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HEMATOLOGICAL STUDIES ON PATIENTS TREATED BY TOTAL BODY EXPOSURE TO X-RAYS

by

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CORNELIUS A. TOBIAS
BIOLOGICAL EFFECTS OF RADIATION

Argonne National Laboratory

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HEMATOLOGICAL STUDIES ON PATIENTS TREATED BY TOTAL BODY EXPOSURE TO X-RAYS

By Bertram V. A. Low-Beer, M.D., and Robert S. Stone, M.D.

INTRODUCTION

The development of chain reacting nuclear power piles with the intense radiations from the fission process and from the fission products brought about the possibility of the accidental or necessary exposure of the entire body of persons to x-rays, gamma rays, and neutrons to an extent never before thought possible. The health division of the Metallurgical Project was faced with the problem of what changes would occur in individuals exposed to more than the "tolerance dose" of 0.1 roentgens, on one or more days. It was thought that the blood picture of such individuals would show a rapid and radical change. The literature, however, contained very little information on the effect of x-ray exposure on persons with relatively normal hematological pictures, and such investigations as were reported were rather confusing because of the objectives of the studies. Hence, it was considered necessary to study the effects of "total body irradiation" with x-rays of varying energy on hematologically normal individuals.

Selection of Subjects

Patients with disease requiring therapeutic irradiation of the entire body were selected for observation in this study. The patients for total body irradiation were selected by physicians on the staff of the University of California Hospital, having no connection with the Manhattan Project and the treatments were administered as part of the normal therapy of these patients. Advantage was taken of the fact that patients were receiving such treatments by making numerous blood studies on them for the Manhattan Project.

The patients with metastatic carcinoma and lymphoma were in the first group studied. They were observed for short periods only because of the probability of their advancing disease causing blood changes unrelated to the exposure to x-rays.

Twenty-nine patients treated between October 1942 and June 1946 have been followed for varying periods of time. Thirteen were women and sixteen were men. The ages ranged from twenty to seventy-five years, as shown in Table 1.

Method of Treatment

The patients were placed in such a position that the whole body was exposed in the one x-ray beam at each session. The anterior surface of the patient faced the x-ray tube one treatment day and the posterior surface the next. The dose in roentgens was measured by a thimble chamber on the skin in the center of the field. Thus the doses referred to in this report are always roentgens on the skin, including backscatter. All

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patients except three received equal fractional amounts at each treatment. The daily exposures were approximately 5, 10, 15, 20, 30, or 50 roentgens and the total exposures ranged around either 100 or 300 roentgens.

The sum of all daily exposures, regardless of which surface was exposed, is called the "total body exposure." This method of summation is not the usual way of describing radiation therapy but it is used here because in occupational exposure with the individuals moving about, no one surface is exposed continuously. From measurements in a given area one could know the total radiation to which a person working in that area was exposed. However, the amount of radiation received by any part of the body surface could not be determined.

The depth dose at ten centimeters in the center of the beam was measured by means of a phantom for each quality of radiation used. The summation of the calculated tissue doses at a depth of ten centimeters is called the "whole body dose." This indicates more accurately the amount of energy absorbed per cubic centimeter throughout the whole body than does the summation of the doses on the surfaces.

Three qualities of x-rays were used, those produced by electric potentials of 100, 200, and 1000 kilovolts. The 100 kv x-rays were produced in a Macklett tube in a Picker oil-cooled, shockproof, 120 kv tube head, activated by a Kelley-Koett 100 kv constant potential generator. The only filtration used was that inherent in the tube and tube head. The 200 kv x-rays were produced by a 200 kv constant potential current from a Kelley-Koett generator passing through a Macklett tube in a Picker oil-cooled shockproof 220 kv housing. The inherent filtration was that of the tube and casing and is said to be equivalent to about 0.25 mm of copper. The added filter was 5 mm aluminum. The 1000 kv x-rays were produced by the Sloan high-frequency generator. The inherent filter was 0.8 mm Cu + 3.2 mm Fe. The added filter was 2.2 mm Pb + 0.6 mm Sn + 1.0 mm Cu + 1.5 mm Al. The pertinent physical factors for each quality of radiation are shown in Table 2.

