The text of this file is a transcription of three articles from an original source. They are reproduced in this manner due to the dearth of pre-existing copies of this material, and because photocopying the physical object was not practical.

Editor: Harold E. Whipple, with L. D. Hamilton consulting.

Title: *Physical Factors and Modification of Radiation Injury.*

Journal information: Annals of the New York Academy of Sciences, Volume 114, art. 1, pp. 1 – 716.

Year: March 31, 1964.

Additional information:

"The papers in Part I of this monograph [including the three transcribed here] were presented at a conference entitled *Physical Factors Modifying Response to Radiation* held by The New York Academy of Sciences on November 29, 30, and December 1, 1962."

Footnotes present in the original text are given in their original position and indicated with a bracketed hash mark and number of reference.

THE DIAGNOSIS, TREATMENT, AND PROGNOSIS OF HUMAN RADIATION INJURY FROM WHOLE-BODY EXPOSURE [Footnote: Research supported by the U. S. Atomic Energy Commission.]

Eugene P. Cronkite

Medical Research Center, Brookhaven National Laboratory, Upton, L. I., N. Y.

Radiation injury from essentially whole-body exposure to radiation will occur accidentally from time to time as a result of critical accidents in handling fissionable materials and in conjunction with reactor accidents. Accordingly, this is an important industrial medical problem completely detached from nuclear warfare.

Historically and perhaps for clinical simplicity, the acute radiation syndrome which varies with the dose of radiation and time after exposure has been subdivided into the central nervous system syndrome (CNS), the gastrointestinal syndrome (GIS) and the hemopoietic syndrome (HS). For those interested in the former two syndromes, the reader is referred to the following references. [#s 1 – 6] For purpose of orientation, doses in excess of 2,000 rad may be capable of producing the central nervous system syndrome in man and doses between 500 and 2,000 will certainly produce a severe gastrointestinal syndrome. Doses less than 500 r will produce a severe intestinal syndrome and as the dose falls beneath 200 r the gastrointestinal symptomatology will be practically absent. Accordingly, from the foregoing broad-dose guide-lines one can predict the clinical picture and also predict mortality since there is no possibility of recovery from the CNS syndrome and we believe that doses capable of producing the severe GI syndrome are sufficient to produce 100 per cent mortality from the HS syndrome even when there has been satisfactory therapy of the former.[#4] For this paper, I shal concentrate upon the diagnosis of radiation injury primarily from a clinical standpoint with the assumption that dosimetric data is either absent or delayed.

Many years ago, a practical clinical classification of radiation injury was proposed.[#3] This classification consists

of three categories: (1) survival improbable; (2) survival possible; (3) survival probable.

Individuals in the survival *improbable group* will have prompt nausea, vomiting, and diarrhea that is intractable. Unless there is drastic fluid replacement, these individuals will die within a matter of a few days. Even with fluid replacement, they will yet experience the sequelae of bone marrow aplasia and pancytopenia and have 100 per cent mortality at a later date.

The *survival possible group* will consist of individuals in whom the nausea and vomiting is relatively brief, subsiding within a period of one or two days and followed by a period of well being. These individuals are suffering primarily from the hemopoietic syndrome and have a spontaneous statistical chance of survival that can be described by the classic sigmoid dose mortality curve. From data published earlier, it has been postulated that the most likely human LD50 is in the vicinity of 300 rads. Harris, from other methods of analyses, has considered the human LD50 to be in the vicinity of 700 rads.[#7] Patients in the survival possible group, after the subsidence of the initial symptoms, will show a typical series of changes developing in the peripheral blood characterized by progressive thrombo-cytopenia, granulocytopenia, and lymphopenia.

The survival probable group consists of individuals who have had either no initial symptoms or mild and fleeting ones disappearing within a few hours. Unless these individuals have sequelae of marrow depression, these patients will show no further subjective effects of irradiation and obviously constitute no therapeutic problem.

