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Human Radiation Injury Diagnosis, Therapy and Prognosis

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THE IMMEDIATE and late effects of ionizing radiation are generally considered as a component part of atomic warfare. With the exception of the laboratories devoted in part to the studies of the harmful effects of radiation,† there is little interest on the part of physicians in our country. The average physician and hematologist chooses to ignore the problem because the magnitude of medical problems associated with atomic warfare makes the problems seem insuperable. In addition, there is a strong feeling on the part of many that nothing can be done for radiation injury anyway. However, this is not true as will be pointed out. In addition, the growing awareness of the public to the hazards of radiation behooves us as physicians to be able to advise learnedly on the hazards and to be prepared to cope with injuries that will inevitably result as the industrial uses of radiation spread and as atomic power plants‡ become commonplace. Man's machines are only as safe as the men who operate them. Since hemopoietic dysfunction occupies a key role in both the acute and long-term picture, hematologists will be called upon more and more to advise labor and management on the hazards: their prevention, control and treatment.

Radiation injury is both dose- and time-dependent in mammals. After very high doses of radiation ca. 10,000 r., death occurs with symptoms related to the nervous system (CNS) syndrome. These deaths occur within a matter of hours. With lower doses ca. 800–10,000 r., deaths occur 3–6 days after exposure with symptoms related to the gastrointestinal (GI) tract. This was observed in Japan and reported by Kikuchi and Wakisaka.[1] With lower doses 200–800 r., hemopoietic deaths occur (sequelae of pancytopenia, infection, hemorrhage, and anemia) 8–60 days after exposure.

There is no treatment for the CNS syndrome. If there were, one would still have to face the GI syndrome, and if one were brought through this phase, one would still have to face the hemopoietic syndrome. In fact, this has been shown

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‡ In operation in Russia, England and the United States. Research reactors in U. S., England, Russia, France, India, Norway, and under construction elsewhere.

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TABLE 1.—*Compartmentation Scheme for Blood Cell Production*

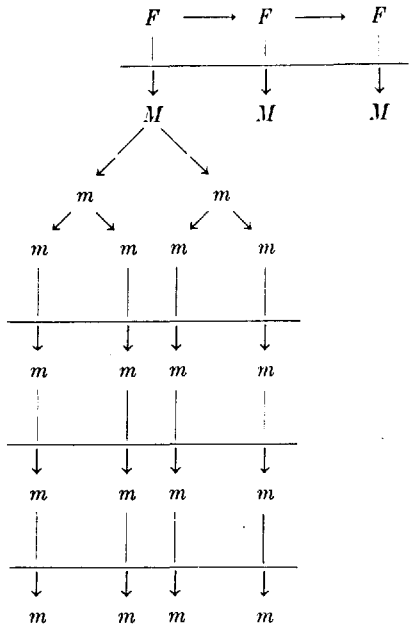
I. Reservoir of primitive undifferentiated cells (*RPUC*)
F (number of progenitors)
^tM (mitotic time)
^tI (interphase time)

II. Multiplication and maturation (*MM*)
M (daughters that enter maturation compartment)
m (daughters undergoing multiplication and maturation)
n (number of mitotic divisions)

III. Maturation and storage (*MS*)
^tMS (time for maturation and storage)

IV. Peripheral blood (*PB*)
P (number of adult cells)
^tP (life span)

V. Extravascular life (*EV*) for leukocytes
^tEV (time out of circulation after release)



experimentally in dogs by Conard et al.[2] that large-scale replacement of fluids, plasma and electrolytes will get dogs over the GI syndrome permitting the gastrointestinal mucosa to regenerate. Then the animals later experience the hemopoietic syndrome and die with the characteristic sequelae of pancytopenia. The hemopoietic syndrome can be significantly altered by various procedures, a subject that is covered in the panel on restoration of hemopoietic tissues elsewhere in these proceedings and will not be considered in length here. I shall concentrate largely on human radiation injury in man. The description of radiation injury goes back to the turn of the century. Heinecke[3, 4] described the atrophy of radiosensitive organs. In more recent years, the dynamics of proliferating tissues, has been better appreciated and was recently reviewed by Leblond and Walker.[5] In reality, the dose and time dependence of the radiation syndromes are, in part, a manifestation of the degree of disturbance in the tissues that normally are highly proliferative and in a state of dynamic equilibrium. Alterations in the granulocytes were considered in detail by Cronkite and Brecher.[6] Radiation disturbs the equilibrium by depressing the production of new cells and possibly may affect life span. The steady state equilibrium can be expressed in a simple equation as suggested by Quastler:

