The Anemia of Trauma

By ELIZABETH TOPLEY AND RUSCOE CLARKE

Keith in 1919 reported the plasma volume and hematocrit of a few battle casualties, and showed that primary hemorrhage was the main factor underlying their subsequent anemia. Observations by Grant and Reeve, Dacie and Homer, Vaughan, Crosby and Howard, and others have defined the position in greater detail especially in war injuries: but confusion still exists on the relative contribution of different factors to the anemia of trauma. This confusion is partly due to mistrust of the reliability of plasma volume estimates on which the evidence of earlier workers had to be based, and partly to lack of precise data on the importance of factors other than primary blood loss—such as a later increased destruction of red cells (Crosby and Howard, Editorial), impaired hemoglobin synthesis (Vaughan) or changes in plasma volume. Many patients with moderate injuries have developed clinical sepsis which itself is responsible for a further fall in red cell volume and hemoglobin level.

This paper is an attempt to define more precisely the relative importance of different factors in the anemia of trauma. It reports the sequence of hematologic findings following civilian trauma in patients whose red cell volumes at the end of primary treatment varied widely both above and below normal. In 20 patients three or more red cell and plasma volume estimates were carried out at varying periods after injury. On these and 37 other patients repeated observations were made of the hemoglobin, red cell count, reticulocyte count and transfused cell count.

Materials and Methods

Clinical details of 22 more thoroughly investigated patients are summarized in table 1. Most of these patients had lower limb injuries, associated with one or more major fractures. Case histories have been reported elsewhere (Clarke et al.). The remaining patients in the present investigation had similar injuries. Clinical infection was rare and large areas of nonviable tissue were not present.

Blood transfusion policy was deliberately varied and such variation was the main cause of differences in the balance between blood lost and blood transfused.

Laboratory Observations

Hemoglobin, red cell count, transfused red cell count and reticulocyte count were estimated on ear capillary blood often daily during the first two weeks and at less frequent

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### Table 1.—Relation between Clinical Details, Red Cell Volume Changes and Venous Hematocrit Day 4-14

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<td>55</td>
<td>65</td>
<td>Hands</td>
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<tr>
<td>36</td>
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<td>54</td>
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<td>+++ +</td>
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<td>35</td>
<td>33</td>
<td>62</td>
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<tr>
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<td>63</td>
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<td>Ulna</td>
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<td>33</td>
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<td>Trochanteric femur: clavicle: 1st rib</td>
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<td>Tib. &amp; fib.</td>
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<td>Femur</td>
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<td>29</td>
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* Blood loss calculated from RBCV and blood transfused (Clarke et al.)

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intervals for at least three months. Oxalated venous blood (Heller & Paul) was used for these tests on the days of volume studies, at which time a hematocrit, white cell count, and blood film were made. In 20 patients plasma and red cell volume determinations were done 1–4 days (usually 1–2 days) after admission, when it was considered that bleeding had ceased. They were repeated 3–12 days later (4–14 days after injury), sometimes once or more during the ensuing weeks, and finally 3 or more months after injury. The final volume determinations were usually performed after readmission to hospital at least three months after injury. Peripheral blood tests were repeated whenever possible at least twice after this "normal" blood volume estimate, and were sometimes continued for many weeks. The results of the last one to three hemoglobin and red cell counts before final discharge was taken as the patient's "follow up normal" level.

Venous hematocrit was estimated by centrifuging oxalated venous blood in Wintrobe hematocrit tubes for 55 minutes at 3000 revolutions a minute in a centrifuge with head radius of 15 cm; 2.5 per cent was subtracted from the hematocrit reading to allow for trapped plasma (Chaplin & Mollison). Hemoglobin was estimated by the oxyhemoglobin method, the optical density being measured photoelectrically. The calibration curve was checked monthly by a standard blood in which the hemoglobin had been determined by a number of methods.

Red cell counts were performed by the method described by Dacie. At least 1,200 cells were counted for each test, the usual practice being to count 240 squares of a Neubauer chamber.

