THE ANEMIA OF THERMAL BURNS*

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ANEMIA has become acknowledged as a common complication of any extensively and deeply burned patient who survives the period of burn shock. The anemia is progressive and is accompanied by debility. It may be so severe that the wounds will not heal unless massive transfusions of whole blood are administered.

The magnitude of the problem of anemia following severe burns is illustrated by the number of transfusions given to four patients before healing was achieved (Table I). These patients were treated in 1943, before the present study was initiated, and, indeed, served as a stimulus for the study. Two of the four patients (Cases 41 and 131)† entered this hospital 8 and 20 months, respectively, after injury, with extensive unhealed granulating wounds of the legs. Both patients were anemic, hypoproteinemic and emaciated. The other two (Cases 13 and 116) entered immediately following their injuries but were unwittingly allowed to become anemic and malnourished before red cell transfusions were started. None of these four patients was treated by expeditious closure of their full-thickness wounds. The necrotic slough was allowed to separate spontaneously, exposing open infected wounds. All were treated with sulfonamides and without penicillin. Numerous skin grafts elsewhere had been unsuccessful in the first two patients. Successful grafting in all was achieved only late after the injury, when the anemia and malnutrition had been partially relieved. The amounts of whole blood given these patients were minimal, certainly not optimal, since all four patients left the hospital with residual anemia and hypoproteinemia.

The origin of the anemia of burns was ascribed, in 1942, by Altemeier and Carter[1] to external loss of blood from the infected granulations. More recently, the frequency with which gross hemolysis and massive hemoglobinuria have

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† The same case numbers are used in all articles on burn patients studied at this hospital under contract with the Committee on Medical Research. Numbers 1 through 39 refer to the Cocoanut Grove fire cases, numbers 40 through 96 to cases studied before the Cocoanut Grove fire, and numbers 97 through 278 to cases studied since the Cocoanut Grove fire.

been encountered in the hours immediately following injury has called attention to an early destruction of red blood cells, allegedly due to the heat itself. Shen, Ham, and Fleming[2] have disclosed an early increased fragility of the red blood corpuscles. The Burns Unit in England, under Colebrook,[3] has extended this observation to find that by 18 hours all the fragile cells have disappeared from the circulation, leaving only the stable cells or those with decreased fragility.

In addition to the observed losses of red cells by hemorrhage from the wound surface and by hemolysis, other causes of a decrease in circulating red cell mass might be postulated. The administration of large volumes of plasma in the therapy of burn shock could theoretically give rise to destruction of cells if the plasma pools contained an excess of anti-A or anti-B agglutinins. Red cells may be destroyed at the inflammatory barrier of the infected wounds; Menkin[4] has shown a deposition of iron in this area. Wintrobe and his coworkers[5] have suggested that such a deposition may be the reason for deviation of iron from the bone marrow. They have observed hypoferremia associated with an anemia

TABLE I

THE PROBLEM—1943
TRANSFUSIONS GIVEN TO FOUR PATIENTS WHO WERE DISCHARGED WITH HEALED WOUNDS BUT WITH RESIDUAL ANEMIA

Case Number	Extent Full-thickness Burn	Whole Blood Transfusions	Duration of Hospitalization
41	20%	4,500 cc.	5 months*
131	15%	6,500 cc.	8 months†
13	28%	12,500 cc.	4 months
116	12%	2,500 cc.	6 months

* Burned 8 months prior to admission to this hospital.
† Burned 20 months prior to admission to this hospital.

refractory to iron therapy in patients with acute and chronic infection. It is also possible that toxins of infectious origin might suppress the regenerative activity of the bone marrow by means other than iron deviation.

These observed and postulated causes of anemia in the burned patient should all create a true anemia, or decrease in circulating red cell mass, which should be differentiated from the false anemia due to an increase in plasma volume resulting in red blood cell dilution. Such a false anemia has been shown to follow soon after the initial period of hemoconcentration. Studies of the redistribution of fluid within the extracellular space at this hospital,[6] and elsewhere,[7] have shown that once the interstitial or extravascular compartment of the extracellular space has been stretched to the maximum such an enlargement of the plasma volume may occur. This enlargement may be produced either by continued fluid therapy in excess of renal output or by beginning mobilization of fluid from the overdistended interstitial space. Clinically, such a fluid shift is recognizable as subsidence of edema which usually starts about 48 hours after the injury; if the wounds are extensive, blood dilution may persist for several days in spite of a large renal output.

The stubborn and disabling character of the anemia has prompted this investigation. We have strived to determine: first, the significance of the observed and postulated causes of the burn anemia; second, how far the customary methods of measuring an anemia suffice for the guidance of therapy and to what extent newer methods of blood volume determinations must be introduced as a clinical routine; and, finally, to record the relative expense in terms of red cells required under different modes of therapy. The expense of treating an established anemia has already been observed (Table I).

METHODS

Studies of the peripheral blood alone may provide an approximation of the extent of an anemia. However, if whole blood is continually lost and dehydration is present, so that refilling of the plasma volume from the extracellular fluid is abnormally slow, hematocrit, hemoglobin, or red cell counts in the normal range may theoretically coexist with striking reductions in the circulating red cell mass. For this reason, as well as a desire to quantitate the loss, one must go beyond a description of the peripheral findings and measure the circulating red cell mass and the changes in this red cell mass after the burn.

Of the methods available to study the red cell mass, the simplest is a measurement of the dye plasma volume and a calculation of the red cell mass from the hematocrit. This method suffers from some systematic error traceable to the fact that the large vessel hematocrit is somewhat larger (about 10 to 15 per cent) than the whole body hematocrit.[8] However, this fault is not insurmountable if the same method is used for serial determinations and there are no acute changes in body fluid metabolism which alter the relationship between the whole body hematocrit and the peripheral hematocrit during the course of the study. The method is also affected by widespread alterations in capillary permeability and presence of other pigments in the serum.

A method which measures the red cell mass directly would be preferred and we have used a measurement of the patient's red cell mass by the injection of red cells containing radioactive iron and a quantitation of the dilution of these injected cells using physical measurements of the radioactivity.*[9,10]

In brief, this technic involves the preparation of radioactive red cells in a donor by the injection of the five-year half-life isotope of iron (as ferric ammonium citrate), over a period of two or three weeks. At the end of this time the activity of the donor may be determined and when it is sufficient to allow measurement of his cells diluted in the patient's cells, the build-up is ceased. At a time when the red cell mass of a patient is to be measured, the radioactive donor is bled of 100 to 500 cc. of blood into citrate and this amount is injected into the patient after careful measurement of the hematocrit of the injected blood. The radioactivity per cubic centimeter of cells in the donor blood, and

* In expressing the results in the figures the red cell volume as measured by calculation from the dye plasma volume is indicated as RV; the red cell volume as measured directly with radioactive cells is indicated as R*V.

in the patient's blood after an hour are then determined. By the extent of the radioactivity dilution the cell volume of the recipient is calculated. The activity measurements are made on a Geiger counter, after digestion of the red cells to ferric hydroxide and electroplating this iron onto a copper planchette.

The application of this method to such a problem as this allows one to carry out two other types of observations. The first has to do with the relative survival

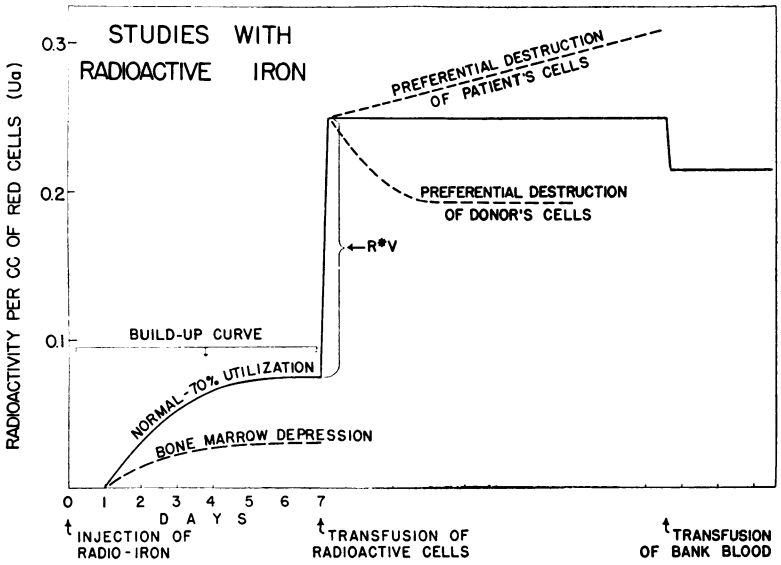

CHART 1.—Diagram demonstrating uses made of the radioactive isotopes of iron; the isotope Fe^{55} (five-year half-life) was employed.

Utilization of Radioiron: An injection of iron as ferric ammonium citrate given at zero-day results in a gradual appearance of the iron in the peripheral erythrocytes as shown in the solid line of "Normal—70% Utilization". An example of depression of this utilization is shown by the dotted line.

Measurement of Red Cell Mass: A transfusion of whole blood from a donor in whom erythrocyte hemoglobin has been synthesized from radioactive iron by multiple build-up injections, results in a sudden rise, the height of which is directly proportional to the red cell mass (R*V), and from this rise the R*V may be calculated.

Subsequent Fate of Cells: Following such a transfusion the concentration of radioactivity in the peripheral blood remains constant under normal conditions (solid line). Destruction of the donor's cells due to poor preservation or incompatability results in a drop in activity (lower dotted line). Active hematopoiesis also results in a fall of activity as ordinary iron is built into new cells.

