encountered in space. In evaluating acute accidental exposures, we find that hematologic changes are not only the most serious clinical effects but also the best biological index of exposure dose. We have attempted to establish typical responses of the adult human being to three different doses of acute total-body irradiation—200 rads, 300 rads, and 450 rads. The curves presented here were established by averaging the results

[1] An operating unit of Oak Ridge Associated Universities, Inc., Oak Ridge, Tennessee, under contract with the U. S. Atomic Energy Commission.



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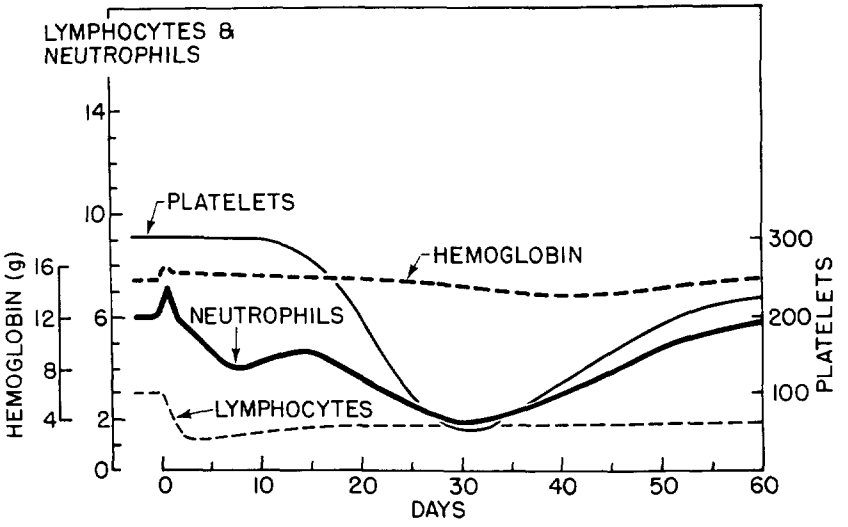


FIG. 1. Typical hematologic response of the human being to a radiation dose of 200 rads. Lymphocyte, neutrophil, and platelet values should be multiplied by 1000. Hemoglobin values are in grams per 100 ml.

of data from radiation accidents and a small number of therapeutically irradiated persons without primary hematologic disease. Several factors impair the accuracy of these graphs, including insufficient data and uncertainties of radiation dosages, and we anticipate that a more accurate set of curves will be available when the ORINS retrospective study has been completed. The present curves are shown in Figs. 1, 2, and 3. We also prepared a curve for 100 rads, but this was even less satisfactory because of the great variability in the data.

Certain generalizations can be made about these hematologic responses. The early decrease in lymphocytes is an excellent index of dosage. The greatest depression in granulocytes and platelets almost always occurs about the fourth or fifth week after exposure and is associated with the major clinical manifestations of hemorrhage and infection. Spontaneous regeneration of the marrow begins by the sixth week if the patient survives this long. When a patient dies of hemorrhage and infection, this does not necessarily mean that the marrow was irreversibly damaged; it means simply that the patient was unable to survive the degree of depression that occurred. The basic potential for recovery cannot be evaluated in this situation.

Treatment consists in a group of measures directed toward carrying the patient over the phase of marrow depression. For the mildest injury all that is needed is a moderately restful environment and avoidance of stress or exposure to infection. For more severe injury a well-organized medical program is needed. In addition to the obvious measures of providing rest and good nutrition, these may consist of:

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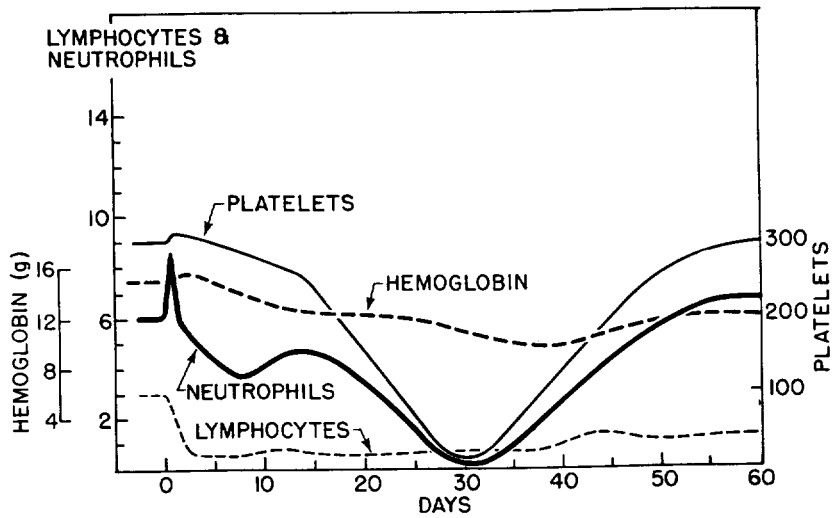


FIG. 2. Typical hematologic response of the human being to a radiation dose of 300 rads. Lymphocyte, neutrophil, and platelet values should be multiplied by 1000. Hemoglobin values are in grams per 100 ml.

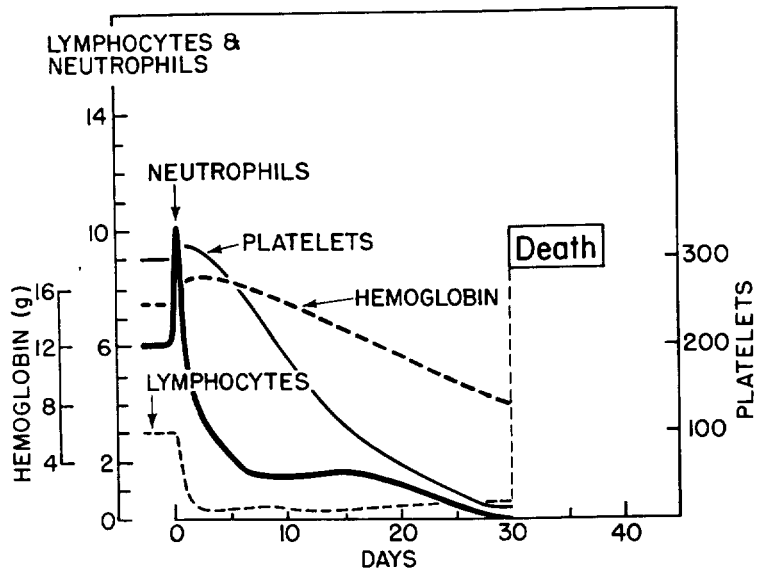


FIG. 3. Typical hematologic response of the human being to a radiaion dose of 450 rads. Lymphocyte, neutrophil, and platelet values should be multiplied by 1000. Hemoglobin values are in grams per 100 ml.

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*1. Anti-infectious measures.* Recent developments in plastic-tent isolators make it possible to isolate the patient from exogenous infections (*11*). Furthermore, with appropriate antibiotics and other measures, one can largely eliminate the organisms already present in and on the patient. We believe that when the patient is not in a sterile environment it is unwise to start broad-spectrum antibiotics before signs of infectious disease develop. However, with these new sterile facilities, it may make very good sense to use antibiotics in advance to get rid of as many bacteria as possible, including the intestinal organisms that are ordinarily nonpathogenic but may become pathogenic in a pancytopenic patient. If infection does result in spite of all preventive measures, prompt and carefully chosen therapy is needed. The importance of gram-negative organisms and of fungus infections is well known in such patients, and identification of the infecting agent is important. Gamma globulin or immune serum may prove of some supplementary value in a patient with an impaired immune mechanism, although little information is available on this point.