$$\frac{F}{{}^tM + {}^tI} = \frac{P}{{}^tP}$$

(Number being born) (Number dying)

where F = the number of primitive progenitors
^tM = motitic time

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^tI = interphase time
P = number of mature cells
^tP = life span of the specific cell.

In this expression, it is assumed that one daughter cell matures and one remains behind to divide again. In the case of the intestinal mucosa, this appears to be the case. In the case of hemopoiesis, particularly erythropoiesis, such a simple situation does not exist. It appears that mitosis and maturation occur simultaneously. In theory, one can establish the following model consisting of at least four compartments feeding from the first to the last compartment. In some instances there is reutilization of constituents of the dying cells for new cell production.

In the first compartment, primitive progenitors are dividing, feeding one daughter cell into the multiplication and maturation (MM) compartment, and one remaining behind to divide again, thus maintaining the progenitor pool. The number entering the MM compartment is

$$\frac{F}{^tM + {}^tI}.$$

In the MM compartment, the cells started down one lineage divide an unknown number of times (n). Hence, the number produced in this compartment is

$$\left(\frac{F}{^tM + {}^tI}\right)_2{}^n.$$

When division is no longer possible, cells are retained for an unknown period of time in the maturation and storage compartment. Thus, one can express the steady state from compartment II (MM) to compartment III (MS) to compartment IV (PB) in the following equation

$$\left(\frac{F}{^tM + {}^tI}\right)_2{}^n = \frac{P}{^tP}.$$

(Number being born) (Number dying)

Certain corrections are necessary to correct for death in mitosis and loss in MS compartment. These losses are probably very small normally, but following irradiation may be very large.* In the case of the red cell, one can balance the right side of the equation and it may be possible to calculate the unknowns on the left side from existing data, or determine experimentally the missing values.

It can easily be seen that the dynamic equilibrium can be upset by changes in the mitotic cycle, in the size of either proliferative compartment ($RPUC$ or MM), by increased losses in these compartments or in MS compartment or changes in life span. This hypothetical model may be helpful in designing experiments.

Radiation is known to affect the more radiosensitive of the population of formative cells and to increase the length of the intermitotic duration. If the formative population is eradicated, total aplasia will result. If the system is

* A more detailed discussion of hemopoietic model will be the subject of a later report.

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essential for life, then death will inevitably ensue. As the dose of radiation varies, the degree of hypoplasia varies. The rate of change in the concentration of the mature element is a function of the life span of the cell. The new steady state level is a function of the number of remaining formative cells. Space does not allow a more rigorous treatment of the dynamic equilibrium of proliferative tissues.

Specific information on human radiation injury comes from various sources. The largest single experience is that of the Japanese at Hiroshima and Nagasaki, reported on by Tsuzuki et al.,[7] Kikuchi and Wakisaka,[1] and Liebow, Warren and De Coursey.[8] More recent studies are those of Tsuzuki,[9] and Kikuchi,[10] on the Japanese fishermen, and of ourselves[11, 12] on the Marshallese and Americans exposed to radioactive fallout. Reactor accidents have contributed significantly.[13, 14] For practical considerations of sorting out casualties, one can divide exposed human beings into three categories in which survival is, respectively, *improbable, possible and probable.*

1. *Survival improbable.* If vomiting occurs promptly or within a few hours and continues and is followed in rapid succession by prostration, diarrhea, anorexia and fever, the prognosis is grave; death will almost definitely occur in 100 per cent of the individuals within the first week irrespective of what the dose estimate may be. There is no known specific therapy for these people; accordingly in a catastrophe, attention will be devoted to others for whom there is some hope.

