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THERMAL, AND COMBINED THERMAL AND IONIZING RADIATION, EFFECTS ON BIOLOGICAL SYSTEMS -- 1 JULY TO 31 DECEMBER 1953

(Semi-annual Progress Report for Armed Forces Special Weapons Project)

E. L. Alpen

USNRDL-421

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U.S. NAVAL RADIOLOGICAL DEFENSE LABORATORY

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USNRDL-421
Progress Report

Technical Objective
AW-6

Thermal Branch
E. L. Alpen, Head

Biological and Medical Sciences Division
Captain A. R. Behnke, Jr. (MC),USN
Acting Head

Scientific Director
P. C. Tompkins

Director
Captain R. A. Hinners, USN

U. S. NAVAL RADIOLOGICAL DEFENSE LABORATORY
San Francisco 24, California

31 December 1953

INTRODUCTION

Principal Investigators

During this reporting period the principal investigators were Edward L. Alpen, A. Kennon Davis, William M. Davis (to 1 December 1953) and William Lee.

Collaborators

Working with the principal investigators were John A. Alexander, HM1, USN, and Janette D. Bigelow (to 1 September 1953).

Objectives

The objectives of this program have been threefold:

(a) To study local effects of radiant thermal energy on animal skin as a function of exposure time, irradiance and pulse shape.

(b) To evaluate the effect of ionizing radiation superimposed on burn injury. The ultimate aims of this study are an understanding of the interaction of the two trauma and a quantitative evaluation of this interaction in terms of lethality and other criteria of damage.

(c) To study the systemic effects of thermal burns with special emphasis on the phase following recovery from shock.

1 LOCAL EFFECTS OF RADIANT THERMAL ENERGY

1.1 Blister Formation and Tissue Temperature in Radiant Energy and Contact Burns

This study has been completed and the results published in U. S.

Naval Radiological Defense Laboratory unclassified report USNRDL-396. The data will appear in a forthcoming issue of the American Journal of Pathology.

1.2 Tissue Temperature in Radiant Energy Burns

This phase of the program has not been pursued and the data presented in Table 1 of the progress report for the last period are a summary of the data available at this time.

2 COMBINED EFFECTS OF IONIZING RADIATION AND HOT WATER BURNS

This phase is now complete and the results are presented in unclassified report USNRDL-402.

3 COMBINED EFFECTS OF IONIZING RADIATION AND RADIANT THERMAL ENERGY BURNS

3.1 Method of Producing Radiant Thermal Burns

All burns described in these studies were produced with the Mitchell carbon-arc projection light described in detail in USNRDL-385. All X irradiation has been accomplished with a Westinghouse 250 KVP therapy unit with the following irradiation characteristics: HVL 1.5 mm Cu using 1 mm Al and 0.5 mm Cu filtration, a 40 in. TSD, and a dose rate of 23 r/min.

3.2 Dose-mortality and Survival Time

This study, as described in detail in the last semi-annual progress report is now complete. The early observation that deaths in rats given radiant energy burns are not as closely restricted to the first 48 hour period as in the case of hot water burns has been substantiated. Frequent deaths occur after radiant energy burns on the third and even occasionally on the fourth day following burning, but as in the case of hot water burns there are only very infrequent deaths following the fourth day in the case of burns alone. When ionizing radiation is superimposed on these burns essentially the same pattern is seen as in the case of

hot water burns. There is increased mortality in the early "shock phase" death period and for the 500 r radiation plus burn combination there is mortality during the period 8 to 20 days in excess of that expected from radiation alone. Table 1 gives the comparative median lethal burn areas as a function of radiation dose. The hot water data have been reported previously and are given for comparison only.

The small differences in LA_{50} may be due to a small error in matching the severity of the lesions under the two methods of burning. The slope of the probit regression lines of response vs log dose indicates a tolerance distribution which is essentially alike with or without radiation as well as for the two types of burning.

3.3 Pathology

No further experimental work has been accomplished on this phase since the last reporting period. The processing of the tissue is nearly complete and further analysis of selected organs will be undertaken.