If the patient's own cells are preferentially destroyed, a relative rise in activity (upper dotted line) would result.

Transfusions of ordinary bank blood result in a sharp fall in activity.

It should be emphasized that the radiation from this isotope of iron is a low energy *beta* ray which produces no known deleterious biologic effects in the small quantities used.

of the donor cells in the patient or the survival of the patient's own cells in his circulating blood. After a patient has received a radioactive transfusion, the radioactivity of his circulating cells will remain constant for long periods of time unless his cells and the donor cells are being destroyed in a differential fashion. For instance, if the patient is transfused with donor cells which have

been inadequately preserved or which are incompatible with the recipient, these cells will rapidly be destroyed and over a period of two or three days much of the radioactivity will disappear from the circulating blood as the radioiron is either excreted or stored again in the marrow for resynthesis. If the donor's cells are healthy, well-preserved erythrocytes, and the patient carries cells in his own blood which are either fragile or are being selectively destroyed at a rapid rate, then the specific radioactivity in the patient's circulating blood should gradually rise, as the patient's inactive cells are destroyed, and the donor's active

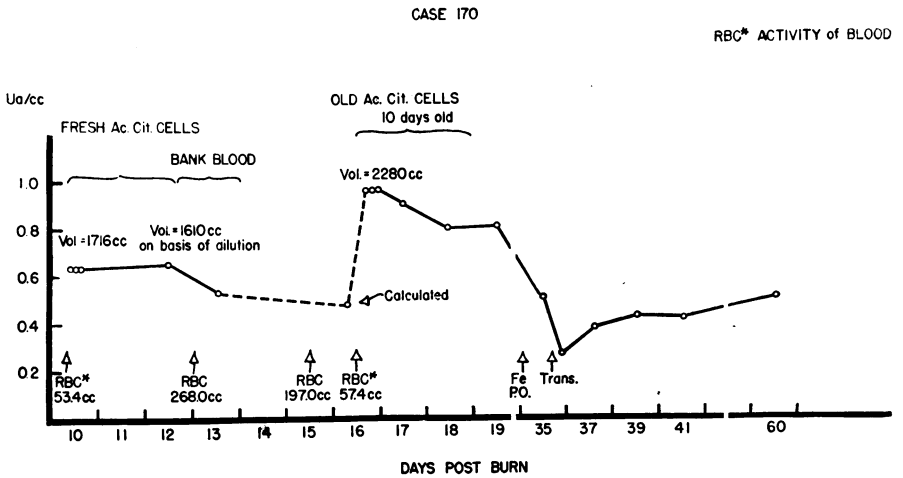

CHART 2.—Case 170: Radioactivity in peripheral blood in a patient with predominantly superficial burns, demonstrating dilution and preferential cell destruction phenomena of the radioactive iron technic diagrammatically represented in Chart 1.

On the tenth post-burn day the patient received 53.4 cc. of fresh, well-preserved radioactive cells yielding a calculated red cell mass (R*V) of 1,716 cc. (All figures in the chart are in cubic centimeters of cells.) On the 13th and 15th days transfusions of bank blood were given totalling 518 cc. of cells. On the 16th day a second radioactive transfusion was given increasing the concentration of cells containing radioactive iron in the peripheral blood. The second calculation of the red cell mass gave 2,280 cc., which figure indicates quantitative retention of the 518 cc. of cells given between the two measurements.

The second radioactive transfusion consisted of blood which had been poorly preserved (temperature inadequately controlled) and the fall in activity thereafter resulted from partial destruction of these fragile cells. Between the 19th and 35th day the patient's own marrow activity under iron therapy plus transfusions of bank blood resulted in a further fall, after which activity is essentially constant up to the 60th day.

cells remain viable. Therefore, over a period of days or weeks after the burn, determinations of the activity in a transfused patient permit one to draw conclusions as to whether or not the patient's own cells, which had been in the patient at the time of the trauma, are being selectively destroyed.

A second application of this technic involves a study of the build-up curves. If a normal individual is given a single intravenous dose of radioactive iron as ferric ammonium citrate, this iron will not appear in the circulating erythrocytes for about 24 hours as it is first taken up in the blood-forming organs and only slowly synthesized into hemoglobin. After this initial latent period the radio-

active iron begins to appear in the peripheral blood as erythrocyte hemoglobin at a characteristic rate and in a characteristic amount which may be described as an exponential rise in activity with a half-period of about three days and a final utilization of about 70 per cent of the injected radioactive iron. If, however, the patient is suffering from some disorder in which red cell formation is depressed, the appearance of this radioactive iron may either be slowed or its final utilization may be abnormally low. Conceivably, there may be situations in which bone marrow activity is increased and the build-up curve, therefore, either hastened or raised. We have not observed such patients, although we

TABLE II

Case 196
Male, Age 51, Weight 80 Kg.
Extent of Burn: 15 per cent total, 1 per cent third degree

RED CELL VOLUMES AND TRANSFUSIONS

Day Post-Burn	Red Cell Mass: Dye Method Cc. Cells	Red Cell Mass: Radioactive Method Cc. Cells	Transfusions Cc. Cells
0	2650		
3		2220	120
4		2470	97
9	3250	2350	114

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes %
0	4.44	18.5	44	
1			48	
2			47	
3			42	0.3
4				0.2
6	5.40	14.0		0.3
8	4.10			0.4
9	4.39		42	0.4
11	5.25			1.0
14	4.58			0.8
16	4.15			1.0

have not applied this technic to patients with such disorders as pernicious anemia in remission or true iron deficiency anemia under treatment. In Chart 1 some of the phenomena observable with radioiron are shown diagrammatically. In Chart 2 an example of such studies in a patient with a circumscribed burn is shown.

Operative blood loss has been computed from the concentration of acid hematin or of the radioactivity in the washings of sponges and drapes. The customary examinations of the circulating blood including reticulocyte counts have been carried out.

The end-products of red cell destruction have been measured in urine and feces because of our interest in the question of whether or not there was any correlation between the amounts excreted and the apparent destruction of red

cells in the blood. Both quantitative urobilinogen determinations[11] and the benzidine test have been carried out on urine and feces. On a few patients the hemoglobin concentration in the serum has been determined in the hours immediately following entry and the blood bilirubin concentration has been followed.

RESULTS

Data have been obtained from the study of four patients with predominantly second degree burns, and 13 patients with deep burns of considerable magnitude.

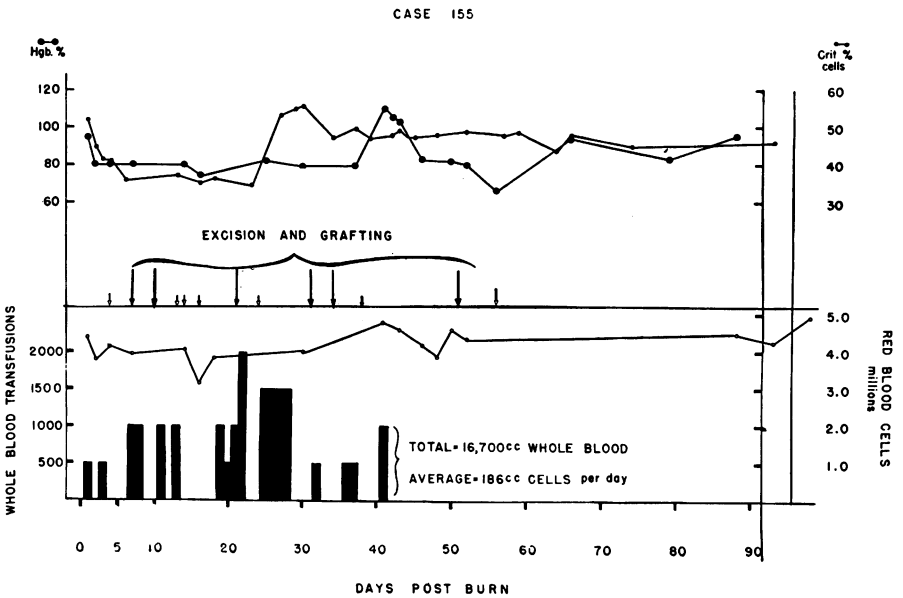

CHART 3.—Case 155: Peripheral blood findings and whole blood transfusions required by a patient with extensive deep burns (41 per cent total, 26 per cent third degree).

The whole blood given according to clinical indications succeeded in maintaining adequate peripheral red cell concentrations despite operations (large arrows) and dressings (small arrows). The amount given, therefore, approximated the requirements, and for the first 42 days averages 186 cc. of cells per day. These requirements included compensation for frank external loss at operation and dressing and for that reason cannot be compared with the red cell balances shown in Charts 5, 6, 7 and 8, which exclude such losses.

Of the latter, nine survived, and could be studied throughout their convalescence; four died of their injury.

1. SECOND DEGREE BURNS AND THIRD DEGREE BURNS OF LIMITED EXTENT

The four patients studied showed little tendency towards anemia. Viewed either from the point of view of peripheral cell concentrations, or red cell mass alterations, there is little significant evidence of red cell disappearance. An ex-

ample of the findings in one of these patients (Case 196) who showed no anemia is given in Table II.