Transfused cell count. In group M positive patients who had received group M negative blood, the M negative red cell count was made after differential agglutination with anti-M serum kindly supplied by Dr. van Loghem. The method was essentially similar to that described by Reeve. The differences were that a constant volume delivery pipette was used; and that the mixtures were made in small ampoules which could be sealed and therefore adequately mixed on a rotary machine. At least 1,200 cells were counted for each test.

Reticulocyte counts. At least 1,000 red cells were counted on blood films made after staining with brilliant cresyl blue in citrate saline (Dacie).

Red cell volume estimations were made by the radioactive phosphorus technic essentially as described by Reeve and Veall with Chaplin's modification. In this method red cells are labeled with radioactive phosphate and injected intravenously. Venous samples are taken at varying periods after injection, and it is assumed that the dilution of radioactivity reflects the dilution of the injected red cells in the general circulation, after allowing for the small leak of radioactive phosphate during this time (0.1 per cent per minute). This dilution factor multiplied by the venous hematocrit gives the "red cell volume." The method is discussed in detail by Reeve. The only innovation was the use of specially manufactured syringes for injecting the labeled cells. Each was more than twice as long as the ordinary 10 or 20 ml. syringe and calibrated gravimetrically to deliver the volume, which varied from 8-9 ml. (on each of 7 syringes there was less than 0.1 per cent difference between 3 measurements). The Luer-loc fitting avoided leaks between needle and syringe.

Evans blue plasma volume. (Reeve). Evans blue was injected with one of these special syringes. The optical density of the standard and samples were read on a spectrophotometer at 630 m to estimate Evans blue, and also 540 m to detect any hemolysis and at 680 m to determine background opacity. Die away curves were plotted on the large majority of patients by taking venous samples at varying periods after injection of the dye. The average rate was 0.1 per cent per minute. The calculation of plasma volume was made on the result of the first sample taken 10–15 minutes after injection, after allowing for the average die away.

**Results**

About half of the patients had red cell volumes on day 1–4 equal to or greater than their follow-up value ("adequately" transfused), while the remainder had red cell volume deficits ("inadequately" transfused). An example of a patient

* Supplied by the Medical Supply Association.
transfused back to a normal blood volume is shown in figure 1. She had a comminuted fracture of the upper femur, bruising of both legs, and a fractured clavicle. After primary treatment, including the transfusion of 1.6 liters of blood, the red cell volume was only 1 per cent below the follow-up value. The hemoglobin, though falling during the second week, never fell below 12.6 Gm. per cent (88 per cent of the follow-up value of 14.3 Gm. per cent). Typical examples of patients with "inadequate" blood transfusions are shown in figures 2 and 3. Figure 2 shows the chart of a patient with deep lacerations of the foot, enormous swelling of the thigh, with an anterior puncture wound complicating a fracture of the femur with wide separation. Operation for the insertion of a Kuntscher nail revealed a large hematoma and extensive tearing of muscle. He was transfused with 4.0 liters of blood. The red cell volume the next day was 33 per cent below the follow-up value. Figure 3 shows the chart of a patient with a fracture of the left tibia and fibula and a dislocated hip. At operation the hip was reduced, the leg wound excised, explored and sutured, the fracture reduced. He received no blood transfusions. The red cell volume two days after injury was 29 per cent below the follow-up value. The peripheral blood findings in these two cases were essentially those described in the past as typical of the anemia of trauma. A period of developing anemia lasting one to two weeks was followed by slow recovery.

The scale of hemoglobin values and red cell counts in these charts is such that were there no change in mean cell hemoglobin the lines would run parallel. Detailed inspection of such charts combined with calculations of mean cell
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Fig. 2.—Chart of patient with fractured femur and soft tissue injuries of thigh, knee and foot. (Male, Case 34, table 1). Red cell volume low on day after injury. "Inadequate" blood transfusion.

