

ADS

ACCIDENTAL RADIATION EXCURSION AT THE OAK RIDGE Y-12 PLANT*—IV

PRELIMINARY REPORT ON CLINICAL AND LABORATORY EFFECTS IN THE IRRADIATED EMPLOYEES

G. A. ANDREWS, B. W. SITTERSON, A. L. KRETCHMAR and M. BRUCER

(Received 7 April 1959)

Abstract—The patients exposed to irradiation in the Y-12 accident have been studied and followed at the ORINS Medical Division Hospital. The five patients with the higher dose levels were kept in the hospital for several weeks following exposure. Epilation began on the seventeenth day. Minimal clinical signs of a hemorrhagic tendency were seen around the twenty-fifth to thirtieth days. Antibiotics were not used prophylactically. A few minor infectious episodes occurred, but were easily managed. Hematologic studies showed the characteristic pattern of changes expected after total-body irradiation. Spontaneous recovery of blood values occurred and the patients have remained in good general condition following the accident.

To clinicians the accident that occurred at Y-12 on 16 June 1958, was of unusual interest and concern. The injury was one of whole-body penetrating irradiation uncomplicated by superficially deposited or internally ingested radioisotopes and uncomplicated by any pre-existing illness in the persons exposed. The dose range was sufficiently high to cause grave concern about the outlook of the exposed persons, and to raise the question of using a highly experimental form of treatment with bone-marrow transplantation.

CHRONOLOGIC OUTLINE

The patients studied included five men exposed to doses of about 300 rads and three with doses below 100 rads. The three men with low doses never showed more than slight or equivocal clinical and laboratory evidences of radiation effects. The present report is confined almost entirely to the five with higher doses. They were admitted to the hospital about 12 hr after the accident. All had nausea and four had vomiting. These symptoms began about 2 hr after exposure and persisted

intermittently for about 48 hr. It is interesting that the one who did not vomit is believed to have been exposed to the second highest dose. The patients did not have fever after exposure. At this time there was no great concern over their immediate condition, which was good, but there was serious concern about the severity of the illness that might develop a few weeks after the exposure.

Biological estimates of radiation dosage were attempted during the first 3 days. In all five, blood lymphocytes fell in the first 48 hr to levels in the neighborhood of 1000/mm³. Reticulocytes did not disappear from the blood films. Early bone-marrow studies showed no massive necrosis and only rather subtle changes in distribution of cell types and cell morphology. Three days after the accident, on the basis of an evaluation of all of the clinical, laboratory and dosimetric information available, a decision was made against immediate attempts at bone-marrow transplantation. At this point, relatives of the patients, who had been asked to come to Oak Ridge to serve as potential marrow donors, were released.

The patients were kept under careful observation. They appeared clinically well after the nausea had ceased. Beginning on the

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

REPOSITORY DOE - FORRESTAL

COLLECTION MARKEY FILES

BOX No. 3 OF 6

FOLDER CRITICALITY MACHINE & SOURCE ACCIDENTS

1005307

seventeenth hospital day they were allowed daily home visits from 2 p.m. until 10 p.m. On the twenty-fourth day these "passes" were temporarily discontinued because the hematologic depression that had been expected was becoming quite prominent. Between the twenty-fifth and thirtieth days depression of white cell and platelet values was serious. At this time physical examination revealed definite evidence of a hemorrhagic tendency. Preparations were made for the immediate use of fresh whole blood or concentrated platelets, but spontaneous recovery occurred without these measures.

On the thirty-ninth hospital day the patients were again allowed to spend a part of each day away from the hospital, and on the forty-fourth day they were discharged. After discharge they became increasingly aware of weakness and especially of a feeling of tiredness or a dull ache, particularly of the thighs. These symptoms gradually decreased and about 6 weeks after discharge they returned to work. Since then they have been in good health without any major manifestations that could be attributed to the radiation exposure.

Fig. 1 helps to correlate the time relationships of hematologic and clinical developments.

ADDITIONAL CLINICAL FEATURES

Soon after the patients were admitted to the hospital, consideration was given to the advisability of using prophylactic antibiotics. It was decided that no antibiotics or anti-infectious chemical therapy would be given unless some definite evidence of infection developed. A few minor infections were encountered but most of them did not occur at a time when the granulocyte depression was pronounced. Patient *E* had a very small furuncle of the external auditory canal on the third day; it cleared up spontaneously. Patient *B* had a large furuncle, in the left gluteal region, which started on the tenth day and was finally incised and drained on the twenty-second day. There was no fever and no specific drug therapy was given for this lesion; however, the same patient developed pharyngitis and a right otitis media on the thirteenth day with a mild temperature elevation and was treated with tetracycline. Patient *C* developed a mild upper respiratory infection

starting on the tenth day and was given no specific therapy. Patient *A* developed acute tonsillitis on the thirty-first day with a temperature of 38.6°C. He was treated with tetracycline.

