THE HEMOSTATIC RESPONSE TO INJURY
A STUDY OF THE KOREAN BATTLE CASUALTY*

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DURING A STUDY of the response to injury by the Surgical Research Team of the U. S. Army in Korea, two observations were made which were the basis for this study. The first was the observation that there was a depression in prothrombin activity following wounding and resuscitation. The second was the observation that there existed a tendency toward a capillary ooze following massive transfusion with stored blood. It is the purpose of this publication to attempt to define the mechanism of these alterations and to discuss the response of the coagulation system to battle injury.

As in the study of other systems, the results of this phase of the study indicate gross alteration in physiology following wounding. The response to severe injury appears to be a response of every system, and presumably every cell in the body. It is not a response of a few hours' duration but one of days or weeks in duration. Even though a particular system may not be directly damaged by the initial trauma, reflex vascular changes, anoxia, toxins, or hormonal influence may simultaneously impair an organ or system so that, theoretically at least, an adequate response may be impossible.

Observations on the Korean battle casualty demonstrate a fall in prothrombin activity, a rise in plasma fibrinogen and platelets, a shortening of the clotting time followed by a rise to normal and the absence of significant amounts of circulating anticoagulants or fibrinolysin.

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METHODS AND MATERIALS

This study was performed during the winter of 1952-53 at a forward surgical hospital in Korea. The casualty usually arrived at the hospital between three and five hours after wounding, with a range of one to nine hours. The soldiers were all young and previously healthy. As a rule, the more severely injured men were selected for study. Shortly after injury, the casualty was treated at the Battalion Aid Station. When needed, plasma or albumin was administered, along with tetanus toxoid and penicillin. The casualty was then evacuated to the Surgical Hospital for definitive therapy, where this study was begun. A total of 11 moderately and severely wounded men was studied from the first postoperative day until evacuation four to ten days later. These casualties had received six to 16 pints of type O stored whole blood. The daily tests consisted of clotting time, platelet count, plasma fibrinogen, and one-stage prothrombin time. On days that significant changes in prothrombin activity were observed, additional tests were carried out to evaluate the effect of the patients' plasma on the prothrombin activity of stored plasma, and to determine the effect of deprothrombinized plasma and heated serum on the patients' plasma. Sixteen additional patients had prothrombin time determination only. These patients had received five to 30 units of blood.

PROTHROMBIN TIME

Prothrombin time was determined by the one-stage method of Quick.[27] The determi-

nation was carried out in duplicate or triplicate, using the optimal volume of calcium chloride to produce the shortest prothrombin time. The maximal variation between determinations on any given specimen was 0.3 seconds.

The diluent for establishing the curve of normal prothrombin activity was normal human plasma treated with tricalcium phosphate gel.[27] Gel-treated plasma is considered to be free of prothrombin and stable factor but contains all the original labile factor.[21, 27] Stored plasma was prepared by refrigerating normal sterile, oxalated plasma at 4° C. for four weeks in an unsealed container. Plasma so treated is considered to be deficient in labile factor.[27]

Plasma deficient in stable factor (Factor VII) was prepared by filtering oxalated ox plasma through 30 per cent asbestos filter pads.[21] Heated serum was prepared by inducing complete clot formation with thromboplastin and incubating the oxalated serum at 58° C. for 30 minutes[29] It is believed that the serum so treated does not contain prothrombin, thrombin, labile factor, stable factor, thromboplastin or fibrinogen.[29]

Fibrinogen determinations were carried out using the Quick modification of the method of Cullen and Van Slyke.[27] Daily normal determinations were carried out and 20 varied from 225 to 400 mg. per 100 ml. of plasma.

Clotting time was determined by using a modification of the method of Lee and White.[28] Siliconed (Desicote) tubes and syringes were used. After venipuncture the syringe was changed to obviate contamination with tissue fluids. Daily normal controls were carried out, and varied from 25 to 40 minutes.

Platelet counts were determined by the method of Brecher and Cronkite.[3] The platelet count of normals varied between 200,000 and 300,000 per cu. mm.