When the hematologic changes that are known to occur following irradiation develop in close temporal relationship to a known large exposure to ionizing radiation, the diagnosis of radiation injury is quite simple and straight forward. However, when the exposure is less or unsuspected, the diagnosis of radiation injury may be extremely difficult. A whole series of hematologic tests for the presence of radiation injury have been published. Ingram and Barnes[#8] have described an increased incidence of bilobed lymphocytes after small doses of radiation. A group of Swedish workers have proposed a complex statistical

analysis of the variance of leukocyte count around the mean in order to detect exposure in the range of a fraction of a roentgen. This is not a practical method. Bond *et al.*[#12] have described the change in the number of desoxyribonucleic acid (DNA) synthesizing cells that are present in the peripheral blood following irradiation in dogs and in the Y-12 irradiation casualties at Oak Ride.[#13] However, this procedure will have limited usefulness because of the long intervals from the time the blood smears are prepared until the film is exposed, developed, and stained in preparation for enumeration of the number of DNA synthesizing cells.

Another and perhaps more useful procedure in the intermediate dose range is the serial determination of the mitotic index of the bone marrow. The mitotic index of normal human bone marrow between the hours of 10 AM and 1 PM is approximately 9/1000 cells.[#14] The mitotic index was studied in the Y-12 casualties and was demonstrated that in the range of 50 – 200 rads there was a progressive decrease in the mitotic index. By the fourth day after exposure in the more heavily exposed individuals, the mitotic index was almost zero. Although the number of individuals was small, there was an apparent dose dependency of the depression. Thus it is believed that bone marrow aspirations performed promptly after an assumed exposure and at daily intervals for a period of 1 week would be most useful in detecting exposure to radiation in the 50 – 200 rad range. It is my belief that the mitotic index that approaches zero by the fourth day indicates exposure in the range of 200 rads or more, and that serious consequences may be anticipated. In addition to straight forward enumeration of the mitotic figures, qualitative changes are also evident. These changes consist of binucleated cells, mitotic bridges, fragments, stickiness and clubbing of the chromosomes which have been quantitated by Fliedner *et al.*[#15] and will be most useful.

It has been stated often by others that the blood count has relatively little prognostic value. Certainly in respect to the lymphocyte this is probably true since doses up to about 200 rad produce a maximum depression in the lymphocyte and further increases in dose do not depress this level further. However, the neutrophil count is extremely useful from a prognostic standpoint as has been demonstrated in dogs. There is a clearcut

difference in the rate of depression of the granulocyte at 100 per cent, 80 per cent, and 10 per cent mortality.[#16]

Another potential means of detecting the exposure to radiation in doses of the 50 – 200 r range is the excretion of beta aminoisobutyric acid (BAIBA). This was studied by Rubini *et al.*[#17] in the Y-12 patients and a significant increase in the excretion was observed.

More recently Thomas and Wald[#18] have tried to make a broader comparison of the blood counts in persons accidentally exposed to radiation. They attempted to reduce various parameters, such as the white cell count, platelet count, hematocrit *etc.*, to a common denominator by assigning "score values" to deviations to the normal. In this way, they arrived at "profiles of injury", on the basis of which five groups in different exposure levels (less than 150, 240 - 365, 400 – 600, 640 – 1350, and 9,200 rads) could be differentiated quite well six days after exposure. Even if only the cumulative scores for total white count are plotted, by day six patients who received more than 400 rads can be reasonably well distinguished from those who received less.

From the preceding it is seen that one can on clinical and laboratory grounds fairly well categorize patients into the relative degrees of radiation injury. This is the first step in the management of radiation injury.

Therapy

The cardinal rule in the management of radiation injury is to do nothing unless there are clear-cut clinical indications for a specific agent or maneuver. In reality, one is confronted with the treatment of a patient who presents the same problems as the management of any other patient with pancytopenia. However, the irradiated patient presents the additional challenge that the aplastic state of the bone marrow may be reversible. Thus, if the patient can be carried through the critical period, he may recover, in contrast to many cases of idiopathic or drug induced bone marrow aplasia.