Three patients were treated with 100 kv x-rays in the beginning, but were transferred to the 200 kv apparatus for the major portion of their treatments. One of these patients (No. 7) received total body irradiation exclusively, one (No. 4) received local irradiation to specific lesions one month after receiving total body irradiation, and one (No. 5) received local irradiation 15 and 19 months, respectively, after the conclusion of total body irradiation.

Ten patients were treated with 200 kv x-rays. Five of them (Nos. 9 to 13) received total body irradiation exclusively. Three had been treated to local areas before the total body exposures, one 5 months (No. 3), one 6 months (No. 2), and one 22 months (No. 8) before. Two had been treated to local areas before, and were so treated again after the total-body exposures, (Cases 1 and 6, Table 3).

Twelve patients were treated with 1000 kv x-rays. Eight of these (Nos. 18 to 25) received total body irradiation exclusively. One had received local irradiation three months before (No. 15); one had received local irradiation twelve months before and was given more two months after (No. 14); two received local irradiation 6 months (No. 17) and

3003935

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8 months (No. 16), respectively, after the total body x-ray treatment.

Four patients were treated with both 1000 kv and 200 kv x-rays (Nos. 26 to 29). Two of these (Nos. 26 and 27) received only 3 and 4 treatments, respectively, on 200 kv. This was necessary because of breakdowns of equipment. It should be mentioned that the tissue dose at 10 cm depth differs by only 2 per cent between the 1000 and the 200 kv x-rays under the above conditions.

Table 3 shows the treatment data and period of observation for each of the patients. The total body exposure does not always equal the dose per day multiplied by the number of exposures. The reason for this discrepancy is that while the aim was to give a set dose per day, the actual amount given varied a little above or below the intended dose. The total-body exposure is the accurate figure.

The longest period of observation (Nos. 9 to 11) was approximately 3 years. The shortest period was 21 days, which was only 4 days longer than the treatment period. One patient (No. 25) did not return after the second treatment. Nine of the patients are still being followed and the results of further observations will be reported at a later date.

Methods of Hematological Studies

On all patients initial hematological studies were made before the first exposure to radiation. It would have been much more satisfactory to have had several blood studies over a period of several days before starting treatment but this was not attained in our clinics. Diurnal fluctuations were avoided by taking the blood samples in the morning whenever possible. During the first three to six days of treatment blood counts were made, one, three, and six hours after treatment. When the treatments continued more than one week, the number of blood counts was reduced to two on each treatment day, one immediately before and one an hour after exposure. After completion of the course of treatment an attempt was made to obtain blood counts two or three times a week for two weeks, then once a week for four weeks, then once every two weeks for the ensuing eight weeks, then once every four weeks during the entire period of observation. Many patients did not keep all of their appointments. During the treatment period each patient was instructed to remain on his regular diet and to take the normal amount of fluid.

The blood samples were taken from the lobe of the ear, and the following laboratory procedures were performed by the methods described.

Hemoglobin Determinations - The Sahli method was used and the grams per cent calculated on the basis that 100 per cent equal 14.5 gm hemoglobin per 100 cc of blood. Three specimens were taken, two were measured. If the variation was greater than 2 per cent, the third specimen was measured and the average of the two readings varying the least from one another was used as the final reading.

Red Blood Cell Counts - Rees-Ecker solution was used for the first tests, but Hayem's solution was used for most of the dilutions. Three samples of blood were taken. The red blood cells from two samples were counted in "Spencer bright line" counting chambers, counting five of the

3003936

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0.04 sq mm areas. The findings of these two counts were averaged. If each of the two counts deviated less than 5 per cent from the mean, then this mean value was used as the number of erythrocytes per cubic millimeter. If the deviation was greater than 5 per cent from the mean, then the third specimen was counted and the two which varied least from one another were used, provided neither varied more than 5 per cent from the mean. If no two counts fell within 5 per cent of the mean, all three specimens were counted and the average of the three counts were used. If the mean of one combination of two counts differed by more than 5 per cent from the mean value of the other combinations of two counts, then all three specimens were discarded and fresh ones taken.