RESULTS

A depression of prothrombin activity to about 50 per cent of normal was observed immediately after operation and persisted one to four days. This fall will be referred to as the "primary fall" (Figs. 1 and 2). The maximal depression in this primary fall was found immediately after operation, resulting in an activity of 34 to 80 per cent of normal.[29, 30] This was followed by a rise to 90 per cent of normal activity or higher before the fourth day. On the third day to the fifth day there was observed another fall to about 50 per cent of normal activity, which persisted until the tenth postoperative day before a return to normal activity began. The maximal depression in the secondary fall usually occurred about the seventh day, resulting in an activity of 20 to 80 per cent of normal.

During the primary fall certain observations were made. In three of six casualties tested the addition of normal plasma, which contained no prothrombin, to patients' plasma caused some improvement in the coagulation defect in the one-stage test. This occurred in the three patients who had the largest transfusions. In all of four patients tested the patient's plasma had less than normal ability to correct the coagulation defect of stored plasma. The inability of the patients' plasma to make this correction was most pronounced in the immediate postoperative period, and was less pronounced as the one-stage prothrombin time rose to normal between the first and third days.

When the heated serum described above was added to the patient's plasma during the immediate postoperative period, there was no correction of the coagulation defect and the heated serum acted as though it were a simple diluent.

During the secondary fall other observations were made. In all of nine patients tested, the addition of normal heated serum to the patient's plasma corrected to some

extent the defect of prothrombin activity. Heated serum of these patients did not correct the defect when added to their own plasma or to the plasma of patients at a similar stage of recovery. The ability of the plasma of patients during this phase of recovery to correct the defect of stored plasma was even better than normal. The addition of plasma which did not contain prothrombin failed to cause the anticipated prolongation of the patient's prothrombin time. In all six of the patients so tested there was evidence that deprothrombinized plasma from normal subjects tended to correct the defect of prothrombin activity in patient's plasma.

Fibrinogen (Fig. 1). Only one patient in the study group had a plasma fibrinogen concentration below normal. The value was not, however, low enough to affect coagulation (182 mg. per 100 ml.). This occurred immediately after operation, and had corrected itself by the first postoperative day. The average postoperative value was 233 mg. per 100 ml., and had risen to an average of 423 mg. per 100 ml. by the morning after injury. The average maximum value was 653 mg. per 100 ml., and occurred between the third and eighth days.

Clotting time in silicone (Fig. 1). Six of the eight patients studied in the immediate postoperative period had clotting times which were more rapid than normal. Seven of 11 patients had a normal clotting time by the first day after injury. In four, the clotting became abnormally prolonged. Of these, two patients returned to normal on the third and fifth days. The other two patients remained abnormal during their entire hospital stay of four and six days respectively. One of the latter developed lower nephron nephrosis and demonstrated a bleeding tendency on the third and fourth days, but no abnormality of the platelet count, fibrinogen or prothrombin activity could be detected that would account for the prolonged clotting time. As a rule, clot retraction was normal, but two patients who had received massive transfusions and had a high hematocrit appeared to have poor clot retraction.

Platelets (Fig. 1). Only one patient had a low platelet count, this being immediately after surgery (190,000 per cu. mm.), and this slight depression was corrected by the second postoperative day. Another patient had a low count (170,000 per cu. mm.) on the first day postoperatively, following continued transfusion. It became normal the next day when transfusion was stopped. In most of the patients the platelet count rose well above normal and reached a peak between the third and ninth day. The maximum counts ranged from 0.48 to 4.2 million per cu. mm. After the fifth day the platelet counts were consistently elevated.

DISCUSSION

Several questions worthy of comment may be raised. Of what does the hemostatic response to trauma consist? Can the critically injured battle casualty produce an adequate hemostatic response to meet the threat of continued bleeding? Does the oozing tendency in some casualties represent a failure in this response? What is the basis for the depression in prothrombin activity?

Fibrinogen. Mathey[25] demonstrated a low fibrinogen immediately after thoracic surgery. Hidalgo[15] has shown that rabbits traumatized with a tourniquet had a fall of 22 per cent in plasma fibrinogen, followed by a rise within 24 hours.