From a purely clinical standpoint one would expect in the event of temporary supression [sic] of bone marrow that

antibiotics, sulfonamides, fresh blood transfusions and/or separated platelets would be effective in prolonging life during the critical period of depression and allow time for spontaneous regeneration of the bone marrow. Unfortunately, the literature is confused on the experimental value of the preceding therapy and there have been reports of actual increased mortality due to the above therapy that would appear clinically indicated. Accordingly, Sorensen *et al.*[#19] revaluated the efficacy of a flexible and individually adjusted antibiotic and transfusion therapy in irradiated dogs. Animals were paired into the treatment group and the control irradiation group. Therapy in the treatment group consisted of antibiotics, transfusions, and fluids. Antibiotic therapy with oxytetracycline was initiated as soon as an animal developed fever or had clinical evidence of infection and was continued until after the fever had subsided. When, in spite of this treatment, the temperature again rose, usually three to five days later, the animals were placed on penicillin and streptomycin. When this was no longer effective in controlling the infection, the dogs were switched to tetracycline. Erythromycin was also used occasionally. The doses were about three times on a per kilogram basis as ordinarily used in clinical medicine.

Blood transfusions were given mainly for keeping the platelet count above the critical level to prevent bleeding. Transfusions were usually started when the platelet count had been 5,000 or less per cubic millimeter for 24 hours. Blood was collected from donor dogs in a solution of EDTA and immediately transfused. Large transfusions were used to raise the hematocrit level and to minimize the probability of repetitive transfusions producing homologous sensitization to platelets. During the critical period, transfusions were given about every 72 hours, depending upon the platelet count. If the hematocrit count was high enough platelet rich plasma was given. Fluids were given as necessary to combat dehydration.

The control dogs developed fevers 7 – 17 days after exposure, with a mean of 11 days. Six of these dogs had cellulitis. Bleeding occurred on the 10-14 day. Nine of the controls died; the mean survival time was 16.2 days with a range from 12-22 days. Necropsies of these dogs showed hemorrhage and diffuse infection.

In the treated group, the survival rate at 400 r was 80 per cent. One dog died from infection on day 16 and one on day 26. Up to the time when treatment was initiated, the dogs in the therapy group showed a similar clinical picture to those in the control group. The survival time of the animals that died in all treated groups up to 550 r was significantly longer varying from 17-30 days in contrast to the 12-22 days in the control group. The mortality at 400 r was 20 per cent, 420 r 40 per cent, at 460 r 20 per cent, and 500 r 100 per cent, and 550 r 80 per cent, in the treated group. The probable effect of the combined antibiotic and transfusion therapy can be summarized schematically in FIGURE 1. [It may be found, as a photographic reproduction, following the transcript of the article proper.] In the lethal-dose range, it is believed that the LD50 of dogs would be shifted to the right from about 275 r to about 450 r leaving an almost vertical dose-mortality curve. This therapy does not seem to be of particular value beyond 500 r. Thomas *et al.*[#20] have shown in dogs that homologous marrow transplantations are successful rarely but only after very high doses of radiation. This leaves us with an unsatisfactory therapeutic vacuum between the highest dose level at which antibiotic and transfusion therapy is effective and the lowest exposure that depresses the immune response sufficiently to allow a homologous graft to take. It is probable that a similar gap exists in man also. In the event that one were to know precisely the dose of radiation and its probable mortality, one is confronted with the paradox that antibiotic and transfusion therapy will be ineffective and to make transplantation effective one would have to give additional radiation in order to depress the immune response. Furthermore, the number of human bone-marrow cells comparable to what is needed to protect dogs could not, in all probability, be obtained from a single human donor.

Therapeutic Outline

1. Do nothing without careful thought being first given to it. One has many hours and potentially days before therapy of any kind is required. If neutron exposure is involved, there is some urgency in obtaining a sample of blood for dosimetric purposes. Some estimate of the neutron dose can be derived from the sodium activation.