3.4 Red Blood Cell Changes

3.4.1 Anemia

A comparison of the effects of 25 per cent and 15 per cent body area burns, 100, 475 and 500 r of total body X irradiation with three combinations of these on blood volume, red cell volume, hematocrit, red cell count, hemoglobin, and reticulocyte population has been made in rats.

Both 15 per cent and 25 per cent body area burns produced an increased blood and plasma volume over the 30 day period studied. Although red cell volume was not appreciably altered after the fifth day a slight reduction in hematocrit, hemoglobin, and red count was observed throughout this period. The sustained reticulocytosis of the burned rat with concurrent normal red cell volumes indicates an accelerated destruction of erythrocytes during the post-burn period.

The exposure to 100 r of ionizing radiation produced only a transient depression of the reticulocyte level. However, 500 r caused a severe anemia with a concomitant fall of all the measured values for 15 days following the irradiation. Blood, plasma, and red cell volumes declined. Hematocrit, hemoglobin, and red cell count fell at similar rates. Recovery was first noted by increased reticulocyte counts on day 15 and all the measured values were normal by day 30.

Irradiation with 500 r and a concomitant 15 per cent burn produced values which followed the patterns observed in the rats given 500 r alone;

namely, a severe anemia developed with concomitant depression of all the measured values for 15 days. Such a combined injury produced an anemia which developed more rapidly than that caused by 500 r alone. The anemia of the combined injury series was detectable on day 8 and, on day 11, was equal to the maximum observed in the irradiated animals on day 15.

The erythrocyte values in rats given a 25 per cent burn and 100 r more closely approximated the values of the burned than of the 100 r irradiated rats. Of the measured values the reticulocyte count proved to be the only useful indicator of exposure to ionizing radiation in this low dosage. Even the fall in this variable was obscured by the fifth day in the reticulocytosis characteristic of the burned rat.

3.4.2 Osmotic and Mechanical Fragility of Erythrocytes

In summary the findings in this phase of the work are as follows:

The osmotic and mechanical fragility of rat erythrocytes have been measured during the 30 day interval following severe and moderately severe burns, 100 and 500 r of whole body ionizing radiation, and combinations of the two trauma.

It has been found that, although it is difficult to demonstrate an increased fragility as early as 4 hours after severe burns, there is most probably an increased resistance to osmotic hemolysis 24 hours later as the result of removal of the most fragile cells. This is a transient finding and normal fragilities are found on the third day. During the recovery period an increased resistance to osmotic hemolysis develops which is discussed as a possible result of increased red cell turnover.

Irradiation produces an increased osmotic resistance at the 500 r dose level but not at 100 r. This change is correlated with removal of fragile cells and increased red cell turnover.

Combination of the trauma brings about essentially additive results insofar as osmotic fragility is concerned.

The mechanical fragility was found to be increased by lethal doses of ionizing radiation and by lethal combinations of ionizing radiation and burns when neither trauma was lethal alone. It is thought that the increased mechanical fragility is a sign of impending death in radiated animals either in the presence or absence of other complicating trauma.

The foregoing information is being published as an unclassified report USNRDL-419.

Those studies which were undertaken to establish the relative resistance to osmotic hemolysis of young red cells with respect to older red cell populations has been completed. It has been established that in the rat the young erythrocyte has a greater resistance to osmotic hemolysis than older cells. The results have been reported in detail in unclassified report USNRDL-409.

3.5 Blood Coagulation Mechanisms

The changes in Lee-White and heparin clotting times as well as platelet concentrations have been completed and are reported in detail in unclassified report USNRDL-413.

3.6 White Blood Cell Changes

There are no important findings in the combined injury insofar as the white blood cells are concerned. The general statements made at the end of the last reporting period were found to be true. That is, the total and differential white counts and bone marrow differentials are essentially those found with irradiation injury. For burns only a moderate leukocytosis with a shift toward the granulocytic cells is found. The bone marrow of burned animals is hyperplastic in all elements, but especially in the erythroid elements. There is evidence here for increased medullary erythropoiesis as well as increased leukopoiesis.