One patient of this group (Case 254) had a total burn of 45 per cent and required energetic plasma therapy for the first 48 hours after his burn. The patient was group A. Studies of the two plasma pools used showed no anti-A antibodies in the first and an anti-A antibody titer of 1 : 64 in the second.* This patient alone of the second-degree group showed an increase in the excretion of

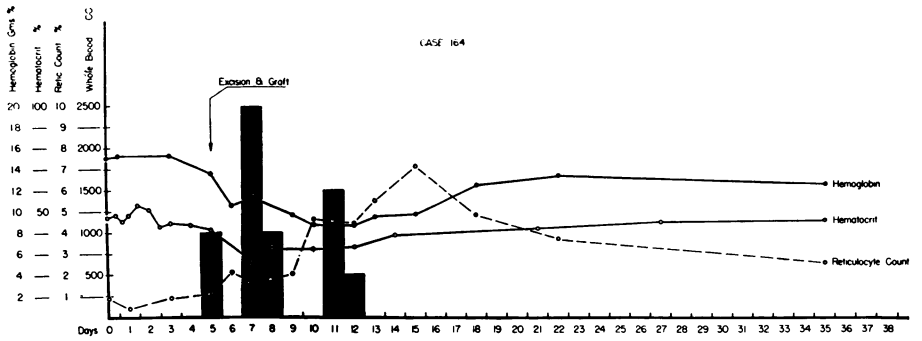

CHART 4.—Case 164: Hemoglobin concentration, hematocrit, reticulocyte response found and transfusions given a patient with moderately severe burns (36 per cent total, 7 per cent third degree).

An anemia became manifest on the sixth day and was not relieved until after the 22d day. Operation on the fifth day was attended by loss of blood presumably inadequately replaced by the 1,000 cc. of whole blood given (vertical black blocks). The red cell volumes (dye technic) were, on entry 2,510 cc., the second day 2,110 cc., and on the seventh day 1,210 cc. Accordingly, on the seventh and eighth days, respectively, 2,500 cc. and 1,000 cc. of blood was given. There was little effect on peripheral hemoglobin concentration and hematocrit but there was a rise in reticulocyte count. On the 11th and 12th days further transfusion again resulted in little immediate change in hematocrit or peripheral hemoglobin concentration but a further rise in reticulocyte count took place. Only after this regenerative response did the peripheral indices rise to normal. The red cell volume on the 27th day was 2,040 cc. These findings suggest (as do those in Case 269, Chart 9) that multiple closely spaced transfusions may be disappointing in their effects on red cell mass. They further indicate that transfusions do not suppress reticulocytosis in such a patient and that marrow regeneration may restore peripheral indices to normal quite rapidly.

urobilinogen in urine and feces during the second week following his burn. The low antibody (isohemagglutinin) titer probably precludes blood destruction from that source as the cause of this pigment excretion.

2. EXTENSIVE THIRD DEGREE BURNS

A. *Red Cell Mass (Dye) and Peripheral Blood Findings in Five Patients Surviving Injury:* These five patients are grouped together as the earlier patients studied before the isotope technic became available. Case 155 (Chart 3) demonstrates the amount of whole blood required to avoid anemia in an exten-

* We are indebted to Dr. Louis K. Diamond for these agglutinin studies which in this patient and in three others studied failed to demonstrate significant un-neutralized antibody titer in our plasma pools.

sive third degree burn patient subjected to early surgery. Case 164 (Chart 4) shows the disappointing effect of closely-timed red cell replacements. There is a subsequent rise to normal red cell count, but only after a striking reticulocyte response which was, in all likelihood, responsible for the return to normal. In Table III the total blood replacement required in these patients is shown.

All of these patients show red cell losses of 100-400 cc. per day during their early course; when one calculates the over-all red cell balance (*i.e.*, net volume change minus net replacement) this loss is apparent though its source, whether surgical or physiologic, is not clear. An example of such data is shown in Table IV. All figures in this table are in cubic centimeters of packed red cells; the

TABLE III

WHOLE BLOOD THERAPY IN PATIENTS WITH EXTENSIVE DEEP BURNS—EARLY SURGICAL CLOSURE

Case Number	Extent Burn Total/3°	Whole Blood Transfusions	Duration of Hospitalization
135	25/15	8,050 cc.	92 days
143	40/34	13,250 cc.	122 days
149	72/38	10,000 cc.	85 days
155	41/26	16,700 cc.	108 days
164	36/7	6,500 cc.	60 days

"loss per day" column indicates the average total loss per day (all sources) in the interval between the determinations. The magnitudes in this category are larger than those in subsequently described red cell balances because they include operative losses, whereas the balances are exclusive of such loss.

B. *Red Cell Mass, Radioiron Studies, Peripheral Blood Findings, and Pigment Excretion in Four Patients Surviving Injury:* The most extensive studies into the causes of the anemia encountered in deep burns were carried out in four patients who entered the hospital within the first hours after injury. All were treated with penicillin from entry. In three the life history of the burn was not disturbed by early operation; in one, excision of dead tissue was carried out on the eighth day after injury. The findings are recorded in detail in the form of case reports.

CASE 210

Case 210.—(Tables V and VI; Charts 5 and 6) : A previously well, 34-year-old housewife, and mother of three, received a flame burn of 31 per cent of her total body surface, 25 per cent of her total surface being a third degree burn. Striking evidence of internal red cell destruction as well as excretion of the end-products of such destruction were demonstrated and the findings correlated well with a somewhat checkered clinical course. Although the patient made a good response to shock therapy, clinically, she seemed sicker during the first week than the extent of the injury would have indicated. On the eighth day an attempt was made to hasten the care of her deep burns and relieve her of the burden of wound infection, by excising the burns under general anesthesia. The wounds proved, in spite of the penicillin, to have developed a deep-seated inflammation and bled profusely on excision. Operation was stopped before half was excised, and none was grafted immediately as had

been planned. Because of the poor clinical reaction to operation, grafting even of the excised area was not started until the twenty-first day. At this time the excised wounds were coated with fiery, infected granulations, while the unexcised were edematous, with evidence of deeper infection. Her later course was one of repeated skin graftings, slow healing, with gradual clinical improvement, and discharge about four months after entry.

Early Hemolysis: On the day of admission the patient showed evidence of nemolysis. A hemoglobin concentration of 0.11 Gm./100 cc. in the serum was observed in the first three hours after injury. Such a high level of free hemo-

TABLE IV

RED CELL VOLUMES, TRANSFUSIONS, AND AVERAGE LOSSES PER DAY (IN CUBIC CENTIMETERS OF CELLS)

Case 143
Male, Age 17, Weight 58.7 Kg.
Extent of Burn: Total/40% 3°/34%

Day	Red Cell Mass (Dye)	Transfusions	Losses Per Day
2	2,130		
6	1,650	420	185
40	1,600	4,750	140
65	1,890	1,125	34

Case 149
Male, Age 20, Weight 66.1 Kg.
Extent of Burn: Total/72%3°/38%

Day	Red Cell Mass (Dye)	Transfusions	Losses Per Day
0	2,750		
2	1,920		400
6	2,350	840	120
42	2,380	3,260	90
85	2,220		

Case 164
Male, Age 32, Weight 71.2 Kg.
Extent of Burn: Total/36% 3°/7%

Day	Red Cell Mass (Dye)	Transfusions	Losses Per Day
0	2,510		
2	2,110	420	410
7	1,210	1,125	400
27	2,040	1,125	15

PERIPHERAL BLOOD FINDINGS

Day	R.B.C. Millions	Hb. Gm.	Hematocrit % Cells
0	6.45		55
2	5.40		47
3	5.07		44
5	3.82	14.4	42
7	5.53	14.2	40
10	3.60	9.6	37
16	3.53	14.4	49
27	3.53	9.6	
34	4.34	13.6	40
45	4.54	14.4	45
75	4.80	14.4	48
103	4.64	15.5	54

Day	R.B.C. Millions	Hb. Gm.	Hematocrit % Cells
0			70
1			57
2			50
4	5.00	12.8	30
6	5.60	11.2	42
9	3.80	11.2	35
13	4.38	11.2	39
25	4.20	12.8	
42	4.40	13.0	48
52	4.20	12.8	45
85			49

Day	R.B.C. Millions	Hb. Gm.	Hematocrit % Cells
0	5.60	18.4	47
1	4.90	17.6	49
3	4.50	15.1	44
7	3.00	11.0	28
13	3.80	9.4	39
18	3.80	12.5	42
35	5.10	12.5	46
42			45
51			50

globin in the serum points to a comparatively large initial destruction of red cells. Only one patient of our series showed a greater concentration, 0.17 Gm./100 cc. in Case 234. The volume of red cells destroyed cannot be computed accurately from the concentration of free hemoglobin in the serum.*

* Hemoglobin injected into the blood stream as free hemoglobin[12] is rapidly removed and it is impossible from the serum value to calculate the total amount released by hemolysis if the hemolysis continues over a period of hours. If the serum concentration is multiplied by the plasma volume, it yields a figure of only 1.9 Gm. of hemoglobin, an obviously low figure. It would probably be more accurate to multiply the concentration by the volume of the entire extracellular space because hemoglobin, being a protein of low molecular weight (68,000), probably equilibrates into the extracellular space even more rapidly than albumin. Its rapid removal by the spleen, marrow, liver and kidney, makes any such calculation but an estimate.

Internal Red Cell Disappearance: The red cell balance, based on periodic measurements of the red cell mass, the addition of all cells lost by sampling and at operation and the subtraction of all given by transfusion, showed an early rapid and later slow disappearance of red cells from the circulation (Table V and Chart 5).

Reference to Table V shows, first, that the dye method for the measurement of the red cell mass checks well with the radioactive technic except in the early phase immediately following the burn. In this phase the presence of abnormal

TABLE V

Case 210

Female, Age 34, Weight 73 Kg.