Fig. 3.—Chart of patient with fractured tibia and fibula and dislocated hip. (Male, Case No. 31, table 1). Red cell volume low on day after injury. No blood transfusion.
hemoglobin, mean cell volume and mean cell hemoglobin concentration have shown no significant deviation from normality in any of these findings. It is therefore possible to use the hemoglobin level, red cell count or venous hematocrit interchangeably as the index of anemia. In practice we have used the venous hematocrit on the day of red cell and plasma volume studies. For daily changes we have used hemoglobin results as probably more accurate than red cell counts and more frequently tested than the venous hematocrit.

The hematologic findings in these and the remaining cases will be discussed in terms of the relative contribution of primary blood loss unreplaced by blood transfusion, of further disappearance of red cells after primary hemorrhage has ceased, and of other possible factors contributing to anemia.

Balance between Primary Hemorrhage and Its Replacement by Blood Transfusion

In an earlier paper hemorrhage was estimated by measurement of external blood loss and limb swelling (Clarke et al.3). There was substantial agreement between such measurements and estimates of blood loss calculated from the red cell volume on the 1st to 4th day after injury and the volume of blood transfused. The major factor influencing the red cell volume after injury appeared to be the balance between blood transfusion and blood lost by primary hemorrhage. In this paper the red cell volume credit or deficit is taken as an indication of the balance between primary hemorrhage and its replacement by blood transfusion. In table 1 the patients are ranked in order of this red cell volume credit or deficit which varied from 48 per cent above to 58 per cent below the follow-up values. The venous hematocrits observed on day 4–14 are also shown in table 1. It can be seen that the first seven patients had a red cell volume credit at the end of their emergency treatment of +15 per cent or more and showed a venous hematocrit on the 4–14th day that was higher than normal. The last eleven patients in table 1 had a red cell volume deficit at the end of their emergency treatment of 19 to 58 per cent and showed a venous hematocrit on the 4–14th day that was lower than normal. These results indicate that the primary red cell volume credit or deficit is contributing to the high or low venous hematocrit on the 4–14th day. On the day of the second red cell volume estimate it was found that the blood volume (Evans blue plasma volume plus red cell volume) had frequently not returned to normal from the high or low level found at the end of primary treatment. For this reason an estimate of the anemia based on a study of daily changes in the peripheral blood might be expected to give a more accurate guide to the initial red cell volume deficit than any single observation.

Inspection of the charts of 57 patients showed a rise of hemoglobin (higher than the day after injury for at least 2 subsequent days) only in those patients who received blood transfusions larger than their actual blood loss. All but these more generously transfused patients showed a fall of hemoglobin during the ensuing two weeks. Patients with a slightly raised red cell volume at the end of emergency treatment showed a slight fall below normal (e.g., fig. 1) during the next two weeks. Patients with a low red cell volume showed a sharper fall during the first week (e.g., figs. 2 and 3). In the large majority of patients, the lowest level was reached by the 14th day.
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Figure 4 shows a scatter diagram of the relationship between red cell volume credit or deficit at the end of primary treatment and the later lowest hemoglobin level. The straight line represents the "expected" hemoglobin if the blood volume and body/venous hematocrit ratio were normal at the time of later hemoglobin estimates, and the red cell volume was the same as it was at the end of the primary treatment. It can be seen that there is a close correlation between the initial red cell volume and the later anemia, but most of the results lie above and to the left of the "expected" line. For example, those patients whose hemoglobin fell 25 per cent or more below normal, all had a red cell volume deficit of more than 15 per cent at the end of their primary treatment. The adequacy of the primary blood transfusion was clearly the major factor influencing the later hemoglobin changes; but other minor factors were also involved.

Further Disappearance of Red Cells

The rate of disappearance of red cells has been deduced from the change in red cell volume (table 1, column 3) and the probable rate of red cell formation derived from reticulocyte counts. The scatter diagram in figure 5 defines the relationship between the reticulocyte peak and the lowest hemoglobin, while examples of repeated reticulocyte counts in the same patient are shown in figures 1, 2 and 3.
Fig. 5.—Relationship between lowest hemoglobin and reticulocyte peak. Figures refer to day after injury of reticulocyte peak.