4 GENERAL SYSTEMIC CHANGES FROM RADIANT THERMAL BURNS

4.1 Mortality-intensity Relationships

Only preliminary studies have been undertaken on this phase of the program but it is clearly evident that mortality is a function of total radiant energy delivered as well as body area burn. This is even true for burns in excess of what in the human would be classified as a third degree burn.

4.2 Anemia of Thermal Burns

4.2.1 Initial Erythrocyte Destruction

Methods for using sodium chromate labeled with Cr^{51} have been standardized and actual measurements on this phase of the problem are now

underway. The initial red cell destruction measurements will be done in relation to the mortality-intensity studies of Section 4.1. The amount of red cells destroyed during burning at various total energy input will be measured.

4.2.2 Erythrocyte Survival and Production

Studies are nearing completion in which Fe^{59} has been injected into rats 2, 7 and 15 days following severe radiant energy thermal burns. The rate of removal of the tracer dose from the plasma and its rate of appearance in the peripheral erythrocyte have been measured. Figures 1, 2, and 3 show the results of these uptake measurements. In each case the rate of utilization of the injected tracer dose of iron has been accelerated in the burned animals. This increased rate of utilization implies a more rapid production of erythrocytes and is characterized by the increased slope of the early portions of the curve. In all cases the final level at which the percentage utilization stabilizes is the same. The implication of this finding is that the iron pool in rapid turnover is essentially the same size in burned and control animals.

Another phase of this study involves the measurement of the mean survival time of erythrocytes following burning. At the completion of the uptake period, i.e. one week, weekly injections of a non-toxic intravenous iron source are given. This material enlarges the iron stores of the animal and minimizes reutilization of iron released from erythrocytes by simple dilution. Measurements of the total amount of circulating radioactivity at various times following the initial injection gives a measure of the fraction of the maximum activity. Figures 4 and 5 represent the data from this study. In Table 2 are listed the times in days required for one-half of the labeled cell population to be destroyed. It can be seen that at 2, 7 or 15 days after thermal injury red cells are being destroyed at a more rapid rate. This destruction in the burned animal seems to be without regard to cell age and removal of new cells begins immediately. The cells of the normal animal survive with only a minimal loss for 20 to 30 days before rapid removal begins.

Transfusion experiments now under way indicate that cells from burned donor rats with an Fe^{59} label subsequent to burning have a normal life span when injected into untreated recipient rats. The same cells injected into burned rats have a rapid rate of disappearance. These findings would seem to indicate that the cells made by burned animals are essentially normal but that some destructive mechanism is accelerated or initiated by burning.

4.3 Capillary Permeability Changes in the Burned Dog

These studies have not yet been initiated.

5 PLANS FOR NEXT PERIOD

5.1 Local Effects of Radiant Energy

The studies requested in SWPEF-3 928.2 of 16 Oct 1953 signed by H. H. Rankin for Chief, AFSWP, are under way. Completion of this project is expected by 31 March 1954.

All other phases of this program are complete.

5.2 Combined Effects of Ionizing Radiation and Hot Water Burns

Complete

5.3 Combined Effects of Ionizing Radiation and Radiant Thermal Energy Burns

The evaluation of the microscopic pathology of combined effects will be pursued. In addition, it is planned to evaluate more thoroughly the changes in erythrocyte mechanical fragility as a prognostic sign of death in animals given the combined traumata.

5.4 General Systemic Changes from Radiant Thermal Burns

5.4.1 Mortality-intensity Relationships

This phase of the program will be actively prosecuted.

5.4.2 Anemia of Thermal Burns

5.4.2.a Initial Erythrocyte Destruction

These studies are now under way.

5.4.2.b Erythrocyte Survival and Production

Transfusion experiments designed to determine the nature of the destructive defect are under way. Repetition of these experiments on splenectomized animals is also planned.

It is expected that a thermal source adequate for burning dogs will be available shortly. At this time studies on the nature of post-burn anemia in dogs will be started.