2. Do a meticulous history and physical examination with special reference to prior chronic infections. Attempt to obtain some estimate of dose involved from the health physicist.
3. Notify responsible authorities including medical, administrative and health physics authorities.
4. Give nothing to the patient, unless it is indicated clinically. Even after doses of the order of 200 r, patients have recovered spontaneously without any treatment at all.[#21] Follow closely the peripheral, granulocyte, lymphocyte, platelet counts and hematocrit.
5. Hospitalize the individuals as rapidly as reasonable until the degree of exposure has been ascertained. Observe the patient closely. The best nursing care and asepsis with all procedures is mandatory. If it is ascertained that the exposure has been in excess of 200 r or the patients conform to the *survival possible* group, reverse isolation should be instituted promptly in order to prevent the introduction of pathogens to the patient.
6. Watch fluid and electrocyte balance closely and correct as necessary with the appropriate solutions.
7. If signs of infection develop, give antibiotics in large doses. Do not give antibiotics prophylactically. It is recommended that antibiotic doses be three times those that are normally utilized. If the temperature is not controlled with the antibiotic employed, switch to another antibiotic immediately. If the temperature rises again, switch to still another antibiotic. The choice of antibiotic of course will, in part, be determined by bacterial cultures but do not wait for the sensitivities to be determined, since overwhelming infection can progress pretty rapidly in the pancytopenic state. Use oral antifungal antibiotics when giving broad-spectrum antibiotics. Do not forget sulfonamides.
8. Watch the platelet count carefully and when it approaches zero observe the patient for signs of bleeding. Watch for the presence of hematuria, cutaneous petechiae, or retinal bleeding. If there is any indication of bleeding give platelets in a single transfusion in amounts equivalent to that found in approximately 1/3 of the blood volume of the patient. The blood must be fresh (less than four hours

old). Follow the patient closely and retransfuse as indicated by the clinical picture. After high doses of radiation, several massive transfusions at three-to five-day intervals may be necessary.

9. Do not use red cells unless indicated by the hematocrit. Do not overload the circulation. Give fresh blood if the hematocrit is low; if platelets alone are needed, and the hematocrit is normal, give platelet-rich plasma instead of whole blood.

It is important to note that after even fairly high doses of radiation therapy may not be necessary. Thus, unless signs of hemorrhage or infection, or extreme depression of the peripheral counts appear, no treatment is needed or indicated. It should be noted that in the Marshallese exposed to high sublethal doses of radiation from fallout, and in the five individuals exposed to neutrons and gamma radiation in the industrial accident at Oak Ridge, no treatment was indicated or required, and recovery was complete. In these individuals, peripheral blood-count depression was severe, and in the Oak Ridge accident, some loss of hair and some evidence of bleeding were noted in these individuals.

The prophylactic use of antibiotics has been recommended by others however, it is felt that this is definitely contraindicated because this may result in unnecessary development of resistant bacteria within the host.

If the dose of radiation is very high, in excess of 500 r, or if the individuals are deteriorating with a very rapid decline in the granulocyte count and platelet count, one must consider homologous bone-marrow transplants. However this will be covered by others at this Conference and the techniques of homologous transplant will not be discussed. However, the selection of individuals for homotransplantation of bone marrow is a difficult one. Certainly if the dose of radiation is ascertained to definitely be in excess of 600 rads one should go ahead and proceed with homologous transfusion of bone marrow. However, as discussed earlier, one can not be very enthusiastic about homologous transfusions of bone marrow because of two pertinent reasons. First, in animals the dose of radiation must be very high in order to obtain a “take” and second, the number

of cells required to protect dogs is so large that a comparable amount could scarcely be obtained from a single human donor.

Let us now assume that an individual has recovered from the acute exposure to radiation and is convalescing. It is now common knowledge to the lay public that the probability of getting leukemia after exposure to radiation is increased. This has become a major consideration and worry in all of the individuals who have been exposed and recovered from substantial doses of radiation. From the work done at the Atomic Bomb Casualty Commission and analyzed elsewhere,[#22 – 25] one can conclude that the probability of leukemia developing is about one to two cases per 10^6 population at risk per year for 10-15 years after exposure. Problems of compensation will unquestionably arise but these are legal and not medical problems. Bond has computed the probability that leukemia developing in an exposed individual was due to the prior exposure to radiation[#26] and his computations are significant. If one assumes that the above incidence induced by radiation is accurate and applicable to all exposure (acute, chronic, intermittent, etc.) one can make perhaps the most pessimistic estimate of what might result from radiation exposure. These figures can be used "to calculate the probability that a given case of leukemia has resulted from a known or alleged exposure." As an example, one can take a case of leukemia in a 30-year-old man exposed previously to 10 r. The natural incidence of leukemia at this age is about 25 cases per million per year. Applying Lewis' figures literally, 10 r may result in 20 leukemias per million per year, or this man's chances of getting leukemia in any one year from his 10 rads are approximately 20 in a million for the first few years following exposure. His total chances are 20 + 25, or approximately 45 per million per year, and the chances that the 10 rad are responsible for his leukemia are approximately 20 out of 45. Because of increasing natural incidence of leukemia with age, the chances of the 10 rad being responsible are approximately 20 out of 54 if he develops leukemia at age 40, 20 out of 169 at age 60, and 20 out of 296 at age 70.