The evidence that an increased rate of disappearance of red cells is continuing for some time after primary hemorrhage has ceased rests on a more than 20 per cent fall of red cell volume, too great therefore to be explained by complete absence of red cell formation (table 1: cases 12, 2, 32, 36), on a fall in red cell volume in the presence of a normal reticulocyte count (table 1: 13 cases) or a very slight rise in red cell volume in the presence of a high reticulocyte count (table 1: cases 1, 29, 31). Every case investigated so far falls into one of these categories.

Six out of the 20 cases with full blood volume studies had had no blood transfusion, so clearly it was the patients' own blood which was disappearing. In 14 transfused patients the contribution to this disappearance of donor as well as recipient cells has been studied by Ashby differential agglutination after transfusion of group M negative cells to group M positive patients. The M negative red cell volume frequently fell more than 1 per cent per day. The shape of the die away curve of M negative cells in the peripheral blood will be reported elsewhere. It was different from that to be expected from the rapid disappearance of stored red cells. All blood used was less than three weeks old, carefully cross-matched, and of the correct A B O and Rh group.

Clinically detectable hemorrhage sufficient to account for the further loss of red cells was absent in all our patients.
Our evidence suggests that in the period under review there was an unexplained disappearance of both patients' and donor red cells.

Further disappearance of red cells was associated in all but the most oligemic patients with a further fall in red cell volume. It can be seen from table 1 that such a fall in red cell volume occurred in 15 out of 18 patients who had two red cell volume studies before any further transfusion. It ranged from 60 to 650 ml. (4–39 per cent of the follow-up red cell volume). The remaining 3 patients showed small rises (10–120 ml.). The average fall in red cell volume was 210 ml. (11 per cent of the follow-up red cell volume). Corroborative evidence for the falls in red cell volume is obtained from plasma volume and hematocrit studies made at the same time as the P32 red cell volume estimates. Fifteen out of seventeen patients showed, by these methods, a fall in the calculated red cell volume.

This further fall in red cell volume is one of the explanations for the later hemoglobin results frequently being above the "expected" line in figure 4.

Other Factors

As judged from repeated reticulocyte counts (figs. 1, 2, 3 and 5) an impaired rate of red cell formation did not contribute to the fall in red cell volume that occurred during the two weeks after injury. An increased rate of red cell formation in the more undertransfused patients appeared to reduce slightly the severity of the anemia.

We have no evidence that altered distribution of red cells in the circulation as measured by the body/venous hematocrit ratio contributed to the changing hemoglobin during the two weeks following trauma.

Changes in total blood volume did affect the level of hemoglobin, venous hematocrit, etc., in the peripheral blood. The important point was that in about half the patients the blood volumes had not returned from the high or low value found at the end of the primary treatment completely to normal, even 4–14 days after injury. This is one of the explanations for the scatter of hemoglobin results lying on a more vertical line than the "expected" in figure 4. The level of hemoglobin or hematocrit of the peripheral blood during the anemia of trauma tends therefore to underestimate the red cell volume deficit or credit.

Discussion

Of the different factors that may contribute to the anemia of trauma we have found the red cell deficit at the end of primary treatment to be the most important. Following whole blood deficiency the plasma volume rose slowly and therefore the lowest hemoglobin was not attained until about a week or more after injury. A further fall in red cell volume, after the end of primary treatment, contributed on average to a fall of only 10 per cent in hemoglobin during the two weeks after injury. Greater falls in red cell volume would probably have occurred if our cases had been complicated, for example, by sepsis. For this reason we will first discuss the clinical material investigated by different workers and then review the evidence for the contributions to the anemia of trauma of (a) the primary red cell deficit, (b) a later fall in red cell volume.

The clinical material reported here is summarized in table 1, and described
in detail in an earlier paper (Clarke et al.). We consider that our conclusions are applicable to the majority of moderately severe injuries in peacetime, including major and multiple fractures. Our cases were not appreciably complicated by clinical infection, by continuing or recurrent hemorrhage, or by large areas of doubtfully viable tissue not removed at primary wound excision. Some of our cases were similar to the injuries reported by Dacie and Homer, Grant and Reeve, and others during World War II. The injuries were less severe and extensive than many of the casualties in Korea investigated by Crosby and Howard and Prentice and his colleagues. These Korean casualties were probably left with considerable volumes of damaged tissue and certainly received large transfusions of universal donor blood.