5.4.3 Capillary Permeability Changes in the Burned Dog

It is planned to do preliminary technique evaluation experiments shortly. If these are successful further work on burned dogs will be undertaken as soon as an adequate thermal source is available.

6. PUBLICATIONS DURING THIS REPORTING PERIOD

1. E. L. Alpen and G. E. Sheline. The Combined Effects of Thermal Burns and Whole-Body X Irradiation on Survival Time and Mortality. Unclassified report USNRDL-402, 18 May 1953.

2. W. M. Davis, J. Bigelow and E. L. Alpen. Changes in Red Cell Volume and Osmotic Fragility of Erythrocytes in the Rat Following Acute Blood Loss. Unclassified report USNRDL-409, 14 August 1953.

3. W. M. Davis, A. K. Davis, W. Lee and E. L. Alpen. Combined Effects of Total Body X-irradiation and Radiant Energy Thermal Burns: I. Study of Blood Coagulation. Unclassified report USNRDL-413, 22 October 1953.

4. A. K. Davis, E. L. Alpen, G. E. Sheline and W. M. Davis. Combined Effects of Total Body X-irradiation and Radiant Energy Thermal Burns: II. Anemia. Unclassified report USNRDL-423.

5. E. L. Alpen, J. A. Alexander, A. K. Davis, and W. M. Davis. Combined Effects of Total Body X-irradiation and Radiant Energy Thermal Burns: III. Osmotic and Mechanical Fragility of the Erythrocyte. Unclassified report USNRDL-419.

Approved by:

A. R. Behnke

A. R. BEHNKE, Jr.
Captain (MC) USN

Acting Head
Biological and Medical
Sciences Division

For the Scientific Director

TABLE 1

Median Lethal Burn Area (LA_{50}) for
Thermal Burns and X Irradiation

Irradiation Dose (r)	Median Lethal Burn Area (LA_{50})	
	Radiant Energy Burns	Hot Water Burns
0	30.8 ± 1.0*	32.8 ± 0.7*
100	27.9 ± 1.8	30.2 ± 1.3
250	-----	26.8 ± 2.0
500	23.2 ± 1.2	23.9 ± 0.9

*Standard deviation of LA_{50}.

TABLE 2

Mean Erythrocyte Life Span after Severe Thermal Burns

Iron Injection (days post burn)	Mean Life Span (days)	
	Burned	Untreated
2	~ 25	~ 50
7	27 33	47 58
15	24 25 27	47 55 56