2. *Survival possible.* Vomiting may occur early but will be of relatively short duration, followed by a period of well-being. During this period, marked changes are taking place in the hemopoietic tissues. Lymphocytes are down within hours and remain depressed for months. The neutrophil count is depressed to low levels, the degree and time of maximum depression depending upon the dose. At the end of the latent period, signs of infection may be seen when the neutrophil count has reached virtually zero 7–9 days or later. Frank purpura, epilation, breakdown of wounds or burns may be seen.

3. *Survival probable.* This group consists of individuals who may or may not had transient nausea, vomiting and diarrhea. Other symptomatology is absent. Blood changes are dependent on dose of radiation and time after exposure.

Since there is today no known way of increasing the survival rate of patients in category 1, our attention will be directed to categories 2 and 3. Category 2 was seen in large numbers in Hiroshima and Nagasaki and the excellent descriptions of Tsuzuki,[7] and Kikuchi and Wakisaka,[1] are expanded upon by the more extensive reports of the Joint Commission,[15] and Le Roy.[16, 17] Suffice it to say that the salient clinical points are the common sequelae of pancytopenia.[18]

The susceptibility to infection is well established and reviewed[6, 19-21] and the pathogenesis involves:

(a) Decrease in number of granulocytes.[6]

(b) Impaired function of the remaining granulocytes.

(c) The reticulo-endothelial system phagocytizes bacteria but does not kill them as readily.

(d) Acquired antibody production is diminished.

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(e) Natural antibody (properdin) titers decrease.

(f) The connective tissue of the skin is altered.

There is little wonder that infection occurs with almost all of the defenses impaired. In fact, infections are generally produced by commensal organisms in addition to pathogens if present in endemic or epidemic states.

The susceptibility to bleeding is well correlated with the platelet depression. However, additional factors may be involved such as lipid antithromboplastins.[22] The earlier concept of Allen et al.[23] that heparinemia is a major cause of bleeding is no longer tenable.[24] Anemia may become severe and appears to be the cause of death in the germ-free animals.[25] In a general sense in animals and in the Japanese, death in category 2 could be well correlated with overwhelming infection, exsanguinating hemorrhage, hemorrhage into vital organs and severe anemia. It is generally believed that correction or treatment of these defects during the first few weeks may permit survival in some individuals who might have otherwise died. This concept of total body irradiation as primarily a pancytopenic state, while very useful, may be an oversimplification. It is simply not known whether correction of the pancytopenic state by adequate transfusion of all formed elements would permit individuals to live indefinitely or whether they would die from some other as yet ill-defined metabolic defect. In fact, spleen shielding, homogenates and bone marrow does not save 100 per cent. Some animals die with regenerating marrow. In addition, many Japanese died with a rapidly regenerating marrow in whom the cause of death was not clear.

From the prognostic standpoint, a re-analysis of the relationship of leukocyte counts to survival in the Japanese at Hiroshima and Nagasaki by Jacobs, Lynch and Cronkite[26] has yielded interesting data. In table 1 correlation between low counts and increasing mortality is evident. In further study, Jacobs et al.[26] studied the leukocyte count in the third, fourth and fifth weeks after exposure and its correlation with ultimate survival. It appears that low leukocyte counts are tolerated better as time goes on, suggesting that other defenses against infection are recovering more rapidly than the granulocyte production.

From the preceding data, it is quite evident that a correlation between leukocyte depression and mortality exists. Since serial counts were not performed on large numbers of human beings in Japan nor on similar groups at the same time interval, it is not possible to establish as elegant a relationship for man as was done by Smith et al.[27] for mice. However, the category 3 type casualty was stud-

TABLE 2.

Lowest WBC in first 35 days	Total No. of people	Died by 9th week	Per cent mortality
0	80	68	85
501	92	51	55
1001	48	16	33
1501	76	12	16
2001	42	13	31
2501	40	1	2
3001	2893	22	1

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ied systematically by Cronkite et al.[11, 12] and will be summarized briefly. In addition to the whole-body radiation of about 175 r., extensive skin contamination resulted in beta burns of the skin.