Extent of Burn: 31 per cent total, 25 per cent third degree

RED CELL BALANCE

		Red Cell Mass		Red Cell Accounts			Red Cell Balance Change Per Day	
Period	Days After Injury	Dye Method	Radioactive Method	Transfusions Given	Samples Taken	Op. + Dressing Losses	Dye Method	Radioactive Method
I	0— 5	2010—(880)	1535—1370	263	68	0		— 90
II	5— 8	(880)—2100	1370—2100	756	18	0		— 3
III	8— 15	2100—2590	2100—2110	2118	39	730	—122	—191
IV & V	15— 34	2590—1560	2110—1410	1600	87	813	— 91	— 74
VI	34— 49	1560—1660	1410—1440	185	52	250	+ 16	+ 11
VII	49— 64	1660—2150	1440—1820	486	28	450	+ 32	+ 25
VIII	64— 86	2150—1860	1820—1720	52	25	68	— 11	— 3
IX	86—114	1860—1850	1720—1440	0	0	0	0	— 10
X	114—127	1850—2130	1440—(800)	0	0	0	+ 22	

(All figures are in cubic centimeters of packed red cells.)

RADIOIRON UTILIZATION

Period	Days After Injury	Radioiron Utilization Per Cent	Per Cent of Normal Utilization
V	28— 34	45.0	65.0
IX	93—102	47.2	68.0

capillary permeability in the wound and hemoglobin or other pigments in the serum may render the dye determination untrustworthy. The table shows, second, under "Red Cell Accounts," the enormous volumes of blood which may be lost by operative excision of a wound eight days after injury from granulating wounds into dressings and in grafting. The figure of 730 cc. in Period III under "Operation and Dressing Losses" represents 1,750 cc. of whole blood lost during the excision of slough. The subsequent figures show how large in aggregate may be the continued small loss into dressings and from grafting. A loss of 75 to 150 cc. of whole blood was determined each time the dressings were changed and a loss up to 200 cc. with each grafting.

The third section of Table V, "Red Cell Balance," details the average loss, or gain, of red cells per day after proper adjustment has been made for transfusions, sampling and dressing and operation loss. In the first five days,

Period I, there was an average disappearance of 90 cc. of red cells per day. From the fifth to eighth days, Period II, an approximate balance was achieved. Immediately following the wound excision, which took place between Periods II and III, there was a severe loss of circulating red cells which lasted through Period V. For the week of Period III approximately 200 cc. of red cells disappeared each day, while in the subsequent 19 days of Periods IV and V an average of 75 cc. per day could not be accounted for. It would appear that the

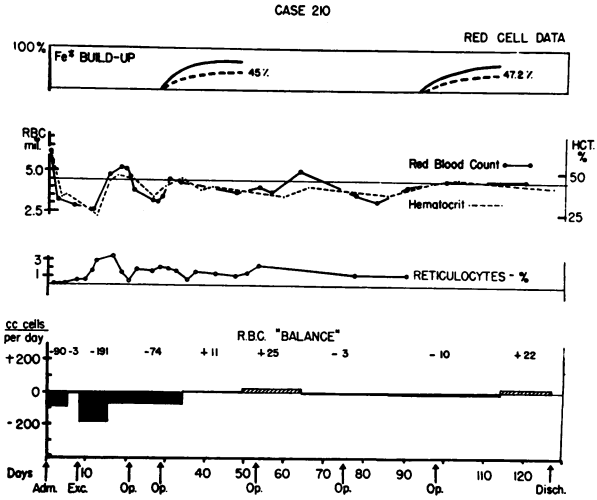

CHART 5.—Case 210: Radioiron utilization, peripheral blood findings and red cell balance demonstrating early progressive red cell destruction in a severely burned patient (31 per cent total, 25 per cent third degree).

The radioiron utilization curves (Fe* build-up) are diagrammatically shown. The solid line indicates the normal curve of 70 per cent utilization. The dotted lines indicate the observed values and on both occasions demonstrate some bone marrow depression due either to iron deviation or toxic depression of the bone marrow.

Red cell counts, hematocrit and reticulocyte counts show an early profound anemia followed by a reticulocyte rise, and later, maintenance of nearly normal peripheral indices.

The red cell balance (cf. Table V) is an expression of the net red cell formation or destruction as elucidated by serial measurements of the red cell mass. In this patient an early destruction is followed by a period of little change (average destruction of 3 cc. of cells per day) and then a secondary red cell destruction correlated in appearance with a partial excision of the burn wound.

Subsequent to the 35th day, destruction and formation are equally balanced, and there is less significant net change in red cell mass.

operative procedure, whether by a nonspecific incitation of metabolic changes or by kindling the infection, had tipped off this renewed internal or hidden red cell destruction which lasted three and a half weeks.

Throughout the second month after injury, Periods VI and VII, this patient achieved a positive balance of red cells; that is, she was able to make more than she was destroying internally. At the beginning of the second month, however, there was again evidence of internal red cell disappearance with a slight negative balance lasting for seven weeks, Periods VIII and IX.

Peripheral Blood Correlation: The examination of the peripheral blood by red blood cell count, hematocrit and hemoglobin concentration (Table VI and Chart 5) revealed for the greater portion of the period of hospitalization a close correlation between the red cell mass and the anemia in the peripheral blood. Only from the second to eighth day, when there was evidence of an enlarged plasma volume, did the peripheral anemia exceed the observed fall in red cell mass; such an anemia is, therefore, termed false. Two and a half months after entry the patient again developed a peripheral anemia, at the time when her red

TABLE VI

Case 210
Female, Age 34, Weight 73 Kg.
Extent of **Burn: 31 per cent total, 25 per cent third degree**

SERUM HEMOGLOBIN

Day + Hour Post-Burn	Hemoglobin Gm./100 Cc. Serum
0+2.5	0.11
0+3	0.11
0+4	0.10
0+4.5	0.06
0+7.5	0.02

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes %
0	6.04	17.7	58	
1		16.3	51	
2	3.25	13.5	44	
3			35	
4			37	
5			34	
6	2.91	12.0	36	0.6
11	2.64	8.0	25	1.7
15	4.80	16.8	44	3.5
21	3.85	14.0	44	2.0
26	3.26	13.5	34	1.2
34	4.30	17.0	42	0.8
42		15.0	41	1.5
50	4.95	14.0	35	1.6
53	4.08	14.3		2.7
56	2.82	12.0	35	
63	5.06	14.5	41	
77	3.70	13.0		1.5
82	3.20	13.8		
93	4.15	12.5	41	1.5
114			39	
127			40	

cell balance reverted to slight negativity. This anemia was repaired coincident with complete healing.

Excretion Products of Red Cell Destruction: Studies of the excretion of the end-products of red cell destruction in this patient (Chart 6) were illuminating as they corroborated in a satisfactory way the measurements already described of the patient's circulating red cell mass. During the first two weeks the patient was in the hospital, she showed consistently positive benzidine test in the feces, indicating that some hemoglobin or heme was being excreted intact

into the gastro-intestinal tract either through the biliary apparatus or through the large bowel mucosa. This is a constant finding in burn patients and has previously been reported,[13] but this patient demonstrated the phenomenon to an unusual degree and for a protracted period. The urine urobilinogen excretion is somewhat elevated on the first observation and then on the tenth day, shortly after the period of zero red cell balance the urine urobilinogen returned to normal.

Radioiron Utilization: During the course of the patient's convalescence, starting on the twenty-eighth day and again on the ninety-third day, two radio-

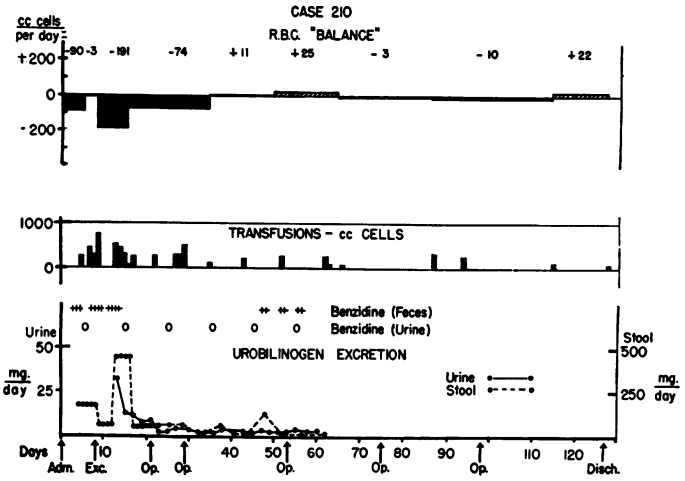

CHART 6.—Case 210: Red cell balance, transfusions and pigment excretion in the same severely burned patient as in Chart 5.

The red cell balance is repeated for orientation. The transfusions, recorded in cubic centimeters of cells, were administered according to clinical indications. It is apparent that their timing follows each of the first two periods of red cell destruction indicated by negative red cell balances.

The urobilinogen excretions are shown in milligrams per day in urine and stools. There is an increased excretion of this end-product of hemoglobin metabolism up to the 15th day, after which it is essentially normal.

Benzidine-reacting material is present in feces in the early period of destruction; the urine benzidine is consistently negative.

iron build-up curves were carried out, both of which showed some depression of bone marrow activity. The first curve showed 45 per cent utilization of the radioiron, which is only about 65 per cent of normal, and the second build-up curve showed 47.2 per cent utilization of the iron which is about 67.5 per cent of normal. As the result of these tests of marrow function a part of the anemia tendency late in the convalescence of this patient may be interpreted as due to inadequate bone marrow response. This, in turn, may be due to one of two factors, either inadequate supply to the marrow of hemoglobin precursors, especially iron, or secondly, alteration in bone marrow function as a result of the presence of a large, infected open wound. The iron utilization curves do not indicate which mechanism was operating.