If large numbers of white cells can be obtained from donors, these may make an effective form of therapy to be used in uncontrollable infections occurring in the severely leukopenic patient (*12*). At present, patients with chronic granulocytic leukemia are the best source of cells, and these cells have appeared to be highly effective in combating infection in patients with acute leukemia who are on suppressive drug treatment. In a few instances temporary hematopoietic grafts of the chronic leukemic cells have occurred. No immunologic complications have been seen, but the use of this therapy in a radiation accident victim would raise the question of the remote but alarming possibility of transplanting leukemia. The use of white cells from normal donors seems not now practical because of the difficulties in obtaining enough cells. It would probably be desirable to separate the lymphocytes from granulocytes, and there are serious unsolved questions about the possibility of immunologic complications if a hematopoietic graft were intentionally or inadvertently produced from cells of the peripheral blood.

*2. Measures to prevent bleeding.* The essential need is to infuse fresh platelets when thrombocytopenia becomes severe. It is difficult to know when to start giving platelets. If bleeding is already occurring from several sites, it may be too late. On the other hand, if platelet therapy is started before it is necessary, problems with platelet antibodies may make difficulties during a later period when the need for platelets is greater. There is no agreement on whether a low platelet count—for example, below 10,000/mm$^3$—in the absence of any petechiae or bleeding is an indication for giving platelets. There is, of course, a great deal of variation from patient to patient in the degree of thrombocytopenia that may occur without clinical bleeding. Observation of the urine for microscopic hematuria may be a valuable index of bleeding tendency. Clinical judgment will determine what degree of thrombocytopenia and clinical manifestations make replacement necessary. Large numbers of platelets may be needed. Patients with high platelet counts due to polycythemia vera make excellent donors.

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*3. Marrow graft therapy.* This treatment, if successful, would correct both the hemorrhagic manifestations and excessive susceptibility to infections. In experimental animals marrow grafts can be achieved after irradiation with great reliability (*13*). The main problems are immunologic complications that may occur if genetic strains are incompatible. In the human being, up to the present, the greatest difficulty has been in producing a primary take (*14*) (except when donor and recipient are identical twins). Only a few examples of delayed immunologic incompatibility have occurred (*15*), but successful primary takes are so few that it is impossible to know what the experience will be when more successful methods are developed for producing marrow grafts in man.

In spite of these uncertainties, therapy with homologous marrow grafts should be considered for patients who appear, on the basis of biological responses, to have received radiation doses likely to be fatal. Probably the timing of the marrow administration should depend on the severity of the injury—if extremely severe an early attempt, perhaps three or four days after exposure, would be appropriate. If the injury is less severe and the need for the graft more doubtful, one might wait until several days or even two or three weeks after exposure.

Autologous marrow-graft treatment is well worth investigation as a back-up therapy for astronauts. The fact that only a small number of men is involved would make the problem much less difficult than it would be if an effort were made to use it on a wide scale in the atomic energy industry or in the military services. The practicability of storing marrow and using it for therapy has been clearly demonstrated in experimental animals (*16*). The practical problems of storing and administering marrow are many, particularly if it were to be made available in the spacecraft for use after solar flares on a long mission.

All the preceding comments refer to experiences with radiation delivered over a very short period, generally less than one day. A somewhat different situation exists with more protracted exposure. This was dramatically shown in a Mexican accident in which persons were exposed continuously or almost continuously from a cobalt-60 source over a period of weeks (*8*). The prolonged illness produced was in contrast to that caused by acute exposure in which we expect death or beginning recovery by the sixth week. The syndrome produced by the more protracted radiation is qualitatively different. Although it still appears that hematologic depression with the associated hemorrhage and infection is the main cause of morbidity and death, there is a striking change in the pattern of development of the damage. We find that the pancytopenia does not reach its greatest severity about the fifth week, as is seen after acute exposure. Instead, there is an extended period of marrow depression without early spontaneous recovery. One of the Mexican accident victims died, mainly of hemorrhage, about three months after the end of the 90-day period of exposure. Her hematologic values are shown in Fig. 4. Another, a man who suffered a lower dose in the same accident, survived the injury but had a hema-