All the patients had some evidence of hair loss starting about the seventeenth day, but in only two of them, patients *A* and *D*, was the hair loss so pronounced that it was obvious to any observer. These two patients developed almost complete baldness of a large rounded area on the back of the head. The other patients had some loss of hair from the head or body but no complete epilation. Three of the patients noticed some soreness of the scalp preceding and during the period of early hair loss.

Slight evidences of a bleeding tendency were apparent, and in one patient quite pronounced manifestations developed. These included petechiae, which were present in small numbers in patient *A* and in large numbers in patient *C*. Patients *A* and *E* had some bleeding of the gums on brushing, and three of the patients had a very small number of red cells in the urine. All these manifestations occurred between the twenty-fifth and twenty-eighth days when the thrombocytopenia was most pronounced.

All of the patients gained some weight (ranging from 3 to 13 lb) during their 44 days in the hospital. Three of them showed a slight early weight loss during the first few days of hospital care.

HEMATOLOGIC CHANGES

Fig. 1 shows the average blood values for the five high-dose patients during the first 60 days after the accident. Averaging of the values is considered justified because the radiation dose and the hematologic response were reasonably uniform in the whole group. Still, there were some differences, and the two patients, *A* and *C*, showed more profound changes in white cell, platelets and red cell values than did the other three. All the men had had previous blood counts done in the dispensary of the Y-12 plant. After the accident a blood count was done in that laboratory between 1½ and 2 hr after the exposure. Subsequent blood work was done in the laboratory of the

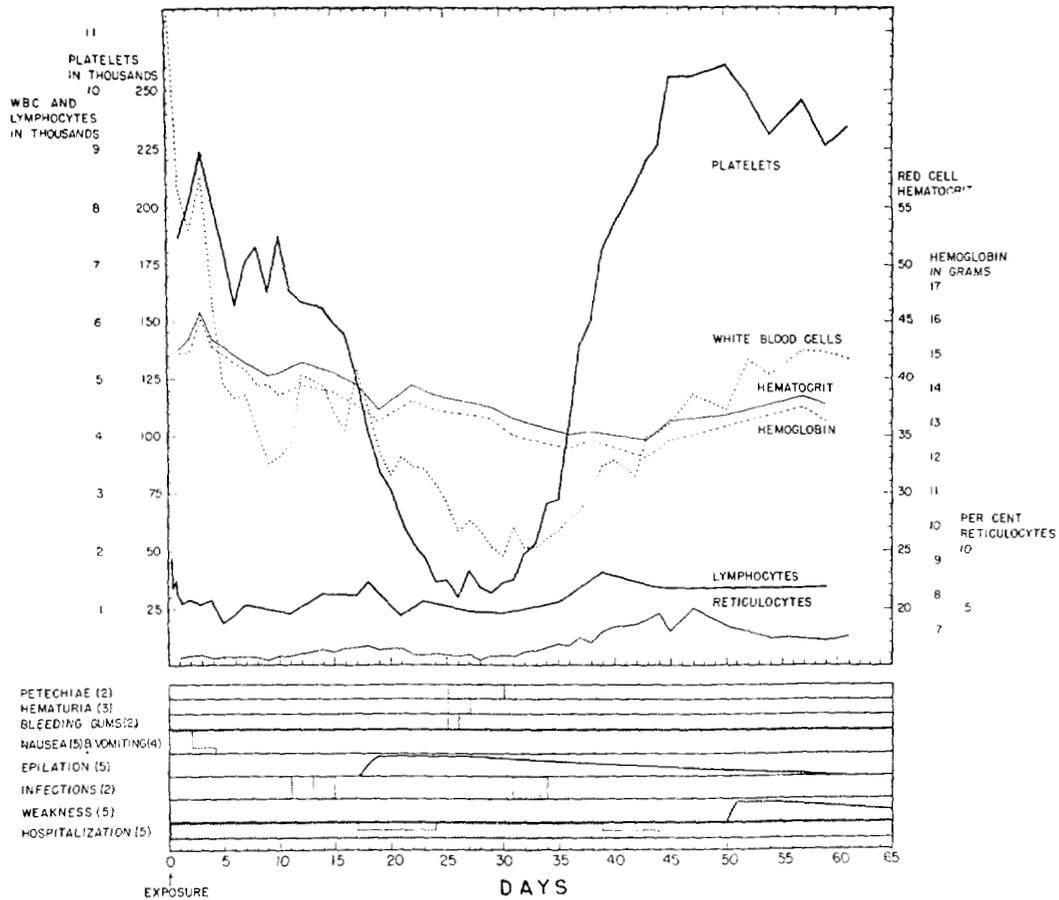


FIG. 1.