Reticulocyte Response: During the maximal period of red cell destruction of the secondary anemia phase, the patient's reticulocyte response rises to 3 per cent in the peripheral blood and is maintained near 1 per cent for approximately two months, indicating little marrow activity as shown also by the poor radioiron utilization.

Summary and Discussion: This patient showed every laboratory and clinical evidence of massive internal red cell destruction. Many transfusions were required to maintain peripheral red cell concentrations within the normal range. There was slight evidence of bone marrow response, as indicated by the reticulocyte count, but this bone marrow response was probably subnormal, as indicated by the impaired utilization of radioactive iron.

TABLE VII

Case 217
Female, Age 26, Weight 92.8 Kg.
Extent of Burn: 78 per cent total, 45 per cent third degree

RED CELL BALANCE

Period	Days Post-Burn	Red Cell Mass: Dye Method	Red Cell Mass: Radioactive Method	Red Cell Accounts: Transfusions Given	Red Cell Accounts: Samples Taken	Red Cell Accounts: Op. + Dressing Losses	Red Cell Balance Change Per Day: Dye Method	Red Cell Balance Change Per Day: Radioactive Method
I	0— 3	2320—1410	—1380	742	59	0	—318	
II	3—11	1410—1690	1380—1250	45	63	0	+ 50	—19
III	11—16	1690—	1250—1930	742	43	135		+23
IV	16—25	—2160	1930—1830	101	10	0	— 14	—21
V	25—49	2160—2200	1830—2150	1850	85	531	— 50	—38
VI	49—71	2200—2160	2150—2010	1470	25	157	— 60	—65
VII	71—98	2160—(1660)	2010—2240	97	59	202		+15

(All figures are in cubic centimeters of packed red cells.)

RADIOIRON UTILIZATION

Period	Post-Burn	Radioiron Utilization Per Cent	Per Cent of Normal Utilization
I	0— 5	15.0	21.0
V	31—36	59.0	84.0
VII	80—85	70.0	100.0

It is difficult to know what rôle the operative procedure on the eighth day played in this anemia which became so much intensified after the operation. It should be emphasized again that the figures for red cell balance are over and above the operative and dressing losses and that, therefore, the increase in anemia tendency after the operation must be related either to continued insensible red cell loss into the wound or to some alteration in metabolism, possibly related to the alarm reaction following the operation. In any event, it is apparent that this patient needed one whole blood transfusion every three days in the first week and an average of one every two days in the next three weeks in order to maintain a constant red cell mass, entirely apart from the blood needed to replace operative and dressing losses.

CASE 217

Case 217.—(Tables VII and VIII; Charts 7 and 8): While tending a coal stove, the clothes of a robust, well-nourished single woman, age 26, caught on fire; 78 per cent of her body surface was burned, 45 per cent of the total body surface being of full-thickness destruction. Shock was successfully prevented with massive doses of plasma intravenously and an equivalent volume of oral fluids. During the phase of gradual resorption of the edema from the interstitial space, her kidneys were able to keep pace by a huge volume output and she had, therefore, only moderate and nonincapacitating hemodilution. Penicillin, in large doses, was started at entry and it was planned to start the excision and grafting of

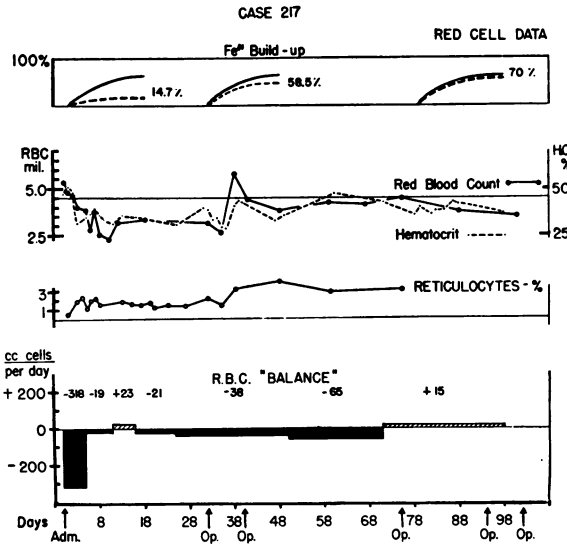

CHART 7.—Case 217: Radioiron utilization, peripheral blood findings and red cell balance demonstrating an early and late progressive anemia in an extensively and deeply burned patient (78 per cent total, 45 per cent third degree).

The radioiron utilization (Fe* build-up) is shown diagrammatically as in Chart 5 (Case 210). The first test done on entry showed little elaboration into peripheral erythrocytes, correlating with the relative lack of reticulocyte response; about the 30th day marrow function had improved, evidenced by better iron utilization as well as increase of reticulocytes to 4 per cent. By the 85th day utilization was normal.

The peripheral counts demonstrate an early profound anemia with relatively little reticulocyte response, followed about the 35th day by a rise with reticulocyte increase coincident with massive transfusion. Thereafter, nearly normal levels were maintained.

The red cell balance is shown as in Chart 5 (Case 210). There is an early massive red cell loss (internal destruction) followed by relative balance until about the 50th day when, for about three weeks, cell disappearance increased again. After this period a slightly positive balance obtained.

the full-thickness wounds on the seventh day. Fever appeared early, however, and had risen to 103° F. by the day before the intended operation. Widespread, moderately invasive infection beneath the deep burns (despite penicillin) was evident at change of the dressings and plans for early operative closure were abandoned. Grafting was eventually accomplished on the granulating base left after spontaneous separation of the slough. The first grafting was done on the fortieth day. The course of this patient was, therefore, less trammeled by operations than Case 210 and the anemia is more characteristic of that which is to be expected as the consequences of the burn alone.

Early Hemolysis: On the day of her burn the patient showed free hemoglobin in the serum to the extent of 0.12 Gm./100 cc., evidence of early red cell destruction.

Internal Red Cell Disappearance: The data on red cell volumes in this patient are shown in Table VII. A radioactive red cell volume was not determined on admission because it was decided instead to carry out an early build-up curve. However, in the patient's first five days, there is a marked destruction of red cells as indicated by the dye method, and as will be seen below this was correlated with urobilinogen excretion and doubtless represents the true situation.

After this initial destruction, the patient goes into a much less spectacular secondary phase than was the case with the previous patient. There is a de-

TABLE VIII

Case 217
Female, Age 26, Weight 92.8 Kg.
Extent of Burn: 78 per cent total, 45 per cent third degree

SERUM HEMOGLOBIN

Day + Hour Post-Burn	Hemoglobin Gm./100 Cc. Serum.
0 + 1	0.12
0 + 1.5	0.10
0 + 2.5	0.10

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes
0	5.30	16.0	43	
1	4.90	18.0	39	1.2
2	4.80	13.6	47	0.0
3	4.00	10.4	33	2.1
4	2.90	12.8		2.5
5	3.91	13.0	35	1.1
8	3.00	10.0	35	1.9
15		13.5		1.8
24		12.5		1.3
32	3.26	11.7	40	2.2
48	3.83	11.5	34	4.0
67	4.20	14.2		
88	3.87	12.0		0.3
101	3.51	9.8		
123	4.35	14.5		
179	4.50	14.4		

struction of red cells varying from 20 to 60 cc. a day for the next two months before the patient finally achieves a positive red cell balance.

Peripheral Blood Correlation: The determinations of the degree of anemia in the peripheral blood (Table VIII, and Chart 7) in this as in the previous patient followed closely the observed red cell mass except during the phase of hemodilution. This phase, or period of false anemia, was encountered from the second through approximately the eleventh day.

Excretion Products of Red Cell Destruction: The data of the excretion of the products of red cell destruction are shown in Chart 8. The excretion of urobilinogen in the urine is initially normal. The subsequently elevated values overlap the periods of red cell destruction. It appears both from the onset and the downward slope of the initial curve that there is a latent period (about 48 hours) between the release of hemoglobin in the circulation and the appearance of

unusual amounts in the urine as urobilinogen. Then from the eighth to sixteenth hospital day, shortly after the period when the patient was in transient zero balance, the urine-urobilinogen was normal. From the eighteenth to the sixtieth hospital day there were intermittent rises in urine-urobilinogen when the patient was destroying 20 to 60 cc. of cells per day. On the twentieth day a cystitis was recognized. There was no rise in excretion following the first grafting on the fortieth day but there was a peak the day

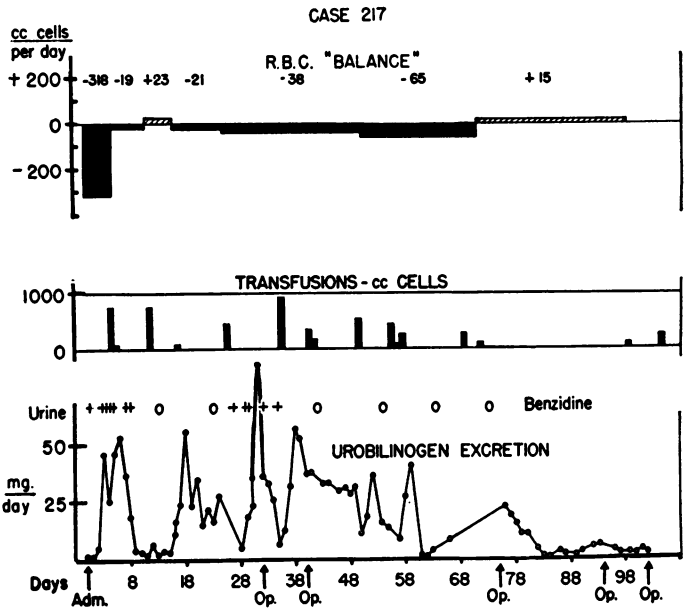

CHART 8.—Case 217: Red cell balance, transfusions and pigment excretion in the same severely burned patient as in Chart 7.