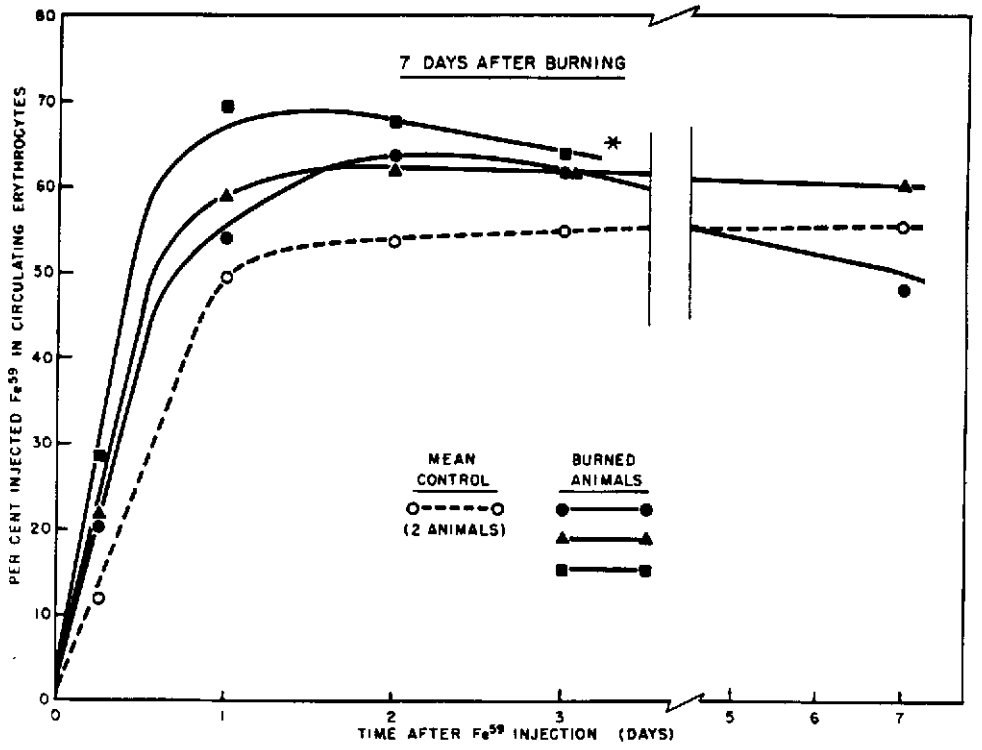

Figure 1 Iron utilization by burned and control rats. The slope of the initial rapid uptake line is a measure of the rate of erythropoiesis. The final level of maximum utilization is a measure of the amount of iron in rapid turnover.

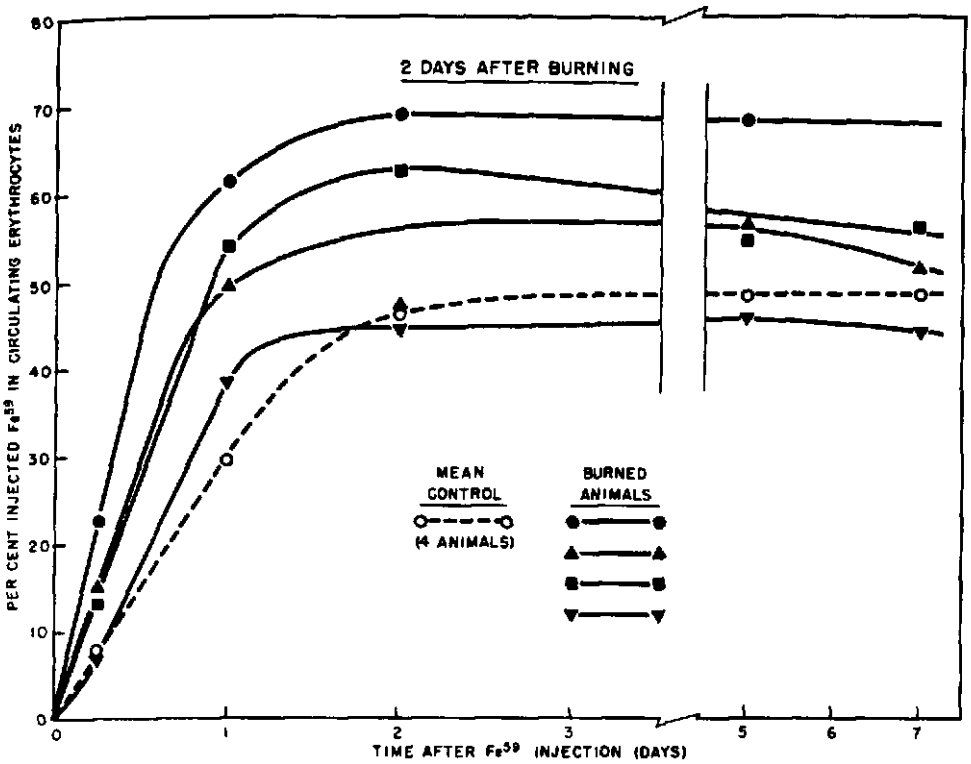

Figure 2 Iron utilization by burned and control rats. The slope of the initial rapid uptake line is a measure of the rate of erythropoiesis. The final level of maximum utilization is a measure of the amount of iron in rapid turnover.