Details on the blood changes are reported elsewhere.[11, 12] Suffice it to say that lymphocytes decreased promptly and were at their lowest level when studied the first four days after exposure. Neutrophils oscillated around the normal for a few weeks and then commenced to decrease, attaining minimum values about 45 days after exposure. Platelets were depressed below controls when first studied on the 10th day and continued to decrease, reaching lowest values. No external bleeding was seen. Pregnancy continued. Menses were excessive in four women. After higher doses, lower counts will be seen earlier for both the leukocytes and platelets.

Infections of a bacterial nature did not develop although granulocyte counts as low as 850 were observed. In view of the previous relationship between leukocyte count and mortality, it is quite evident that these people received a dose of radiation that is close to the lower limits of the lethal range. These people were under daily medical supervision. They were examined daily and serial blood counts were performed. No prophylactic therapy of transfusions were given nor were antibiotics or other drugs used unless there was a specific clinical indication. In a general sense, the Marshallese received about the same amount of whole-body radiation and internally deposited radionuclides as the Japanese fishermen. However, the Japanese fishermen apparently received more severe skin burns. None of the Marshallese nor the less severely exposed Americans developed any sign of hepatitis whereas 18 of 23 of the Japanese fishermen did. Accordingly it is our contention that the most likely explanation for the hepatitis in the Japanese is that it was serum hepatitis induced by repeated blood transfusions and not a radiation-induced hepatitis because this has not been observed in experimental animals with comparable and greater doses, nor was it seen after Hiroshima and Nagasaki, nor was it seen in the Marshallese, nor following any of the reactor accidents. The liver can and has been injured in animals by massive doses of radiation, but there is no evidence that liver dysfunction is induced by doses in the lethal range, i.e., less than 800 r.

Before concluding, I want to summarize the preferable treatment of radiation injury of man.

First, on the basis of the Marshallese experience, it can be concluded that *no prophylactic therapy* is needed for this degree of radiation injury. Careful observation, good nursing care, and treatment on an individual basis of any condition that may arise are of cardinal importance. Antibiotics, in general, should not be given prophylactically, and should be administered only if infectious processes develop that would be treated with antibiotics in the absence of any history of overexposure to radiation.

Admittedly there is a point where one will wish to consider the prophylactic use of antibiotics. When one studies the data on correlation of leukocytes with mortality, one will seriously consider antibiotics when leukocytes fall below 1000/mm^3. However, it is still desirable to withhold as long as possible because

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bacteria may become resistant to the drugs, thus depriving the individuals of the possible later benefit of these agents. Under conditions of a major castastrophe where careful continuous observation is not possible, a better case exists for the widespread empirical use of antibiotics, particularly in individuals with burns (beta or thermal), wounds or other trauma. In this situation, the oral antibiotics appear to have first call. Wide spectrum agents such as tetracycline, oxytetracycline and chlortetracycline are available. Tetracycline is the probable drug of choice with full therapeutic doses from 14 to 30 days when most of the infectious deaths were observed.

Blood obviously has a role. It should never be given prophylactically but only when indicated by clearcut clinical and laboratory findings. Fresh whole blood by direct silicone multiple syringe technique without anticoagulant or collected in plastic bags with EDTA or platelet transfusions may be of some value in controlling purpura and spontaneous bleeding for a limited period of time. The use of drugs without clear indication is discouraged because of the unknown and possibly harmful effects on the irradiated individual whose metabolism is deranged. At present there are no specific prophylactic or therapeutic agents that should be stockpiled for use in the hematological depression and the resulting disease state following exposure to total-body irradiation. However, laboratory data on animals clearly indicate that radiation-induced hemopoietic depression can be influenced in several ways:

a. Accelerated restoration of aplastic tissue by transplantation of genetically acceptable totipotential cells with substantial increase in survival.

b. Alteration of the blood picture by "triggering" known physiologic stimuli for hematopoiesis with slight increase in survival.

c. Substitution therapy (WBC and platelet transfusion) altered the clinical picture but did not significantly increase survival as yet.

d. Restoration of antibody production by non-cellular factors in which the influence upon survival is not yet recorded.

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