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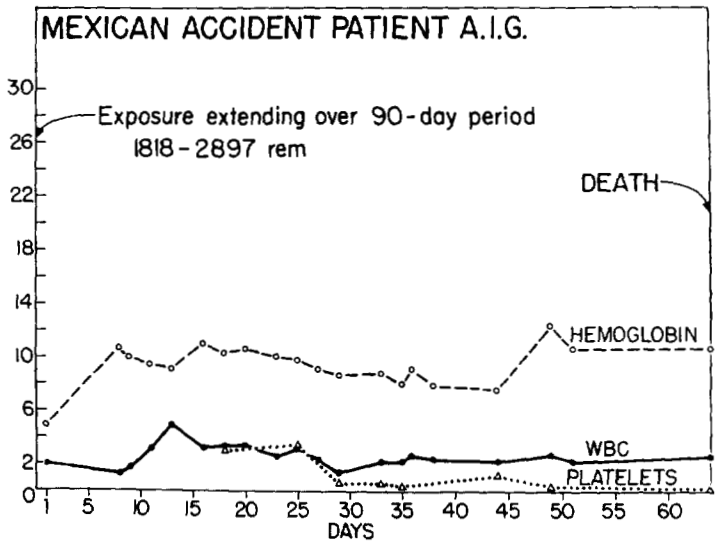


FIG. 4. Hematologic values in a woman exposed over a prolonged period of time to cobalt-60, with delayed fatal outcome (from Martinez *et al.*, *8*). White blood cell values should be multiplied by 1000, platelet values by 10,000. Hemoglobin is in grams per 100 ml.

tologic depression of mild degree that began to improve gradually after about three months (Fig. 5).

The syndrome of chronic hematologic depression produced by protracted radiation is probably more difficult to treat than that produced by a single short exposure. Instead of being faced with the need to carry the patient through only a relatively brief period of pancytopenia, the clinician would need to provide continuous support, perhaps with platelet transfusions, over a very long period. It is not known whether such a patient would be receptive to a marrow graft, but work in experimental animals indicates that a good effect can be obtained after extended exposure (*17*).

Radioprotective agents might prove of real value to astronauts. The greatest problems of chemical protection are the toxicity of the drugs, the brevity of their benefit, and the need to give them in advance of the exposure. There is the possibility of brief, predictable periods of high exposure in space and also the likelihood that at least in some missions it would be permissible for all or part of the crew to be temporarily incapacitated by the drugs. Chemical treatments that might be administered after exposure to enhance recovery have as yet been of only mild benefit; improved forms of these would, of course, be highly welcome in dealing with radiation accidents and exposures in space.

In conclusion, it should be reemphasized that there is a great need for information on repeated and protracted exposures in man. This is particularly true for the space

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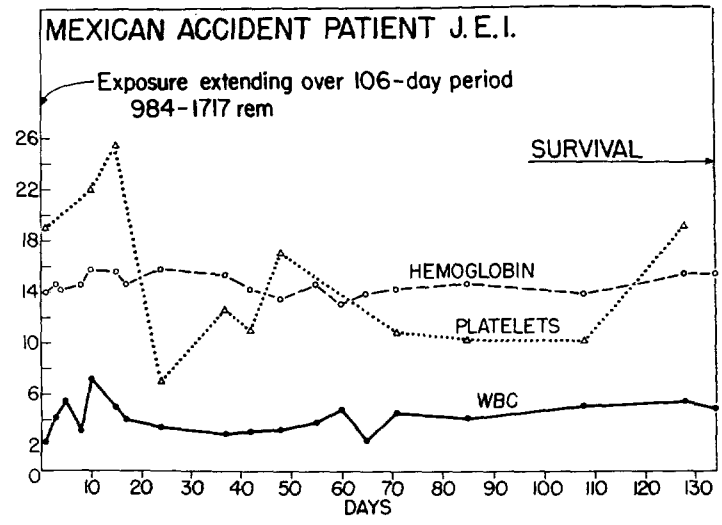


FIG. 5. Hematologic values in a man who survived a prolonged exposure to cobalt-60. Moderate but protracted marrow depression was seen (from Martinez *et al.*, *8*). White blood cell values should be multiplied by 1000, platelet values by 10,000. Hemoglobin is in grams per 100 ml.