In only one of the patients studied could a deficiency of fibrinogen be demonstrated. In the immediate postoperative period this plasma fibrinogen was 180 mg. per 100 ml. but this deficit is not sufficient to predispose to a hemorrhagic tendency or to affect the prothrombin activity.

Many authors have shown a rise in plasma fibrinogen as a response to various forms of stress. Operation, induced pyrexia, shock, injection of necrotising substances, injection of hepatic toxins are among some of the precipitating factors.[10, 13, 14, 15, 25]

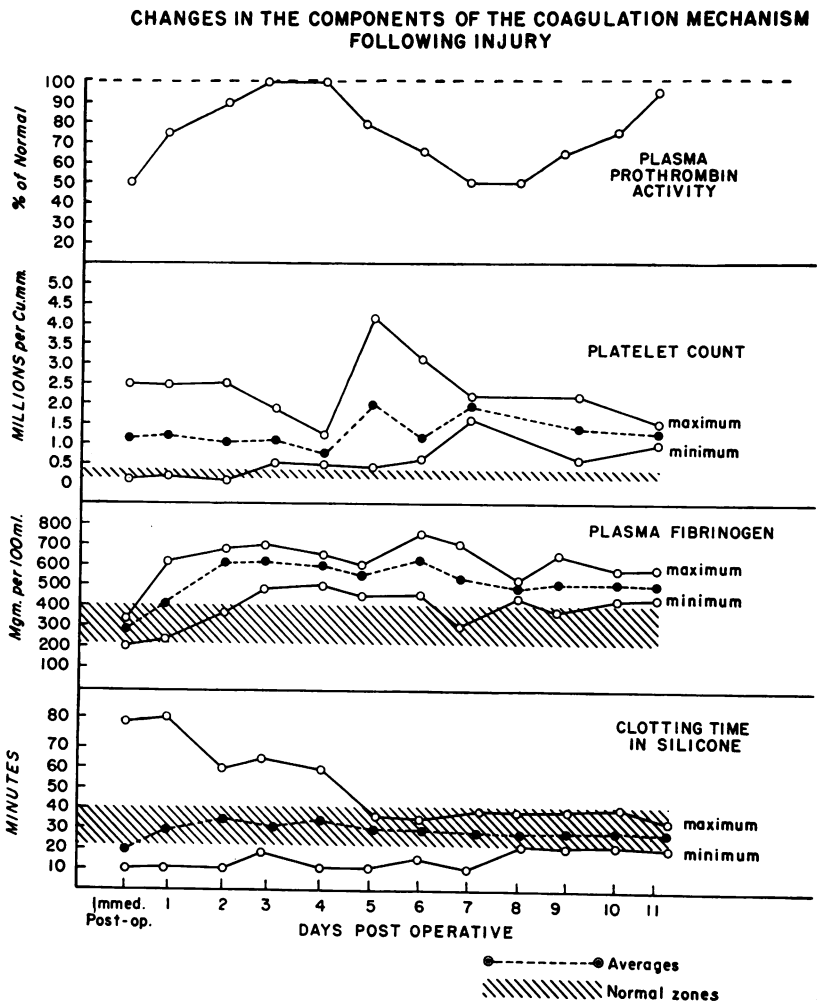

FIG. 1. Changes in the components of the coagulation mechanism in eleven battle casualties.

It is believed by some of these workers that a rise in plasma fibrinogen is a specific response to stress, and the failure of such a rise is indicative of an inadequate response. Henriques[14] demonstrated that adrenalectomy or fasting, along with exposure to cold, decreases but does not abolish this response in the plasma fibrinogen. Foster[10] demonstrated that small doses of hepatic toxins stimulated fibrinogen while large doses depressed the formation of fibrinogen.

It can be seen from our data that there was a normal or slightly depressed plasma fibrinogen in the immediate postoperative period but that this was followed by a rise above normal in all casualties studied. The maximal concentration was found about the sixth day after injury (Fig. 1). An elevation was maintained six days or longer.