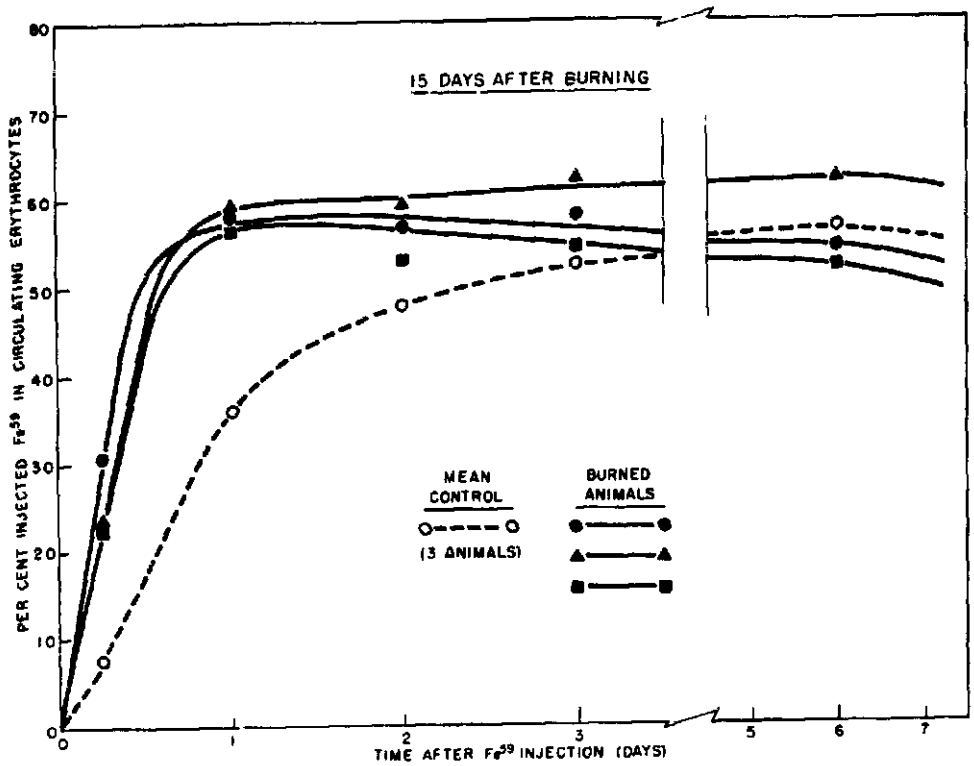

Figure 3 Iron utilization by burned and control rats. The slope of the initial rapid uptake line is a measure of the rate of erythropoiesis. The final level of maximum utilization is a measure of the amount of iron in rapid turnover.