The red cell balance is repeated for orientation.

Transfusions (recorded in cubic centimeters of cells) were administered according to clinical necessity, and in this case there was no external loss from early operative excision.

Pigment excretion in the urine shows a striking rise, starting four days after entry, presumably in response to the early internal destruction shown by the negative balance. Excretion returns to normal on the ninth day only to rise again and remain elevated with occasional peaks until the 85th day, when, with slightly positive red cell balance internal destruction has evidently ceased.

Benzidine-reacting material is excreted in the urine coincident with the urobilinogen peaks.

following grafting of the back on the seventy-fifth day. After the eightieth hospital day the urine excretion figures remain in the normal range despite further surgery.

The urine shows a positive benzidine test during the high peaks of urobilinogen excretion indicating that either heme or hemoglobin is being excreted in the urine along with the metabolic end-product, urobilinogen.

Radioiron Utilization: The regenerative activity of the bone marrow was tested during three stages of the patient's convalescence. Radioiron was injected intravenously the day of entry and its elaboration into circulating red cells was

observed during the succeeding six days (Table VII and Chart 7). (In order to make this measurement, no radioactive transfusions were given during these days.) Only 21 per cent of the expected activity appeared in the circulation, indicating a severely depressed activity of the marrow. The second injection of radioiron was made on the thirty-first day. The marrow was more active than before but still somewhat depressed, the elaboration of the iron being 84 per cent of the expected normal. Such marrow synthesis is interesting in view of the extensive areas of open infected wounds. Six weeks later, two and a half months after entry, activity of the bone marrow was normal as judged by the third injection of radioiron.

Reticulocyte Response: The rise in bone marrow function as indicated by the second injection of radioiron was accompanied by a reticulocyte response from 2 to 3 per cent, and later 4 per cent (Chart 7).

Summary and Discussion.—As did the previous patient, this extensively and deeply burned patient showed evidence of massive internal destruction of red cells. Also, like the previous patient, she passed through a prolonged period of disordered physiology, with high fever, water retention and severe clinical illness. Both patients developed large open wounds.

Both showed an early acute red cell destruction of 100 to 300 cc. per day and lasting about four days. This phenomenon is interpreted as being the destruction of red cells whose viability had probably been altered by exposure to heat while circulating in the burned area at the time of the burn, though we have no proof of the veracity of this interpretation.

After this initial destruction, both patients show a transient period of essentially zero red cell balance followed by a secondary phase of red cell destruction not as spectacular as the early loss. In the first patient this secondary phase is quite acute, apparently related to the operative procedure carried out at that time. No such operation was carried out in this second patient and her later curve is smoother. Both patients showed late destruction far on into their convalescence which is correlated with occasional relapses of their anemia. An increased urobilinogen excretion corroborated the data derived from the volume measurements. Evidence of bone marrow suppression was found in both patients as subnormal levels of iron utilization. The reticulocyte counts correlated with the observed changes in iron elaboration but did not give indication in themselves, therefore, of the degree of deficiency of the red cell mass.

Case 260

Case 260.—While celebrating her impending departure for a tuberculosis sanitarium, the clothes of a 27-year-old, childless housewife, caught on fire, burning 28 per cent of her body surface, 12 per cent of her total surface showing full-thickness destruction. In anticipation of her developing a progressive anemia it was planned at entry to follow the erythrocyte changes and postpone all possible influences, such as transfusion and early operation, until the nature of the anemia was established. Her red cell mass was immediately measured with radioactive red cells. Her wounds were dressed without débridement or cleansing, and she was started on penicillin. The first grafts were placed on freshly excised wounds on the ninth day. The remaining areas were grafted at approximately weekly intervals, and the patient was discharged at the end of three months.

To our surprise she developed no true anemia. It was also true that she never developed a negative nitrogen balance. Both of these findings may be attributed to the relative absence of invasive infection and to a continuously good appetite.

From the third to the fifth days a mild anemia was observed in the peripheral blood. This was interpreted as a false anemia since the red cell mass (by radioactive technic) at entry was 1,475 cc., and seven days later 1,490 cc. Between these virtually identical determinations, 138 cc. of cells had been removed in sampling and no transfusion had been given. Though no significant alteration in the red cell mass was observed, there is evidence of excretion of the end-products of red cell destruction in supernormal quantities. From her fifth to

TABLE IX

Case 269
Male, Age 60, Weight 89 Kg.
Extent of Burns: 27 per cent total, 20 per cent third degree

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes %
1	5.63		59	1.1
2	5.09		47	1.4
4	4.09		40	1.1
6	4.68		39	1.0
8	4.20	11.2	35	1.0
10	3.20		37	
20	3.50		34	1:0
30	3.90		39	
47	3.95	11.5	38	0.5
68	4.00	9.5		1.0

tenth days the patient excreted, intermittently, slightly increased amounts of urobilinogen, the first peak being on the fifth and sixth days and the second peak following immediately her excision and grafting on the ninth day. Associated with this evidence is the presence of weakly positive benzidine-reacting material in the urine from the second to the seventh days, the period during which, it will be recalled, she showed a transient peripheral anemia. It is also of interest that during the latter phase of this period, the patient showed a definite reticulocyte response, suggesting that from the tenth day forward, her bone marrow could compensate for any red cell destruction.

CASE 269

Case 269.—(Tables IX, X and XI; Chart 9): This patient, age 60, apparently drunk when trying to fill a kerosene stove, was burned when his oil-soaked trousers ignited. Burned around the legs and lower trunk, he crawled into bed and was seen first by a doctor the next day. Twenty hours after injury he reached the hospital, showing extensive deep burns of the legs, buttocks, scrotum and perineum. It was estimated that 27 per cent of the body surface was burned, three-quarters of the burns being full-thickness.

Whole blood-transfusions and early operation were purposely withheld in order to learn the character of the anticipated anemia. The patient was given penicillin intramuscularly. The burn slough was allowed to separate spontaneously and the first grafts were

applied on the thirty-sixth day. Subsequent graftings were accomplished periodically. The patient was discharged on the one hundred and twenty-sixth day.

Early Hemolysis: There was no elevation of serum hemoglobin on admission to the hospital.

Internal Red Cell Disappearance: The circulating red cell mass was measured by the radioactive technic four times during the patient's convalescence.

TABLE X

Case 269
Male, Age 60, Weight 89 Kg.
Extent of Burn: 27 per cent total, 20 per cent third degree

URINARY EXCRETION OF BILE PIGMENT

Day Post-Burn	Urobilinogen Mg./24 Hr.	Benzidine
0	0.0	
1	13.6	—
2	8.2	±
3	6.2	±
4	17.4	±
5	23.9	—
6	13.4	—
7	7.4	—
8	5.8	—
9	14.8	—
10	14.0	—
11	17.3	—
12	8.3	—
13	9.5	—
14	8.2	—
15	8.7	—
16	8.7	—
17	6.6	—
18	10.8	—
19	6.1	—
20	4.2	—

TABLE XI

Case 269
Male Age 60, Weight 89 Kg.
Extent of Burn: 27 per cent total, 20 per cent third degree

RED CELL BALANCE

Period	Day Post-Burn	Red Cell Mass (Radioactive)	Transfusions	Samples Taken	Red Cell Balance
I	0–12	2780–1773	0	150	—72
II	12–25	1773–2077	147	40	+15
III	25–34	2077–2564	1311	150	—85

(All figures are in cubic centimeters of packed red cells).

The measurements were made on the day of entry, the twelfth, twenty-fifth and thirty-fourth days. During the first 12 days, between the initial and second volume studies, there was a disappearance of 857 cc. of red cells, or 72 cc. of cells per day. The disappearance of these cells was shared in equal proportion by the patient's cells and those from the radioactive donor. Since the latter were not in the body at the time of the injury, this disappearance presumably was not the direct result of heat on cells.