References

1. Gerstner, H. B. 1958. Acute radiation syndrome in man. Military and Civil Defense Aspects. U. S. Armed Forces Med. J. **9**: 313-354.
2. Cronkite, E. P. & V. P. Bond. 1960. Radiation Injury in Man. Charles C Thomas. Springfield, Ill.
3. Cronkite, E. P. 1951. Diagnosis, prognosis, and treatment of radiation injuries produced by atomic bombs. Radiology. **56**: 661-668.
4. Conard, R. A., E. P. Cronkite, G. Brecher & C. P. A. Strome. 1956. Experimental therapy of the gastrointestinal syndrome produced by lethal doses of ionizing radiation. J. Applied Physiol. **9**: 227-233.
5. Brecher, G., E. P. Cronkite, R. A. Conard & W. W. Smith. 1958. Gastric lesions in experimental animals following single exposure to ionizing radiation. Am. J. Pathol. **34**: 105-119.
6. Quastler, H. 1956. The nature of intestinal radiation death. Radiation Research. **4**: 303-320.
7. Cronkite, E. P. & V. P. Bond. 1960. Diagnosis of radiation injury: An analysis of the human lethal dose of radiation. U. S. Armed Forces Med. J. **11**: 249-260.
8. Ingram, M. & S. W. Barnes. 1951. Experimental confirmation of previously reported unusual findings in blood of cyclotron workers. Science. **113**: 32-34.
9. Helde, M. & T. Wahlberg. 1953. Some observations on relation between radiation dose measures and blood changes. Acta Radiol. **40**: 435-442.
10. Helde, M. & T. Wahlberg. 1954. On inconsistencies between radiohematologic observations. Acta Radiol. **42**: 75-80.
11. Helde, M., T. Wahlberg, A. Fosberg, B. Swedin, C. J. Clemedson & A. Nelson. 1958. Radiation dose measurements in leukocyte counts in rabbits. Acta Radiol. **50**: 477-489.
12. Bond, V. P., T. M. Fliedner, E. P. Cronkite & G. Andrews. 1961. Desoxyribomic; eoc acid synthesizing cells in the blood of man and dogs exposed to total body radiation. J. Lab. Clin. Med. **57**: 711-717.
13. Brucer, M., Ed. 1959. The Acute Radiation Syndrome. A Medical Report on the Y-12 Accident. June 16, 1958, Oak Ridge Institute of Nuclear Studies, U. S. Atomic Energy Commision, ORINS-25.
14. Fliedner, T. M., E. P. Cronkite, V. P. Bond, J. R. Rubini & G. Andrews. 1959. The mitotic index of human bone marrow in

healthy individuals and irradiated human beings. Acta Hematol. **22**: 65-68.