It is interesting to note that this response does occur in a severely wounded casualty who is in a state of severe negative nitrogen balance. Two of the casualties were polycythemic after massive transfusion. Neither of these patients demonstrated the depres-

sion of the fibrinogen associated with polycythemia vera.

In the course of carrying out fibrinogen determinations, the presence of significant amounts of fibrinolysis could have been detected had fibrinolysin been present. None of the patients in this group demonstrated gross lysis of the fibrin clot which was incubated for 30 minutes at 37° C. as a part of the fibrinogen determination.

Blood Platelets. In a review of the literature by Warren,[34] a rise above normal of blood platelets in the postoperative period has been regularly observed, except for two dissenting opinions. It was agreed that the elevation begins between the fourth and eighth day, and persists in some cases until the sixteenth day. A few workers had found a fall in platelets during the first three or four days after operation. It should be emphasized, however, that our study was performed on men with massive tissue destruction, and this destruction occurred prior to anesthesia.

Our data are of interest in that minimal depression in platelet count was observed in the early postoperative period of some patients, and indeed there was a rather marked elevation in most of the patients studied, some elevations being to 4,500,000 per cu. mm. The maximal elevations occurred on the fifth and sixth days (Fig. 1).

In all the patients studied past the fourth day there was a consistent elevation above normal. This elevation persisted until the patient was evacuated ten to 13 days after injury.

The platelets were certainly present in adequate numbers. It should be pointed out that some of these casualties had had virtually a replacement transfusion with stored blood, which is known not to contain viable platelets.[16] It is conceivable that the greater number of large immature platelets that we observed microscopically had a qualitative defect based on a deficiency of one of the platelet factors that developed as a result of the mass production of large numbers of platelets. Some casualties who had received 20 or more pints of stored blood did develop a tendency to ooze. This was probably not based on some defect within the prothrombin system because the degree of depression in the prothrombin activity demonstrated should not be accompanied by a hemorrhagic tendency. We also found it was not due to a deficiency of fibrinogen. It may have been caused by some vascular phenomenon or plethora but not all patients with the oozing tendency were polycytemic. The phenomenon was also observed in patients who were shown to be anemic from blood loss. Another possibility could be a deficiency within the platelet.[19]

It is generally accepted that there are four known platelet factors.[33] Three are concerned with the activation or inhibition of the prothrombin mechanism (anti-heparin, thromboplastin, and SPCA). The fourth factor, a substance which has been named "Serotonin,"[35] is involved in producing local vasoconstriction at the site where it is liberated from the platelets. Since these casualties had virtually received a replacement transfusion with stored blood known to contain no viable platelets and were called upon to produce large numbers of platelets in a short period of time, these platelets may well have been deficient in "serotonin." This possible deficiency was, however, not proven.

Coagulation Time. A shortening of the clotting time of whole blood in response to stress has been established. Cannon[5] in 1914 demonstrated that the injection of adrenalin caused a reduction in the clotting time. Other workers[8, 9, 11] have demonstrated a shortening of the clotting time on the first postoperative day followed by a subsequent rise.

Smith[32] demonstrated that there was usually a shortening of clotting time following the administration of ACTH. Gray and Lunt[12] demonstrated that there was reduction in the clotting time after hemorrhage. They also demonstrated that after exclusion

of the abdominal circulation hemorrhage was no longer accompanied by a fall in clotting time. Adrenalectomy did not prevent the reduction in the clotting time following simple hemorrhage. These authors interpreted their observations as evidence that there was an interplay between the adrenals, intestine and liver in the response of the clotting time to hemorrhage.

From these observations there is little doubt that the adrenal glands do play a role in the response of the coagulation mechanism to trauma.

One factor operating in the battle casualty could contribute to the reduction in clotting time during the early postoperative phase. Several authors have demonstrated that the administration of antibiotics shortens the clotting time of blood.[18, 23, 24, 26] The effect is usually transient but it should be pointed out that all patients under study were receiving massive doses of antibiotics, often by continuous intravenous drip.

It is interesting to note that the majority of patients did have reduction in the clotting time following injury and operation. In some cases the clotting time remained below normal, in others it rose above normal, and in others it rose only to normal.