Medical Division. Blood films from the previous work at the Y-12 dispensary were reviewed so that criteria for differential counts could be uniform in the series. Fig. 1 shows only the work done after the accident. Base line counts, all within normal range, are not placed on the chart because they were all obtained many months earlier, but they are of importance in ruling out any pre-existing abnormality.

The most immediate change was a fall in lymphocytes. Two hours after the accident the average was around 1800, and by 48 hr it had fallen to slightly above 1000. Most of the fall in lymphocytes occurred within the first 48 hr, and after that the lymphocytes remained fairly uniformly depressed showing a slight rise after the thirtieth day. In two patients

there was a rise in the total white cell count within 2 hr (unless for some unknown reason they had a leukocytosis at the time of exposure). This elevation in white count was chiefly accounted for by an increase in granulocytes. By the fourth day the leukocytosis had disappeared and the white counts were within low normal values. Between the tenth and eighteenth days there was apparently a slight transient rise in the total white count. Then there was a distinct fall, with lowest values between the twenty-fifth and thirty-fifth days followed by recovery with low normal average levels reached by about the fifty-fifth day. These changes in the total white count are due chiefly to variations in the number of neutrophils present. Abnormal giant neutrophils were

present
abnorm
through
The
shown
fluctuat
such as
After th
in the
being
thirtieth
there w
some p
occurred
radiation
thromb
Cha
values
The g
reached
days;
these
about
radiation
in the
rather
reticuloc
and f
high
Bo
frequ
after
total
red
seen
cytes
after
was
the
Betw
days
plas
prof
a r
prio
wer
the
reg
S

1005309

present early after irradiation. Other types of abnormal cells were seen in small numbers throughout the period of study.

The blood platelets may or may not have shown early increase above normal. The fluctuations during the first 2 weeks are not such as to be given any special significance. After that period there was a pronounced fall in the number of platelets with lowest values being reached between the twenty-fifth and thirtieth days. During the recovery phase there was a rebound to above normal values in some patients; the most pronounced elevation occurred in the patient who had had the highest radiation dose and who had shown the greatest thrombocytopenia around the twenty-fifth day.

Changes in the hemoglobin and hematocrit values were pronounced in only two patients. The greatest depression of red cell values was reached between the thirty-fifth and fortieth days; the lowest hematocrit value in one of these patients was about 30 and in the other about 25. These were the ones with the highest radiation dose and the most profound changes in the white cell and platelet levels. Recovery in hemoglobin and hematocrit values occurred rather gradually but there was a distinct reticulocyte increase between the thirty-fifth and fiftieth days, especially in one of the two highest-dose patients.

Bone-marrow studies were performed at frequent intervals. During the first 5 days after irradiation there was no striking drop in total cellularity but a slight relative decrease in red cell precursors. Giant granulocytes were seen and degenerative changes in megakaryocytes became prominent. On the ninth day after the irradiation the drop in total cellularity was pronounced and degenerative changes in the megakaryocytes were more prominent. Between the twenty-fourth and thirty-ninth days the marrows showed pronounced hypoplasia, and by this time there had been a profound decrease in granulocyte forms with a relative increase in red cell precursors and primitive and nondescript cells, some of which were difficult or impossible to identify. By the fifty-fourth day, the marrow showed active regeneration with hypercellularity.

Special studies done by FLIEDNER and his

associates at the Brookhaven National Laboratory on this same group of patients, to be published elsewhere,⁽¹⁾ indicated a striking depression of the mitotic indices in the marrow, particularly on the fourth day after irradiation.

BIOCHEMICAL CHANGES

Many routine and specialized laboratory procedures were applied to the blood and urine of these patients, both as a matter of scientific interest and in an effort to evaluate their clinical condition as accurately as possible.

For the most part, the results were within the normal range of values or were not clearly ascribable to the effect of exposure. The taurine and β -aminoisobutyric acid excretion were, however, of greater interest. The preliminary results are summarized in Table 1.