15. Fliedner, T. M., E. P. Cronkite, G. Andrews & V. P. Bond. The diagnostic and prognostic value of bone marrow examinations after ionizing radiation (To be published.)
16. Cronkite, E. P. & G. Brecher. 1955. The protective effect of granulocytes in radiation injury. Ann. N. Y. Acad. Sci. **59**: 815-833.
17. Rubini, J. R., E. P. Cronkite, V. P. Bond & T. M. Fliedner. 1959. Urinary excretion of beta aminoisobutyric acid (BAIBA) in irradiated human beings. Proc. Soc. Exptl. Biol. Med. **100**: 130-133.
18. Thoma, G. E. & N. Wald. 1959. The diagnosis and management of accidental radiation injury. J. Occupational Med. **1**: 421-447.
19. Sorensen, D. K., V. P. Bond, E. P. Cronkite & V. Perman. 1960. An effective therapeutic regimen for the hemopoietic phase of the acute radiation syndrome in dogs. Radiation Research. **13**: 669-685.
20. Thomas, E. D., C. A. Ashley, H. L. Lochte, A. Jaretzki, O. D. Sahler & J. W. Ferrebee. 1959. Homographs of bone marrow in dogs after lethal whole body radiation. Blood. **14**: 720-736.
21. Cronkite, E. P., V. P. Bond & C. L. Dunham. Some Effects of Ionizing Radiation on Human Beings. A report on the Marshallese and Americans accidentally exposed to radiation from fallout. TID 5358, Supt. Documents U. S. Govt. Printing Office. Washington, D. C.
22. Cronkite, E. P., W. C. Moloney & V. P. Bond. 1960. Radiation leukemogenesis: an analysis of the problem. Am. J. Med. **28**: 673-682.
23. Moloney, W. C. & M. A. Kastenbaum. 1955. Leukemogenic effects of ionizing radiation on atomic bomb survivors in Hiroshima City. Science. **121**: 308-309.
24. Wald, N. 1958. Leukemia in Hiroshima City atomic bomb survivors. Science. **127**: 699-700.
25. Heyssel, R., A. B. Brill, L. A. Woodbury, E. T. Nishimura, T. Ghose, T. Hoshino & M. Yamasaki. 1960. Leukemia in Hiroshima atomic bomb survivors. Blood. **15**: 313-331.
26. Bond, V. P. 1959. The medical effects of radiation. Proc. Natl. Assoc. Claimants Compensation Attorneys.

SEQUENTIAL MANIFESTATIONS OF ACUTE RADIATION INJURY VS. "ACUTE RADIATION SYNDROME" STEREOTYPE

M. Ingram, J. W. Howland, C. H. Hansen, Jr. [Footnote: Present address: Armed Forces Radiobiology Research Institute, National Naval Medical Center, Bethesda, Md.]

University of Rochester Medical Center, Rochester, N. Y.

These comments are concerned with some aspects of the acute radiation injury problem that appear to deserve additional emphasis. The comments are greatly influenced by our experiences at Rochester with the Lockport Incident, and especially with problems that have arisen in the clinical management of the most seriously injured casualty. A description of the incident, as well as a summary of some of the later clinical observations, have already been published and are reviewed only in abbreviated form in the present report.[#1,2]

The Lockport Incident refers to accidental X-ray exposures received by nine civilian radar technicians working at an Air Force radar station, part of the SAGE network, in Lockport, New York, near Niagara Falls, in March, 1960. A newly installed klystron tub, which serves as a voltage amplifier for the radar transmitter, failed to function properly when voltage was applied, and the exposed men were engaged in a troubleshooting operation.

The klystron tub has a copper anode approximately 14 inches long surrounded by a stainless steel shell through which water is circulated for cooling. The radiation is pulsed at approximately 250 cycles per second; pulse width six to eight μ-seconds; "on" time approximately 7.2 seconds per hour. The assembly is shielded with lead sufficient to reduce the X-radiation to MPE levels and a sign on the permanent shielding cautions the operators that it is dangerous to operate the tube with the shielding removed because of the radiation hazard. The upper portion of the shield, a lead cap covering the anode, weighs about 950 pounds and can be removed when it is necessary to make repairs or replace the tube.

During the trouble-shooting operation, both the cap and the permanent shielding were removed for easier access to the tub and its tuning mechanism. The men assumed, quite erroneously, that if the tube produced no radio frequency, neither did it produce X-rays. Exposures were sustained over a period of approximately two hours while the men took turns making adjustments on the tube, reading the service manual aloud to the manipulators, or observing each other during attempts to find and correct the trouble. During this time, the tube was operated at about 60 per cent of full voltage, producing X-rays of about 150 KeV; average current about 90 mA.

The most seriously injured men worked closed [sic] to the tube, sometimes at its face, one of the men sustaining a small thermal burn on one arm where it touched the hot tube. The less seriously exposed men looked on for only a few minutes. As the men worked farther from the tube face, they were exposed to lower doses, but these doses were delivered to a larger part of the body. Most of the uncertainty in dosage estimates reflects difficulty in determining, several days after the exposures, how much time each man had spent at various positions relative to the tube, whether he was bending over the anode, sitting or standing when reading the service manual, and so forth.