None of the patients who demonstrated a prolonged clotting time had an abnormality in the platelets, prothrombin time or plasma fibrinogen to account for this alteration. Only in the immediate postoperative period was clot retraction poor, and when this was observed, it was usually associated with a high hematocrit which might have acted as a mechanical factor to cause poor clot retraction. In none of the patients studied nor in the large numbers of battle casualties observed was phlebothrombosis encountered. In view of the high platelet count, elevated plasma fibrinogen and occasional reduction in clotting time, one might have expected a thrombotic tendency.

Prothrombin Activity. An incomplete review of the literature revealed that other workers had observed variations in prothrombin activity after surgical procedures. Bromstron[4] reported that in a study of 101 non-icteric patients, operation under local or pentothal anesthesia was not accompanied by a fall in prothrombin activity. With other anesthesia a fall to 90 per cent of normal activity was observed, the maximal fall being on the fourth day. He believed there was no correlation between the prothrombin activity and severity of trauma or the amount of blood lost.

Allen[2] observed that only one of 106 patients undergoing extra-biliary surgery had a postoperative fall in prothrombin activity. Patients with obstructive jaundice had a fall in prothrombin activity which was related to the number of days vitamin K was given in the preoperative period. It is of interest that vitamin K in no way affected the fall in prothrombin observed in the battle casualty.

Warren[34] demonstrated a fall to about 70 per cent of normal activity during the first week after elective surgery. Fowler[11] has reported no fall in prothrombin activity after operation but in some cases a rise in activity. It should be pointed out that *all* of the casualties studied had a *fall* in prothrombin activity.

Various factors can modify the one-stage prothrombin time. The known factors include prothrombin, labile factor, stable factor (preconvertin, Factor VII), antihemophilic globulin and similar factors, the platelet factors, anti-thrombin and heparin.[33] There may well be others that are still unknown.

It seems unlikely that the depression in prothrombin activity in the severely wounded was due to an anticoagulant. Six of the ten patients studied had a normal clotting time by the morning after injury, and it is safe to assume significant amounts of anticoagulant were not present in these patients. Four of the ten patients did have a prolonged clotting time after the first day. These patients had depression of prothrombin activity of the same degree as did pa-