Table 1. Taurine and β -aminoisobutyric acid (BAIB) in the urine of accidentally irradiated humans

Subject and interval after exposure	Taurine (mg/day)	BAIB (mg/day)*
A (365)† 4th day	273	54.8
A (365)† 16th day	146	
C (339) 1st day	204	38.4
E (236) 4th day	231	15.7
F (68) 4th day	109	13.6
I (0)‡	103	7.5

* To convert mg/day to μ M/day, multiply the numbers in this column by 1000/103.1.

† The numbers in parenthesis are the doses in rads (γ + neutron).

‡ This was an ambulatory patient who had carcinoma of the lung but had not been exposed to any irradiation.

These results were obtained by applying the quantitative column chromatographic procedure of MOORE *et al.*⁽²⁾ to aliquots of 24 hr urine collections.

The taurine excretion is elevated both 1 day and 4 days after exposure. By the sixteenth day taurine excretion had returned to the normal range in patient A. Taurine excretion is somewhat variable among normal individuals and is influenced by dietary intake. These are serious limitations if one desires to use the level

of taurine excretion as an indicator of the amount of irradiation to which the subject has been exposed. If one considers only the levels at 4 days, there appears to be a correlation with dosage. The small number of values available and the exception of patient *C* at 1 day make such a conclusion highly tenuous, however.

The β -aminoisobutyric acid excretion is elevated after irradiation in all of the subjects and appears to be correlated with dosage. This confirms RUBINI's⁽³⁾ general conclusions from his study of these same patients. Other agents, causing DNA breakdown, can cause an elevated BAIB excretion; furthermore, some non-irradiated people habitually excrete 30 mg or more of this substance daily. An elevated excretion of this substance does not, therefore, necessarily indicate an exposure to irradiation.

DISCUSSION

This particular radiation accident provides much information on the changes following whole-body irradiation in the sublethal range. The fact that the patients were treated with great conservatism, without blood transfusions and with minimal antibiotics, seems to indicate that such conservative therapy is justifiable. Indeed, at the present state of our knowledge, such treatment may be preferable when the dose is believed to be definitely sublethal. One of the greatest problems is determining the dose fairly early after the irradiation. It is of value to pursue both physical measurements and estimates based upon clinical and laboratory observations of patients. A few examples of such studies can be cited here. General observation of the severity and persistence of the nausea and vomiting, and of the presence or absence of fever, is important. Significant temperature elevation in the first 48 hr would suggest a dose higher than that encountered in the present series. A pronounced fall in the lymphocytes suggests that the dose has been in the dangerous range, but the relationship is not clear between further increments in dose (in the range of 300 and 1000 rads, for example) and further depression in the lymphocytes. In the present series of cases the reticulocytes did not show any very

pronounced fall during the first 3 or 4 days. It may be that by counting a large number of cells and obtaining a statistically accurate reticulocyte count, it would be possible to make an estimate of dosage. If there is an unequivocal fall in reticulocytes during the first 5 days, it is probable that the dose is higher than in the present series. Sodium activation studies, either based upon total body counts or blood radio-assays, have been shown to be of great value in estimating the neutron dosage. Early studies on β -aminoisobutyric acid and taurine may be established as valuable indices of radiation dosimetry.

Comparison of our experience with earlier reports of similar accidents and with the atom-bomb casualties in Japan, and the Marshallese Islanders makes it appear that whole-body irradiation produces rather predictable changes in man. The time sequence of these changes tends to remain fairly uniform for a given species over quite a large dose range, but there are very striking differences in the time sequence among different species. Small animals, in which much radiobiological research is done, show both the development and the recovery of the hematologic changes in a much shorter time than do human beings. The explanation of the delay in the development of maximal hematologic changes is quite complicated. Although the normal survival and life cycle of the different cell types are undoubtedly important, the timing of the changes cannot be explained entirely on this basis.

The study of the five patients in the Y-12 accident adds significantly to the information available on irradiation effects in human beings. More detailed information and analysis based on this experience will be presented.

REFERENCES

1. T. M. FLIEDNER, E. P. CRONKITE, V. P. BOND and J. R. RUBINI, *Acta Haemat.* In press.
2. S. MOORE, D. H. SPACKMAN and W. H. STEIN, *Analyt. Chem.* **30**, 1185 (1958).
3. J. R. RUBINI, E. P. CRONKITE, V. P. BOND and T. M. FLIEDNER, *Proc. Soc. Exp. Biol., N.Y.* **100**, 130 (1959).