program because these are the types of exposures to be anticipated. In a small number of observations, Tubiana *et al.* (*18*) have observed great sensitivity of patients to second doses of total-body irradiation for kidney-graft procedure. In our limited experience with smaller (50 and 100 R) doses of total-body irradiation given to patients with chronic blood diseases, we have not been so much impressed by the enhancement of sensitivity when a second dose is given several months after the first. Obviously, the conditions of our studies are very different from those of Tubiana *et al.*, and more information is needed on this problem of the persistent damage and sensitivity to later doses after apparent recovery from total-body irradiation.

Our future needs, obviously, must include collection of further data on radiation effects in man. This information will be vital for understanding the radiation accidents that are bound to occur despite the carefully devised preventive measures in effect. The same information may prove very useful to the space program, although the seriousness of the radiation exposures that will be incurred in outer space is not yet well known.

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# Treatment of Radiation Injury

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*Reprinted from the*
JOURNAL OF THE MISSISSIPPI STATE MEDICAL ASSOCIATION
October 1966, Vol. VII, No. 10, Pages 534-538
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# Treatment of Radiation Injury

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WITH THE GREATLY INCREASED opportunities for use of atomic energy that developed as a result of World War II, there was an obvious need for more information about mechanisms and treatment of radiation injury. In addition to the possibilities of mass casualties from nuclear weapons, there are increasing exposures to radiation in peacetime activities. The spread of nuclear power carries with it the possibility of reactor accidents.

Even though the industries related to atomic energy have been among the safest in the world, and have a magnificent record of preventing radiation accidents, there are still a few inadvertent exposures of human beings, and with the greatly increasing numbers of nuclear installations it is reasonable to suppose that such accidents will continue to occur occasionally in spite of the best efforts to prevent them. Furthermore, the exploration of outer space involves a whole new problem of dealing with the radiations that will be encountered there.

Interest in radiation effects in the human being did not begin, of course, with the development of World War II; knowledge on this problem had been expanding ever since the discovery of radiation late in the last century. The earlier studies involved mainly radiation to only local parts of the body rather than to the whole body. In addition, much of it was concerned with chronic radiation delivered over a long time. Recent research has expanded to cover all types of dose rates from very low to very high and all types of partial-body irradiation. In the present discussion we shall be mainly concerned, however, with exposure of the whole body occurring in a very short time, as might happen in a nuclear accident. The information outlined here represents the work of many investigators, and no effort will be made to list by name those who have contributed to it.

*Interest in radiation effects in the human being began with the discovery of radiation late in the last century. The author notes that radiation injury is one of the less serious hazards in our environment, but it is a significant problem about which much is now known.*

It is sometimes thought that radiation injury is rather mysterious and that little is known about it; on the contrary, few environmental hazards have been so well studied. The United States Atomic Energy Commission has supported a vast research effort in this area during the last 20 years and one of the most gratifying results has been that information of much broader importance than the treatment of radiation injury has arisen from this research program.

The greatest amount of information on radiation effects is, of course, available from studies in experimental animals. Many of the phenomena seen after radiation occur in all mammalian species, and significant predictions about man can be made from these studies. Nevertheless, differences between man and other mammals make it necessary to look for direct information in the human being.

From the Medical Division, Oak Ridge Institute of Nuclear Studies, an operating unit of Oak Ridge Associated Universities, Inc., under contract with the United States Atomic Energy Commission.

Read before the Symposium on Nuclear Medicine, 98th Annual Session, Mississippi State Medical Association, Jackson, May 11, 1966.

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This information comes from the Japanese exposed at Hiroshima and Nagasaki and Marshallese Islanders exposed to fallout in the Pacific. These groups include rather large numbers of patients, but the information on the Japanese was, of necessity, very limited and poorly documented. The investigations on the inhabitants of the Pacific Islands have been very complete and well documented; they involve a type of exposure that is somewhat inhomogeneous and somewhat protracted.