Symptoms appeared during exposure in the casualty in question, the first symptom being severe headache soon followed by nausea and vomiting. This man left work for home, stopping en route at the U. S. A. F. dispensary at Niagara Falls, New York. When the dispensary medical officer made a telephone check with the Lockport radar station, he was advised that preliminary measurements made with a survey meter in the tower in question indicated that the dose rate had not exceeded 250 mr per hour near the unshielded anode. Since this dose rate was incompatible with the appearance of symptoms of acute radiation injury after exposure for not more than two hours, it was concluded that the etiology of the illness was something other than exposure to ionizing radiation. Subsequently it was found that the GM-type dose-rate meter, which had a maximum range of 5 r/hr., was paralyzed by the intense bursts of radiation delivered during μ-second intervals. Furthermore, it had not been calibrated for 150 KeV radiation. Definitive dosimetry, using a prototype tub at Schenectady, New York, operated under conditions simulating

those in the Lockport tower, indicated that the dose-rate at a distance of 20 cm. from the anode was approximately 500 x 10^{-6} r per μ-second or 50.4 r per minute of exposure. Present best estimates of exposure dose for the most seriously injured man are approximately 300 r to the trunk and at least 1,500 r to the head.

Since the time of exposure, the casualty in question has shown a continuing series of clinical changes. Although for the sake of brevity, these are listed without associated discussion; it will be apparent from the list that they included symptoms referable to the central nervous system, vascular system, gastrointestinal system, hematopoietic system, skin, eyes and testes. TABLES 1 and 2 indicate the protracted nature of the symptomatology in this man. [They may be found following the transcript of the article proper.]

Aspects of the acute radiation injury problem that I would emphasize may be summarized as follows:

1. Radiation workers are unlikely to receive uniform whole-body exposure to homogenous radiation. Indeed, papers presented at these meetings testify that it is difficult to effect such exposures even when one deliberately attempts to do so in larger experimental animals and in therapeutic irradiation. Marked variation in doses absorbed by various body regions have been characteristic of the majority of radiation accidents. This characteristic of accidental exposures has important therapeutic implications. In the case described in the present discussion, for example, the high probability that marrow bearing areas in the legs, at least, had received a relatively small dose was not only an encouraging prognostic sign; it was also a contraindication to marrow transplantation.
2. Those of us who occasionally lecture to students and participate in writing didactic reports about acute radiation injury find it convenient to describe the clinical picture as a relatively stereotyped sequence of three predominant phases, usually referred to as central nervous system, gastrointestinal and hematopoietic. This generalization provides a useful pattern with which to compare observations from experiments or clinical studies

and it is a helpful teaching aid. Most of us, however, have some tendency to become convinced rather readily by our own words, especially when they repeatedly express an idea publicly. This characteristic renders one susceptible to accepting, somewhat too readily, an oversimplification of the clinical picture in acute radiation injuries. Although clinical responses of patients receiving whole-body therapeutic irradiation may be expected to conform reasonably well to the classical descriptions of whole-body exposure to large radiation doses, the clinical course after accidental exposures is far less likely to fit a pattern predicted from observations on uniform whole-body exposures. The appearance of symptoms attributed to central nervous system injury in the Lockport Incident casualty is a good example of this.

3. Acute radiation injury may give rise to a long, uninterrupted sequence of clinical manifestations of the injury, as in the case described. These may have important implications in therapy and they are of central importance in a patient's emotional adjustment, as in his physical adjustment, to his injury.
4. A vast amount of confusion has arisen because of our failure to emphasize sufficiently the differences between treatment of acute radiation injury under conditions yielding mass casualties, namely in military medicine and civilian defense, and treatment of relatively few casualties from occupational exposures under peacetime conditions.

Treatment of radiation injury under conditions of civilian disaster or military combat requires a special approach. It is likely to be necessary to employ triage, for example, and to make prompt and early decisions about the prognosis and the use of medical supplies in individual cases. Thomas and the group at Cooperstown and other investigators using whole-body irradiation as preparation for organ transplantation have shown that even severely ill patients can tolerate surprisingly large exposures if appropriate highly skilled medical supervision and elaborate special facilities are available. In handling mass casualties, however, it is clearly impossible to make such facilities available for each individual. The two kinds of situations call

for the use of different diagnostic criteria, different therapeutic measures, different attitudes, difference facilities, supplies and so forth. I should like to recommend that problems arising from these differences are, *per se*, sufficiently important to everyone to deserve a thorough review and that a review or study conference be held specifically for this purpose.