Considering first the contribution to the later anemia of the red cell deficit at the end of primary treatment, Grant and Reeve review earlier work and describe plasma volume and hematocrit estimations on civilian and war injuries. From these data they showed that many patients had low red cell volumes shortly after injury, and that the early red cell loss was the major cause of the anemia that developed by “hemodilution” during the first 2 to 3 days. Dacie and Homer made similar observations on 15 patients at 48 hours and again a week later. Their data showed that in many patients the hematocrit level had ceased to fall by the end of the first week after injury. They demonstrated the major contribution of the red cell deficit at 48 hours to the later anemia, but questioned the validity of their evidence because they were using the Evans blue plasma volume technic. Crosby and Howard and Prentice and his colleagues refer to a later anemia that appeared to be little related to the early red cell volume credit or deficit. This may be due to the differences in clinical material described above, and possibly to the fact that they estimated the red cell volume after primary treatment before early postoperative blood loss into tissues had ceased. Our findings on cases of civilian injury using the radioactive phosphorus red cell volume technic as well as the plasma volume and hematocrit support the evidence of Dacie and Homer. In the patients reported here the major cause of anemia in the two weeks following injury was a red cell volume deficit at the end of the primary treatment. This deficit has been shown in a previous paper to be largely explained by the balance between blood transfused and blood lost to the outside and into limb swelling (Clarke et al.). Our results show the large contribution to the anemia of trauma of such blood loss unreplaced by blood transfusion. We have found that anemia has frequently been absent when the red cell volume has been restored to about 110 per cent of the follow-up normal. It frequently falls only to about 10 per cent below normal if blood transfusion is just adequate to replace blood lost.

The red cell volume changes after blood transfusion, operation and the cessation of hemorrhage have been studied in very few injuries. Grant and Reeve using plasma volume and hematocrit demonstrated some fall in red cell volume during the period of observation (104 hours after injury); Dacie and Homer using the same technics showed on average little or no fall in red cell volume between the 2nd day and a week later. Their cases were very anemic, had a reticulocytosis, and therefore probably showed an increased new formation as well as an increased rate of disappearance of red cells. Prentice and his colleagues
refer to a substantial further fall in red cell volume, probably, as we have already
discussed, because of the differences in clinical material and the timing of blood
volume studies. We have found on average a further fall of red cell volume of
10 per cent of the “normal” follow-up red cell volume. Such data suggests that
in moderately severe civilian injuries further falls in red cell volume are not
clinically important in the absence of evident complications. The small falls in
red cell volume are of interest to the clinician because their presence explains
the small fall in hemoglobin that we have so frequently observed even in patients
whose red cell volumes have been returned to normal or above normal by primary
blood transfusion.

The following evidence suggests that the cause of the fall in red cell volume
is not an impaired rate of red cell formation but rather an increased rate of dis-
appearance of red cells. The reticulocyte count has been used as evidence of the
probable rate of red cell formation. Our results (fig. 5) extending the observa-
tions of Dacie and Homer⁴ indicate an order of reticulocytosis and rise in hemo-
globin level similar to that found following gastric (Schiodt⁵) and artificial
hemorrhage (Ebert, Stead and Gibson⁶; Finch, Haskins and Finch⁷). The pa-
tient with a severe anemia of trauma (e.g., hemoglobin 9 Gm. per cent, reticulo-
cytes 4 per cent) due to primary unreplaced blood loss has sometimes shown
a rise in blood volume during the ensuing week, presumably due to an increased
production of red cells. Such evidence suggests that in undertransfused cases
an impaired rate of red cell formation is certainly not, and in more generously
transfused cases an impaired rate of red cell formation is probably not, con-
tributing to the anemia. We have presented evidence that an increased rate of
disappearance of both patient’s and transfused red cells occurred in all our cases
of severe limb injury. We do not know the biological significance of this red cell
disappearance in the process of repair following trauma and hemorrhage. Today
such a red cell disappearance can be more easily differentiated from the anemia
of inadequate blood replacement because it is possible to assess more precisely
how much blood is lost and replace it early by adequate blood transfusion.