Radiation accidents have involved only a small number of persons. The clinical results have generally been exceedingly well studied but the dosage delivered can not always be determined accurately. Studies in which total-body irradiation is applied for therapeutic purposes have been done on quite large numbers of patients, and the results have been carefully measured, but the main disadvantage is the preexisting disease that alters the response. At our laboratories in Oak Ridge a careful retrospective study is being done on a large number of patients treated clinically. This work is supported by the National Aeronautics and Space Administration and the U. S. Atomic Energy Commission.

## ANIMAL EXPERIMENTATION

It is apparent that while we must rely very heavily on work in experimental animals, where conditions can be very well controlled, we need also to evaluate as thoroughly as possible the various types of information relating to human beings. Each one of these human groups has certain advantages and disadvantages for evaluation of radiation effects and prediction of the response of normal persons.

There is very little experience in the human being with doses in the extremely high range; that is, above 3,000 or 4,000 rads. On the basis of animal studies the consensus is that the most obvious manifestations would be those of damage to the central nervous system and that survival would not be more than two or three days. In two clinical experiences that have involved such high doses, in addition to neurological manifestations, there have been profound cardiovascular effects with a state of shock a major factor. At slightly lower doses the effects are mainly gastrointestinal, and patients are likely to die within 10 days, of electrolyte imbalance and infections.

At still lower doses of 1,000 rads or less, the chief manifestations are related to the hematologic system. A profound depression of the bone marrow results in hemorrhage and infection, and these are the most likely causes of death. When death occurs as a result of hematologic depression, it is usually from the third through the fifth week after exposure; this is considerably later than the time of death from the higher doses which produce the central nervous system or gastrointestinal syndrome. The hematologic type of damage has been the most common in human experience and it seems probable that radiation accidents, experience in outer space, and even most of the potential military exposures would be likely to involve these dose levels rather than the much higher ones that produce chiefly gastrointestinal or central nervous system manifestations. Therefore, the fact that the hematologic type of damage can be effectively countered by therapy is of considerable importance.

## CHANGES IN BLOOD

After a dose in the midlethal range, the blood picture exhibits a rather characteristic pattern of events. There is likely to be a brief leukocytosis, lasting only a few hours and representing a mobilization of granulocytes already formed. The granulocyte level will then gradually fall for a week or so and then may show an abortive rise so that at about 15 days it is higher than it was at 10 days, perhaps up into the low normal range. After this abortive rise at 15 days, the granulocyte count falls progressively until around the 30th day when it reaches its lowest point. If the patient survives, by the 35th or 40th day regeneration of the granulocytes is likely to be under way and they return to normal levels.

The platelets show a pattern quite similar to that of the granulocytes, perhaps lacking the initial brief rise above normal and without such a clear-cut abortive regeneration. The nadir, however, occurs at almost the same time as that of the granulocytes, perhaps a very few days earlier, and recovery follows a similar pattern. The lymphocyte levels show a quite different evolution. They fall very promptly and within 48 hours reach a point almost as low as they will ever reach. The degree of this lymphocyte fall is a valuable early index of the degree of radiation injury. Red-cell values change much less, relatively, because of the long life span of the normal red cell, but a mild anemia may be produced several weeks after exposure.

## DEATH OR SURVIVAL

This hematologic picture is closely correlated with the problem of death or survival. If the patient can live through the period of greatest leu-

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kopenia and thrombocytopenia, then spontaneous recovery will occur. If the patient dies at four weeks, this does not mean that there has been permanent marrow ablation; in fact, we know very little about permanent marrow ablation as a radiation effect. Such a death should probably be interpreted as a temporary marrow damage so severe that it could not be survived.

Effective therapy consists of several measures. In addition to general factors such as rest and adequate nutrition, one should try to protect the patient from exogenous infection. This can be done with some of the newer plastic isolators or other techniques for keeping bacteria away from the patient. Antibiotics can be highly effective in treating infections that occur. Some of these infections are from normal bacterial inhabitants and involve organisms that would not usually be pathogenic.