White Blood Cell Count - Turck's diluting solution was used. Four 1 mm square areas were counted. In all other respects the procedures for taking samples and evaluating the counts were the same as described for the red blood cell count.

Platelet Count - Rees-Ecker diluting solution was used. The platelets were counted in a "Spencer bright line" counting chamber. The platelets in one 1 mm square area were counted for each specimen. The evaluation of the platelet counts of each of the samples was the same as stated for the red and white blood cell count.

The pipettes and counting chambers used were certified by the National Bureau of Standards.

Differential Leukocyte Count - Smears were made on cover glasses and stained with Wright-Giemsa stain. One thousand cells were counted. The results were recorded in percentage of cells observed and then translated into "absolute counts" on the basis of the total white blood cell count.

In nine patients the lobation of the nucleus of the polymorphonuclear neutrophilic leukocytes was studied by the Cooke and Ponder modification of Hargraves' method. In accordance with this method the total number of lobes per 100 neutrophilic leukocytes was counted and the resulting figure was designated the "lobation index." For greater accuracy, when the differential leukocyte count showed 70 per cent or more neutrophilic leukocytes the number of lobes in 400 cells was counted, but when the differential leukocyte count showed 69 per cent or less neutrophilic leukocytes, only 300 were studied. The number of one-lobed, two-lobed, three-lobed, etc., neutrophilic leukocytes seen were recorded.

Sternal Marrow Studies - The specimens were obtained by the needle puncture method and smears were made on cover glasses. The smears were stained with Wright-Giemsa stain and differential cell counts were made on two smears from each patient. At least two hundred cells were counted for each differential count. On four patients these studies were made both prior to and some months after treatment. On five other patients, only one sternal marrow study was made of each and it was done several months after the end of treatment.

Prothrombin Concentration was determined by Quick's method in eleven patients. In two patients determinations were made prior to and shortly after the end of the course of treatment, but in nine patients the determinations were made only after the end of treatment.

3003937

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Sedimentation Rate was determined by Wintrobe's method in fifteen patients both prior to the beginning of and after the conclusion of treatment.

Packed Red Corpuscle Volume was determined by Wintrobe's method on eighteen patients before and after treatment.

Icteric Index determinations were made on eighteen patients both before and after treatment.

RESULTS

The charts and graphs of sixteen of the twenty-nine patients treated are reproduced (Figs. 1A and B to 16A and B). These show the numbers of the principal blood cells and of the grams per cent of the hemoglobin throughout the experiment. The lobation index of the neutrophilic leukocytes is included when known. These sixteen charts were selected as the most complete.

Although 29 patients were treated in this series, only 26 had a sufficient number of blood counts to be of value in an analysis of the hematological response to total-body x-ray exposure.

In the absence of reliable statistical data concerning the range of normal fluctuation in the hemoglobin content, erythrocyte count, and absolute numbers of the various leukocytes, we have considered the following variations from the pre-treatment values as significant: for the hemoglobin content and the number of red blood cells-15 per cent, for the total number of white blood cells, of polymorphonuclear neutrophilic leukocytes, and of lymphocytes-40 per cent; and for the number of monocytes-100 per cent.

From a study of the charts and graphs it is evident that the deviations of any of the factors studied at the 1, 3, and 6 hour intervals after each treatment were neither consistent nor significant.

Comparisons of the effect of different individual doses are difficult because of the small number of patients observed in each group. However, one fact stands out. Patients who received individual doses of 15 r or 20 r showed a significant decrease in the number of lymphocytes after a total of 40 r had been given. On the other hand, patients who received individual doses of 5 r or 10 r showed no such decrease after a total of 40 r had been given. However, in all cases there was a significant decrease in the number of lymphocytes by the end of the treatment period. No such consistent change was observed in the number of the other white blood cells at this time, although variations from the pre-treatment values occurred. Patients who received treatment with x-rays generated by either 100 kv, or partly by 100 kv and partly by 200 kv showed a less marked tendency toward deviations in the number of the white blood cells during and at the end of the treatment, even though they received total doses of 300 r.