We would disagree with the statement that “the anaemia which follows severe
injury presumably reflects the general post-traumatic protein katabolism, and
should not be treated prophylactically by the administration of blood in excess
of that needed to restore circulatory efficiency” (Editorial, 1955).⁸ In our cases
the red cell deficit causing the anemia was established by the end of primary
treatment, and was due to bleeding. There was indeed some evidence (Flear and
Clarke⁹) that increased protein catabolism during the following fortnight is
at least in part prevented by adequate primary blood transfusion. In consid-
ering the need to restore circulatory efficiency it is becoming increasingly clear
that pulse rate and blood pressure do not provide an accurate indication of the
red cell volume deficit; and that it is necessary to prevent oligemia from hemor-
rhage by transfusion in amounts determined by (1) careful assessment of the
volume of blood lost (Clarke et al.⁵), (2) the clinical state of the patient and,
(3) consideration of the factors underlying the later fall in red cell volume.
The common anemia of civilian trauma is largely preventable by adequate
primary blood transfusion, where such adequacy is considered in terms of the
normality in volume and composition of circulating blood.
ANEMIA OF TRAUMA

In many patients such primary adequate blood transfusion is clinically desirable, but its full quantitative application must be based on increasing knowledge of the underlying processes and a sober appraisal of the advantage of blood transfusion in relation to its risks.

SUMMARY

1. The anemia of civilian trauma (mainly limb injuries) has been studied in 57 patients.

2. In 22 patients the red cell volume, after primary blood loss has probably ceased, has been compared with the follow-up “normal” red cell volume. The red cell volume credit or deficit is taken as an index of the balance between primary blood loss and blood transfused, and was found to be the major factor contributing to the later polycythemia or anemia. The evidence suggests that an anemia of trauma due to unreplaced primary blood loss is still a common finding in civilian injuries today.

3. A further red cell volume estimate in 20 patients on the 4–14th day after injury showed on average a further fall of 11 per cent of the red cell volume. Evidence is presented for considering that there is a further disappearance of red cells after primary blood loss has ceased in all patients—even in those whose red cell volume did not fall.

4. The evidence suggests that the anemia of trauma is largely preventable by adequate blood transfusion in the majority of civilian injuries.

SUMMARIO IN INTERLINGUA

1. Le anemia de trauma (specialmente vulneres del extremitates) esseva studiate in 57 patienstes civil.

2. In 22 patientes le voluminse erytrocytic determinate post le cessation probable del perdita primari de sanguine esseva comparate con le subsequente voluminse erytrocytic “normal.” Le resultante surplus o deficit de voluminse erytrocytic esseva acceptate como indice del balanscia inter le perdita primari de sanguine e le sanguine transfundite. Il esseva constatate que illo es un major factor contribuente al disveloppamento subsequente de polycythernia o anemia. Nostre datos pare imisdicar que anemia de trauma, resultante de non-reimplaciate perditas primari de sanguine, es ancora in nostre dies un constatation commun in vulneres de personas civil.

3. In plus, le estimation del voluminse erytrocytic, executate in 20 patienstes inter 4 e 14 dies post le vulneration, revelava como valor median un reduction additional del voluminse erytrocytic per 11 pro cento. Nos presenta datos in supporto del conception que le cessation del perdita primari de sanguine es sequite in omne patienstes per un disparition additional de erythrocytos—mesmo se le voluminse erytrocytic mostra nulle reduction.

4. Nostre datos indica que anemia de trauma es altemente prevenibile in le majoritate de vulnerations civil per le administration de adequate transfusiones de sanguine.

REFERENCES

ELIZABETH TOPLEY AND RUSCOE CLARKE


The Anemia of Trauma

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