## CAUTION ON ANTIBIOTICS

This raises the question of whether one should try in advance to sterilize the gastrointestinal tract with antibiotics. At the present moment the best opinion is that this should not be done unless a sterile environment can be provided. The prophylactic use of antibiotics is very questionable in these patients, and much more information is needed about it, but there is no question about the advantage of treating a known infection once it exists. Since these infections in the leukopenic patients may be fulminating, it is necessary to start treatment as soon as a severe fever develops, but only after appropriate cultures have been taken from all likely sites of infection. The antibiotic can later be adjusted after the bacteriologic reports are available.

We know that gram-negative organisms are a common cause of trouble. We also know that fungus infection may be important and that *Candida* is a very common problem. Because of this, it may be worthwhile to give nystatin prophylactically to patients with very severe neutropenia. The choice of antibiotics depends upon the most likely infection or preferably upon the proved bacteriologic identity of the specific invader. Chloramphenicol has sometimes been considered unacceptable because in a few patients it is known itself to produce profound marrow depression. My impression is that one should not rule out chloramphenicol if the nature of the infection is such that it should be used, and we have seen beneficial effects with this antibiotic in irradiated patients. Still, it is of course a dangerous drug and should not be used for trivial reasons or where the indication is not clear-cut.

Someday we may be able to administer large numbers of normal white cells to such patients, and in fact the cells from patients with granulocytic leukemia have been shown to be of value in combating infections in certain patients with profound leukopenia. The possibility of inducing a graft of hematologic tissue with such blood cells presents serious problems and at the present time the use of this form of therapy is limited, partially because of the difficulty in obtaining the cells. Nevertheless, we should remember that administration of such cells is a very potent weapon in any severely leukopenic patient who appears to be dying from uncontrolled infection.

## HEMORRHAGE

The other major manifestation is hemorrhage, and this can be treated by giving platelets from healthy donors. Usually it is not recommended that treatment be started until the need is quite clear. Some patients tolerate a rather low platelet count quite well, and unless the low platelet count is complicated by some clinical manifestations of a hemorrhagic tendency it is doubtful that it in itself should be used as an indication for therapy. Once the need for platelets is clear we may need to give very large amounts, using multiple donors; for example, a patient might require platelets from two to six units of blood daily.

If it appears, shortly after exposure, that the patient has been exposed to a lethal amount of irradiation and it is believed that the supportive treatment with antibiotics and platelets is not likely to carry him through the period of marrow depression, then a marrow graft might be considered, although this is a highly experimental form of therapy and has not had much success in the human being as yet.

## SPLENIC SHIELDING

Perhaps we should review briefly the development of marrow-graft studies in relation to radiation. It has long been known from animal experiments that if a small part of the bone marrow could be completely protected during the exposure, the rest of the body could accept a very high dose without a lethal result. Quite a number of years ago attention was focused upon the fact that in the mouse the body could be protected by shielding the spleen. If an abdominal incision is made and the spleen is exteriorized and protected behind a lead shield, a mouse can survive a dose of radiation that would otherwise be lethal. The

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spleen in the adult mouse, of course, contains many more hematopoietic elements than does the spleen of the adult human being.

For some time there was a vigorous difference of opinion among investigators about the nature of protection by splenic shielding. Some were convinced that the protected spleen yielded an obscure biochemical material of hormonal nature that stimulated the bone marrow to recover, while others were equally convinced that the spleen supplied living precursor blood-forming cells that moved from the spleen into the bone marrow and caused recovery. It was soon found that bone-marrow cells from a healthy donor would also greatly facilitate recovery and the same question existed about the nature of the effective agent, whether it was the living cell or some chemical factor. After a time a whole group of ingenious experiments demonstrated that the living cell was the important thing and that a true repopulation of the marrow was produced by these techniques.