Acknowledgment

This report is based on work performed under contract with the U. S. Atomic Energy Commission at the Atomic Energy Project, University of Rochester Medical Center, Rochester, New York.

References

1. HOWLAND, J. W., M. INGRAM, M. MERMAGEN & C. L. HANSEN. 1961. Diagnosis and treatment of acute radiation injury. W. H. O. Geneva. Pp. 11-26.
2. INGRAM, M., J. W. HOWLAND, C. L. HANSEN & C. R. ANGEL. 1962. Influence of and Treatment of Acute Radiation Injury. W. H. O. Geneva. Pp. 11-26.

TABLE 1

EARLIER MANIFESTATIONS OF INJURY AFTER ACCIDENTAL X-IRRADIATION

Time after exposure	Major manifestations of radiation injury
1-2 days	Headache, nausea, vomiting, thirst, irritability, fatigue, restlessness, tinnitus, chill, sialitis, temporomandibular joint pain, conjunctivitis, erythema and edema (face and shoulders), photophobia.
3-7 days	Morning nausea, weakness, erythema, fatigue, severe lymphopenia, decreasing leukocyte count.
2nd wk.	Erythema, onset of epilation, morning nausea, fatigue, glossitis, vesicular stomatitis, falling leukocyte and platelet counts.
3rd wk.	Erythema, epilation, morning nausea, fatigue, falling leukocyte and platelet counts.
4th wk.	Maximal leukopenia (minimal value ~ 1300/mm.^{3}) and thrombocytopenia (minimal value ~ 35,000/mm.^{3}), few small petechial showers, erythema and edema of right axillary skin, few vesicular oral lesions.
5th and 6th wk.	Conjunctivitis, episcleritis (right), afternoon temperatures slightly above usual levels (not febrile), leukopenia and thrombocytopenia.
7th and 8th wk.	Acute febrile illness, diffuse encephalopathy without localizing signs or meningeal signs, (tinnitus, changing parasthesias of arms and face, ataxia, somnolence without delerium [sic], depression, diffusely abnormal EEG), severe exacerbation of facial and conjunctival edema.

TABLE 2

MANIFESTATIONS OF INJURY BEGINNING OR RECURRING TWO MONTHS OR MORE AFTER ACCIDENTAL X-RAY EXPOSURE

Time after exposure	Major manifestations of injury
3 mo.	Transiently increased tinnitus.
3 mo.	Severe lymphedema of right arm.
3 mo.	Hyperesthesia, right arm and face.
5 mo.	Acute chorioretinitis, right > left (exudates, hemorrhages).
5 mo.	Increased irritability, poor sleep, right temporomandibular joint pain, eye

	discomfort on lateral gaze, gait slightly ataxic when pupils dilated for eye exam.
6 mo.	Transient albuminuria without N retention.
6 mo. (first noted)	Transient aspermia.
9 mo.	Severely decreased visual acuity, right.
10 mo.	Further loss of scalp hair (right), eyebrows and lashes, frequent morning nosebleeds (mild), markedly decreased lachrymation.
20 mo.	Cataract, right lens.
24 mo.	Cataract, left lens.

CLOSING REMARKS FOR SESSION ON TREATMENT OF RADIATION INJURY IN MAN

F. Stohlman, Jr.

St. Elizabeth's Hospital, Brighton, Mass.

There appears to be no wide difference in the approach to the treatment of acute whole-body radiation injury. Initially, treatment should be conservative. If this appears ineffective, bone-marrow transplantation may be considered. There is no great urgency in man, however, in administering bone marrow. From the early studies in rodents one would have thought that bone marrow, to be effective, should be given during the first several days after radiation, but as Mathé's studies suggest, in man transplantation even as late as three or four weeks may prove successful. This permits a greater latitude in evaluating the patient and the effect of conservative treatment. I think it should be emphasized, however, that the dose-range in which bone-marrow infusion may be helpful if [sic] quite narrow. It should also be emphasized that in considering bone-marrow transplantation, there is a risk associated with the collection of large amounts of bone marrow from normal human beings. This problem in the future may be circumvented by using stored marrow obtained at necropsy.