During the second period, between the second and third red cell volume determinations, the patient showed a net red cell gain averaging 15 cc. of cells per day, and the concentration of radioactivity of his circulating cells slowly decreased as further evidence of regeneration. In the third period, between

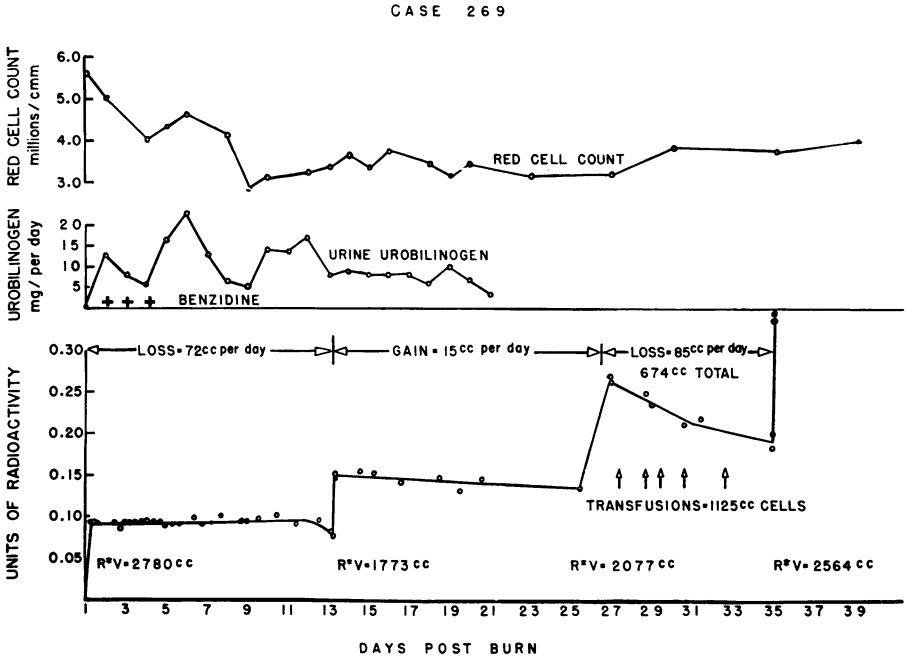

CHART 9.—Case 269: Red cell counts, urobilinogen excretion and radioiron data showing an early progressive anemia in a severely burned patient (27 per cent total, 20 per cent third degree).

Whole blood transfusions were withheld until the 27th day post-burn except as necessary to measure the red cell mass (R*V). To such purpose, radioactive transfusions were given on the first, 13th, 26th and 35th days. A peripheral anemia developed in the first ten day with a falling red count, evidence of increased urobilinogen excretion and a loss of 72 cc. of cells per day (average) during the first two weeks. During this time the radioactivity of the patient's red blood cells (resulting from an active transfusion the first day) did not alter significantly, indicating that his own cells and those of the radioactive donor partook equally of the destruction.

From the 13th to 26th day the red cell count remained stationary, urobilinogen excretion was not elevated, and the patient showed an over-all gain of 15 cc. of cells per day (average); the peripheral radioactivity fell slightly, indicating active regeneration sufficient to prevent further anemia but not sufficient to compensate entirely for previous cell losses.

Starting on the 27th day the patient was given five transfusions totalling 1,125 cc. of cells. The red count rose very little and the red cell mass increased only 500 cc. (The drop in radioactivity was due to dilution of the active cells by bank blood, cf. Chart 1.) The findings suggest that multiple closely spaced transfusions may give disappointing results in terms of red cell mass changes.

his third and fourth cell volume determination, the patient was given five whole blood transfusions, totalling 1,125 cc. of cells, as well as the small amount of radioactive cells given him, but the total increment in volume was only about 500 cc. The calculated destruction of cells during this period is 674 cc. The

period involved is eight days long and the cell destruction per day, therefore, averaged 85 cc.

The reason for this massive disappearance of red cells and failure to rebuild completely the red cell mass is not clear. The downward slope of the curve of concentration of radioactivity in this last period of observation is what should be expected from the increase in size of the red cell mass, the radioactive cells remaining in the circulation. Whether the entire disappearance was at the expense of the recently transfused cells cannot be determined from the findings. The patient showed no untoward clinical reaction to his transfusions.

Excretion Products of Red Cell Destruction: The disappearance of red cells in the initial period was accompanied by a rising excretion of urobilinogen which reached a peak on the fifth day after injury of 23.9 mg. Following this

TABLE XII

Case 234
Male, Age 68, Weight 60 Kg.
Extent of Burn: 55 per cent total, 45 per cent third degree

RED CELL VOLUMES, TRANSFUSIONS, AND RED CELL BALANCE

Day Post-Burn	Red Cell Mass (Radioactive)	Transfusions	Samples Taken	Red Cell Balance
0	2030			
3	1600	75	59	148
7	1420	300	76.5	100

(All figures are in cubic centimeters of packed red cells.)

Day + Hour Post-Burn	Serum Hemoglobin Gm./100 Cc.
0 + 8	0.16*

* Earlier serum hemoglobin estimations showed larger amounts of hemoglobin to be present, but a quantitative result was not obtained because of the inaccuracy of the colorimeter in dealing with high hemoglobin concentrations in undiluted serum.

peak there was a gradual decline during the 20 days the measurements were made. There was but a transient and early excretion of benzidine-positive material in the urine.

Summary and Discussion: This patient showed two periods of red cell destruction with a period of red cell regeneration and increase in red cell mass between. The early period of destruction and the relative constancy of red cell radioactivity constitutes evidence that in this patient, at least, the anemia was not due to selective destruction of the patient's own cells on the basis, for instance, of heat sensitization or fragility. It suggests that the red cell destruction included proportionately both the patient's own (burned) cells and those (unburned) infused from the radioactive donor.

The later period of destruction demonstrates the occasional costliness of repeated transfusions. More than half of the volume of cells given in five transfusions disappeared during the eight days during which they were administered.

C. *Red Cell Mass, Radioiron Studies, Peripheral Blood Findings and Pigment Excretion in Four Patients Not Surviving Injury:* The four extensively and deeply burned patients of this group are of considerable interest due to variations from the preceding group of surviving patients.

Case 234.—(Table XII): An elderly man showed all the phenomena we have come to associate with the burn anemia—hemoglobinemia, hemoglobinuria,

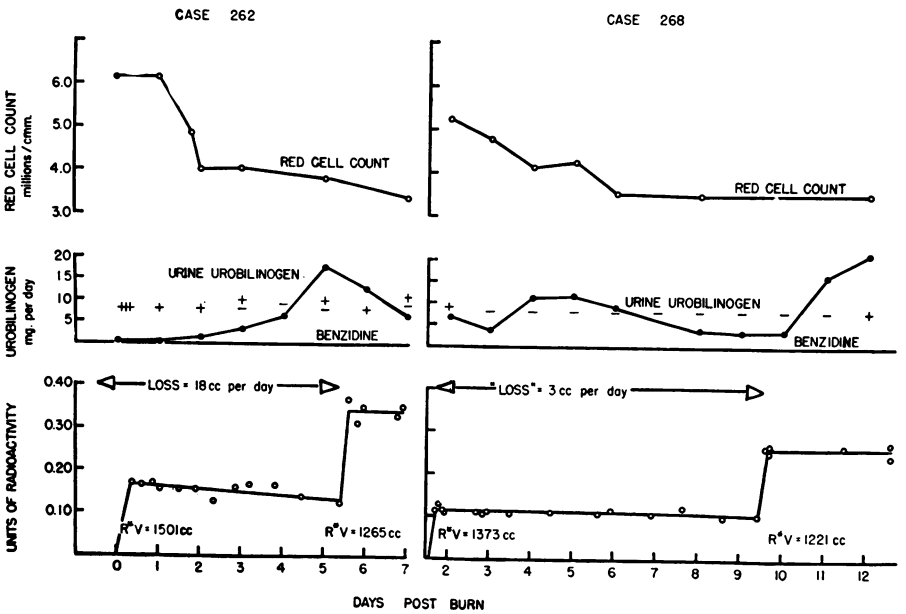

CHART 10.—Cases 262 and 268: Red cell counts, urobilinogen excretion and radioactivity data indicating mild cell destruction in two severely burned, aged patients dying of their injuries (male, age 64, 85 per cent total, 58 per cent third degree; female, age 83, 62 per cent total, 22 per cent third degree).

The rapidly developing peripheral anemia indicated by the fall in red cell count was not accompanied by a comparable decrease in red cell mass and is, therefore, a false anemia. Both patients showed an increase in urobilinogen excretion, Case 262 also showing considerable excretion of benzidine-reacting pigment in the urine. This evidence of red cell destruction was accompanied by a slight fall in red cell mass (R*V) in Case 262. In Case 268 the average loss of 3 cc. of cells per day is within the limits of error of the method.

The radioactivity concentrations in both cases, which resulted from active transfusions given soon after injury, remain approximately constant; the slight fall in Case 262 may be significant, which would indicate active cell regeneration during the period of destruction.

red cell destruction, as indicated in volume measurements, and even jaundice.* The other three, however, all showed evidences of cell destruction which seem to be disproportionally small in relation to their massive and fatal injuries.

* We have seen little clinical jaundice. It is our impression that in a group of sulfanilamide-treated patients clinical jaundice is more frequently encountered than in a series treated with penicillin. This may be traceable to the fact that the blood pigment released in the blood stream by early hemolysis can be metabolised efficiently by the liver if it is not also suffering under the load of an hepatotoxin, such as a sulfonamide.

Case 262.—An elderly man showed a slight rise in urobilinogen excretion but his volume changes showed little evidence of red cell destruction. Multiple determinations of his cell radioactivity after radioactive transfusions showed a slight lowering of activity compatible with slow destruction of the donor cells (Chart 10).

Case 268.—(Chart 10): An aged woman showed no benzidine-positive material in the urine, an unique finding for such an extensive burn (62 per cent total) which was fatal in 13 days. The cell volume data and cell activity data show no departure from normal.

Case 231.—A male, age 36, with a skin burn of 68 per cent, 39 per cent of his total surface being full-thickness, succumbed on his sixth day to the pulmonary effects of the burn and disordered fluid metabolism, with pulmonary edema. An iron build-up curve carried out during his five days of life after the injury showed an essentially normal utilization, a departure from the data recovered from the first two patients of the previous group (Cases 210 and 217). This patient also showed an increase in urobilinogen excretion and a strongly positive benzidine reaction in the urine as evidence of hemolysis.