## GENETICS OF DONOR

It soon became apparent that the genetic relationship of the donor animal to the host was extremely important. When cells from animals of a different strain or different species were given, there was likely to be good protection against the immediate radiation death but the protected animals soon began to die of a peculiar disease of immunologic nature. This was characterized by wasting, failure of hair growth, lack of lymphocytes, and some abnormal skin manifestations. This was referred to as secondary or homologous disease or foreign-bone-marrow disease. "Runt disease" is a variant of it produced when the immunologic incompatibility is established very early in life. There was again an area of controversy and uncertainty about whether the major immunologic reaction was host versus graft or graft versus host. There is now good evidence that a major share of the problem is a reaction of the graft against the host although some element of host-against-graft may be present.

To avoid this problem in marrow-graft experiments in mice, all one needs to do is to select donor mice of exactly the same inbred strain as the host. Inbred strains of mice are so uniform that they are all like identical twins to each other. However, in the human being there have been only a few instances in which there was need for a graft and an identical twin was available to serve as a donor. One might think that close familial relationship between brother and sister or mother and child would avoid these problems, but in fact only identical twins are really genetically compatible. Table I shows the various genetic relationships and gives examples in animals and human beings. Only with autografts or isologous grafts

TABLE I
DONOR-HOST RELATIONSHIPS

| | *Examples* | |
|---|---|---|
| | EXPERIMENTAL | HUMAN |
| Autologous | Same animal | Same person |
| Isologous (Isogeneic) Same genetic type | Inbred strain of mice | Identical twins |
| Homologous (Allogeneic) Same species | Different strains of mice | Siblings, parents, or unrelated persons |
| Heterologous (Xenogeneic) Different species | Rat to mouse | Ape to man |

is there complete freedom from immunologic complications. With homologous tissues the incidence and severity of incompatibility vary greatly from case to case. With heterologous grafts the difficulties tend to be very severe.

Apparently these problems of genetic compatibility and immunologic reactions are of great importance in relation to marrow grafts and, in fact, all types of tissue transplantation in the human being. Methods are being sought to select unrelated donors that happen to have the right genetic traits. There are also efforts to treat the immune disease by drugs, and this can be done with some success by means of cytotoxic agents that suppress antibody formation. However, it should be pointed out that in the human being most efforts to achieve marrow transplantation have resulted in absence of take rather than a successful take with frank secondary disease. The diagnosis of secondary disease in the human being is somewhat difficult. There seems no doubt that it has been produced in some studies on patients with acute leukemia and it may be that in the future secondary disease will be the biggest problem after the present roadblock, that is, failure of take, has been overcome in the human being.

## MARROW GRAFTS

As things now stand, we believe that in a desperate situation it would be justifiable to attempt to use a bone-marrow graft in human beings ex-

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posed to a lethal dose of radiation. Probably the graft would be given within the first week or 10 days but not necessarily within the first 48 hours. The optimum result to be hoped for would be a temporary survival of the graft with eventual rejection by the recovering host.

The studies stimulated by the urgent need to understand radiation injury have had wide application beyond that originally anticipated. Most notable has been the advance in transplantation immunology. Although work on grafting of donor skin has been going on for many years, the efforts to transplant other organs have been mostly in recent years. These attempts have made extensive use of the information derived from radiobiological experiments. A related area of great progress is genetics; here again the studies stimulated by the radiation problem have been of great importance and have extended to include fundamental work in molecular biology.

On a more clinical level, the progress in radiobiology gives promise of being of assistance in handling certain problems of marrow depression from drugs and unknown causes that simulate radiation injury. Another indirect result of interest to clinicians is the application of radiobiologic data to problems of radiation therapy to local areas of the body for the treatment of cancer. The availability of teletherapy sources containing radioisotopic sources has greatly improved the depth-dose distribution. Factors that enhance the sensitivity of malignant tissue or protect the normal tissue have received great emphasis recently, and much of this advance is related to the general work in radiobiology.

Radiation injury is one of the less serious hazards in our environment, but it is a significant problem about which much is known. Effective treatment is available for radiation damage, but extremely high doses produce injury that cannot be controlled by methods now available. Investigations of man's response to radiation have been exceedingly fruitful and have had applications far beyond the original scope of the work. ★★★

Institute of Nuclear Studies (37831)

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