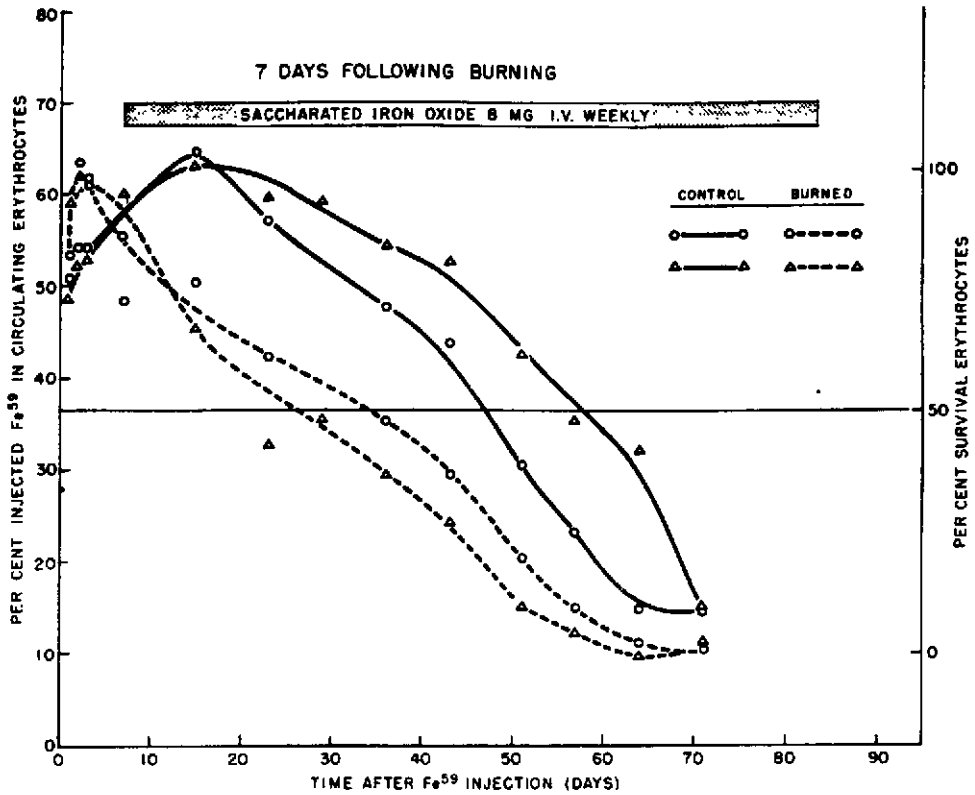

Figure 4 Disappearance of iron from the circulating erythrocytes 7 days after burning.

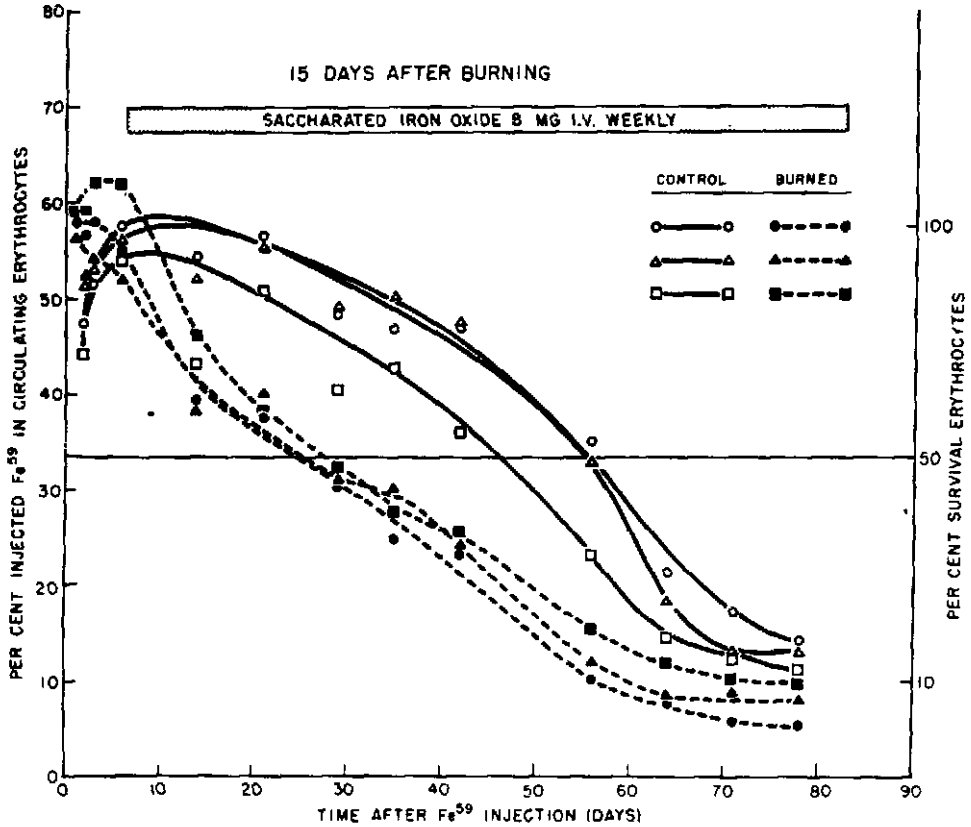

Figure 5 Disappearance of iron from the circulating erythrocytes 15 days after burning.

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1. Thermal radiation - Physiological effects
2. X irradiation - Biological effects
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