TABLE XIII

CELL CHARACTERISTICS

Case	% Burn Total/3°	Day Post-Burn	R.B.C. Millions	Hb. Gm. %	Hematocrit % Cells	M.C.V.* Cμ§	M.C.H.† γγ ‖	M.C.H.C.‡ %
Normal			4.5–5.0	16.0 ± 2	47 ± 5	90–105	32–38	26–30
170	15/17	9	3.9	11.0	41	105	28	26
		15	4.3	12.4	44	103	30	28
260	28/12	7	3.1	12.6	36	115	40	35
		34	2.8		34	120		
135	25/15	14	3.7		37	100		
149	72/38	5	3.5	12.0	39	111	38	34
155	41/26	1	4.3	15.1	50	116	35	30
		16	4.1	12.6	36	93	32	35
		30	4.0	12.6	56	140	32	23
		40	4.8	17.5	48	100	35	35
		55	4.3	10.6	48	110	25	23
210	31/25	11	2.6	8.0	25	95	31	33
		28	3.5	11.5	38	100	33	33
217	78/45	4	3.9	13.0	34	87	34	39
		18	3.5	12.0	35	101	35	34

Explanation of Table:

* M.C.V. = Mean Corpuscular Volume.

† M.C.H. = Mean Corpuscular Hemoglobin.

‡ M.C.H.C. = Mean Corpuscular Hemoglobin Concentration. The normals are taken from Wintrobe, *et. al.*,[5] except for M.C.V. which is based on our normal R.B.C. of 4.5–5.0 million.

§ Cμ = Cubic micron (.001 mm. = 1μ).

‖ γγ. = One thousandth of a gamma (.000001 mg.).

3. OTHER HEMATOLOGIC OBSERVATIONS

The red cell characteristics encountered at various times during the care of patients is shown in Table XIII. These data are representative of the whole group. Some macrocytosis with slight tendency to hyperchromia are the only significant abnormalities.

COMMENT

Anemia or a decrease in circulating red cell mass is a complication of the deep burn. All of our patients developing a significant anemia, have had burns with full-thickness destruction, usually of 10 per cent or more, of the body surface. Patients with superficial burns of more than 20 per cent of the

body surface may exhibit a false anemia due to hemodilution from an increased plasma volume. In patients with either full-thickness or superficial burns, this false anemia must be differentiated clinically from the true anemia. In the false anemia the treatment depends upon with-holding fluid and allowing renal excretion to keep pace with the resorption of edema fluid. In the true anemia red cells in the form of whole blood transfusions are needed.

In the patient with an extensive full-thickness burn the true and false anemias may coexist. Examination of the patient clinically for stage of edema formation or resorption, of the urine output for diuresis, of the serum for protein dilution, and of the peripheral erythrocyte indices for red cell concentration provides good clues as to the extent of the false anemia. There is no wholly satisfactory substitute, however, for an objective measure of the red cell mass by any one of the several available methods, and such measurements should form a part of the clinical care of an extensively burned patient.

The true anemia of burns develops in three stages; only one or two of the stages may be encountered. The first stage stems from the initial hemolysis connected with the injury and is the least severe of the three. The second stage takes place during the first week or ten days. It may be, in part, related to injury of the red cells, but has other causes, including depression of the bone marrow. The third stage appears in the third or fourth week, has multiple causes, including hemorrhage from the wound, and may persist until the wounds are closed. Between the second and third stages a transitory period of positive red cell balance has been observed in some patients.

From the practical point of view the development of anemia must be constantly suspected in severely burned patients, its extent accurately measured and the red cell deficit met with whole blood transfusions. At the peak of destruction in the second and third stages as much as 500 cc. of blood (250 cc. of cells) may be required each day. In addition, the blood lost in grafting must be replaced. If only grafts are cut, but 100 to 150 cc. may be lost. If excision of the wound is to be carried out before grafting, preparation should be made to replace much larger quantities. Bleeding from excision of recently burned, freshly edematous wounds is limited to a relatively few large vessels, while that from older, more inflamed than edematous wounds may be profuse from numerous small vessels. As much as 1,750 cc. of whole blood has been lost during the excision of extensive, inflamed wounds.

The recent suggestion of Moyer and Coller[14] that whole blood rather than plasma be employed to maintain circulating blood volume after severe burns involves consideration of *Rh* typing, the effect of high hematocrit on blood viscosity and cardiac output, and other questions which are beyond the repair of anemia. The amounts of red cells employed in such treatment far exceed the requirements imposed by the burn anemia, and any results claimed for such therapy cast little light on the extent of this anemia.

Of the factors which may participate in producing the red cell loss in the three clinical stages, the following deserve mention:

1. *Early Hemolysis and Cell Fragility:* Our findings corroborate the pres-

ence of early severe hemolysis in most (but not all) deeply burned patients. The total mass of cells involved in this initial hemolysis does not exceed 10 per cent of the red cell mass. We have no evidence that the increased fragility is due to the heat and not to some other disturbance, for example, in fluid distribution or enzyme activity, which continues to operate for some time after injury.

2. *Blood Destruction by Un-neutralized Plasma Antibodies:* In spite of the theoretic possibility, we have no convincing evidence that un-neutralized plasma antibodies played a rôle in cell destruction in any of the patients included in the present study.

3. *Blood Loss through an Open Wound:* As the burned tissue sloughs away, an open wound is produced which may cover a large area of the patient's body surface. It is clear that any operative procedure, however minor, produces red cell losses from this large surface. It is not so obvious, however, to what extent red cells may leak from this wound into the dressing, there to be digested by bacteria and the hemoglobin converted into a metabolic end-product which removes its color, obscuring the extent of the cryptic hemorrhage.

4. *Infection:* All of our patients showing hidden progressive disappearance of red cells had large open infected wounds. Contamination and subsequent infection is truly inevitable in any deep burn, even with the massive use of penicillin and other agents directed at the infecting micro-organisms.[15] Yet not all of the patients with extensive infected wounds developed anemia. No difference in the types of infecting organisms was noted in those patients developing anemia from those with none.

Infection is doubtless important but until a third degree burn of considerable extent can be maintained without infection by the use of some, as yet unknown, antibacterial agent, it is impossible to separate the factors of iron deposition in the inflammatory barrier and infectious toxemia from the rôle played by a slow-leaking hemorrhage from the large open wound.

5. *Disordered Iron Metabolism and Depressed Marrow Function:* The impaired elaboration of radioactive iron into the hemoglobin of circulating red cells of our patients points to disorder of iron metabolism and depressed bone marrow function as an important factor in the anemia of burns. (This statement is made in spite of the fact that in one patient, later dying of his injuries, a normal utilization was observed.) The low reticulocyte counts generally encountered in our patients and the occasional macrocytosis confirm a depressed marrow activity.

In addition to the mechanism studied by Wintrobe, there are in burned patients other possible causes for disorder of iron metabolism and hemoglobin synthesis. Gastro-intestinal tract function is grossly disturbed. Edema, ulceration, gastritis, all may play a rôle. Liver function may be altered. These factors might lessen iron absorption and hemoglobin synthesis. The impaired utilization of radioactive iron of our patients could not have been due to impaired absorption, however, since the iron was injected intravenously.

6. *The Alarm Reaction:* It is impossible at present to do more than speculate on the importance of the alarm reaction in red cell destruction and bone

marrow depression. Prolonged negative nitrogen balance with transient negative potassium balance has been found in all but one of our cases.[16] If this is an outward manifestation of cell breakdown and the release into extracellular fluid of substances normally intracellular, it is conceivable that the red cells may partake of the process, or perhaps the nucleated erythrocyte precursors in the marrow which more closely resemble other body cells in their vital processes. Another possible explanation is that protein synthesis is blocked; the formation of globin may be retarded, hindering hemoglobin production.

That the alarm reaction or adaptation syndrome[17] is in some manner implicated in the progressive anemia is suggested by the observations that the one patient not showing a negative nitrogen balance did not develop an anemia, and by the rapid increase in cell disappearance following operation (Case 210). Operation is a well-known stimulus of the alarm reaction.

7. *Multiple closely placed transfusions* were occasionally found to be disappointing in restoring red cell volume. On the other hand, no evidence was found to support the contention that transfusions inhibit marrow activity. Undoubtedly the gradual replacement of losses as they occur is more economical of blood as well as more physiologic. Delay in blood replacement is followed by substitution of extracellular fluid for the lost red cell mass, with restoration of total blood volume and a low peripheral red cell concentration. Delayed replacement produces an expanded blood volume which results in an increased cardiovascular load and, possibly, compensatory destruction of a portion of the infused cells.

SUMMARY

An anemia of varying severity may be present in burned patients. If not repaired, it will retard healing, prolong hospitalization and jeopardize the healing of skin grafts. This anemia has been investigated by serial studies of the red cell mass and bone marrow activity, employing a radioactive isotope of iron and by measurements of pigment excretion.

The anemia is found only in patients with full-thickness burns; it may, in rare cases, surprise one by its absence, even during the acute phase in patients with fatal burns.

True reductions in red cell mass must be distinguished from the false anemia of hemodilution encountered early in the patient's course. The therapy of each differs.

Multiple influences including hemolysis, cryptic wound hemorrhage, iron deviation, gastro-intestinal absorption, infection and marrow depression enter into the etiology of the anemia.

Its anticipation and early replacement is far preferable to late recognition and delayed transfusion.

While clinical observation may provide the astute surgeon with many clues as to the state of the red cell mass, and may help to distinguish true anemia from false (hemodilution) anemia, there is no adequate substitute in the clinical care of a severely burned patient, for serial objective measurements of the red cell volume.

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