At approximately 30 days after conclusion of treatment all patients who received a total of 300 r, with x-rays generated by 1000 or 200 kv, or partly by 1000 and partly by 200 kv, showed a significant but temporary decrease in the number of all blood cells, while those patients

3003938

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who received total doses of only 100 r with 1000 kv x-rays showed significant deviations of only the number of white blood cells. At approximately 60 days after conclusion of treatment there was again a significant decrease in the number of white blood cells. The decrease which occurred at 60 days after conclusion of treatment was in turn followed by recovery to pre-treatment values. In general, however, the recovery of the number of lymphocytes lagged behind that of the other white blood cells.

Significant variations in the number of the different types of white blood cells were observed at various times later than 60 days after the end of treatment. The approximate times at which these were observed are shown in Table 4.

The effect on the lobation index was studied in 9 cases. The patients received varying individual and total doses. A decrease in the number of lobes per 100 cells occurred in eight of these patients at approximately the twentieth day following onset of treatment. In one instance the decrease was first noted on the fiftieth day following onset of treatment. This change persisted for varying periods of time and occurred irrespective of upward or downward deviations in the number of polymorphonuclear neutrophilic leukocytes. It extended into the post-treatment period.

A significant decrease in the number of erythrocytes and in the grams per cent of hemoglobin was observed in some of the patients during the course of treatment. A recovery to or even above the pretreatment values was observed in these patients toward the end of, or shortly after conclusion of the treatments. In some of the patients marked changes occurred in the number of erythrocytes and in the hemoglobin concentration at approximately 100 days after conclusion of treatment, in others at any time from 100 to 600 days. These changes consisted of a decrease in the number of erythrocytes accompanied by a rise in the concentration of the hemoglobin and an increase in the packed cell volume of the red blood cells. This is the blood picture of a macrocytic anemia. A return to the pre-treatment values of both the number of erythrocytes and the hemoglobin concentration was observed in all patients. The changes that were observed in the number of erythrocytes and in the concentration of hemoglobin during and after the course of treatments could not be correlated with the quality, the individual fractions, or the total amount of radiation given.

The platelet count did not change significantly during or after treatment in any of the patients.

The sternal marrow studies which were made on 9 of the patients revealed no abnormalities. However, these studies cannot be considered as adequate because they were made both before and after treatment on only 2 patients. On the other 7 patients they were made only after treatment.

The prothrombin concentration did not deviate beyond the normal limits in the 11 patients for whom it was determined.

The sedimentation rate of the erythrocytes was determined on 15 patients. No significant deviations from the pre-treatment values were observed at any time.

No changes were observed in the icteric index of the 18 patients for whom it was determined before and after treatment.

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SUMMARY

1. Hematological studies were made on 29 patients who were treated by exposing their whole bodies to x-rays generated by 100, 200, or 1000 kv. Twenty-six of them were observed for sufficiently long periods of time to be of use in this study.

2. Significant changes in the number of blood cells were observed in all of the patients and some of these changes appear to be relatively constant.

3. The most consistent change was a decrease in the absolute number of lymphocytes following treatment, irrespective of the size of the dose and the physical factors of treatment. This decrease was followed by a return to normal in the post-treatment period.

4. A decrease in the number of nuclear lobes per 100 neutrophils was a consistent finding in the 9 patients for whom the lobation index was studied.

5. The number of monocytes varied greatly as a result of exposure to radiation, but always returned to normal. The most frequent change was a large increase in numbers during the course of treatment.

6. After the conclusion of treatment, frequently near the 30th and 60th days, significant deviations in the total white blood cell count and in the counts of the separate types of leukocytes were observed at intervals varying most often between 150 to 300 days, and in some patients as late as 680 days.

7. The erythrocyte counts and the concentration of the hemoglobin occasionally showed a decrease during the course of treatment, followed by a recovery to pre-irradiation levels in the early post-treatment period. In the late post-treatment period a temporary macrocytic hyperchromic anemia was observed in many patients.

No changes in prothrombin concentration, sedimentation rate, icteric index, or platelet count of any of the patients was observed.

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