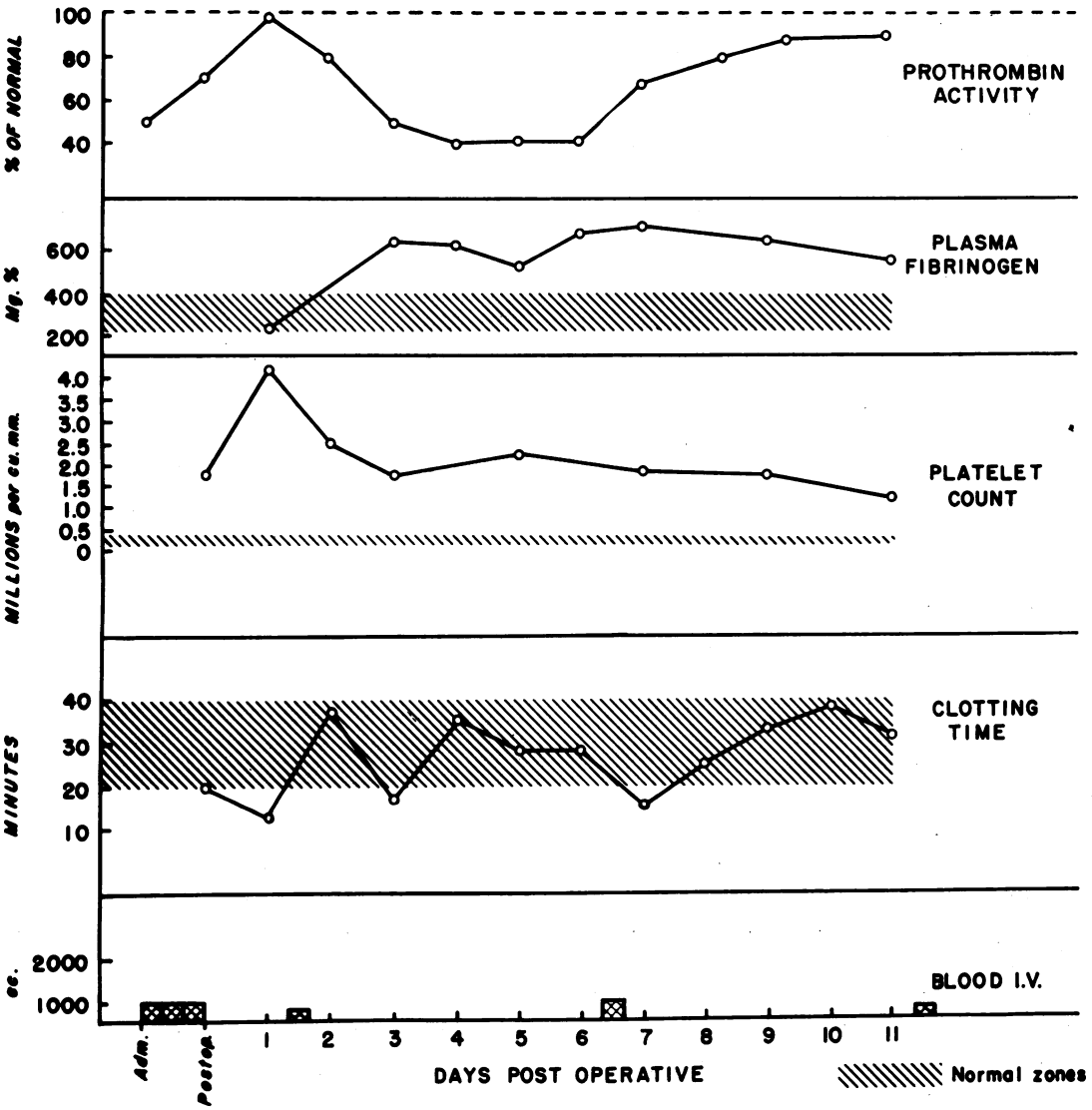

FIG. 2. A representative patient in the series. The patient, a previously healthy, 21-year-old white male, was wounded by artillery shell fragments. In the forward area the casualty received penicillin and tetanus toxoid but no intravenous therapy. Four hours after injury, examination at the Surgical Hospital revealed two penetrating wounds of the abdominal wall. The patient was anesthetized with intravenous pentothal and ether. During a two-hour operation, three perforations of the small intestine and one of the stomach were repaired. During the operation the patient received 3000 ml. of type O bank blood 15 days of age. Following operation the patient did well and developed no complications. On the first and sixth postoperative days the patient received additional blood.

tients with normal clotting times. The prolonged clotting time in these four patients could have been on the basis of an anticoagulant but this was not proven.

It was shown, however, that these patients had, in addition, the same abnormality of prothrombin conversion that was possessed by the other six patients who had a normal clotting time.

There was certainly no lack of fibrinogen to account for the depression in prothrombin activity.

The evaluation of prothrombin itself is open to question. In some patients it was possible to correct the prothrombin time to normal by the addition of plasma that did not contain prothrombin, or heated serum that contained no prothrombin. This suggested that there was little or no lack of prothrombin in these patients, and that these diluents supplied the deficient factors. In other patients, where the use of prothrombin-free reagents improved but did not completely correct the depression in prothrombin activity, there may have been some deficiency of prothrombin but this was not proven. It was observed that the use of vitamin K (100 mg. daily, intramuscularly) on five patients did not correct the depression in prothrombin activity in either the primary or secondary fall. Vitamin K-1 oxide was not used.

The optimal volume of calcium solution required for the one-stage prothrombin time was established each day for each patient. Immediately after large transfusions of citrated blood the volume of calcium solution required was no greater than was required for the same patient on the succeeding days, provided the hematocrit remained the same. This suggested that the citrate received during massive transfusions did not produce sufficient alteration of physiologically available calcium in the plasma of these patients to influence the coagulation. A review of the literature failed to reveal reports indicating that variations in plasma calcium influence coagulation in the living subject.[1, 17, 31]

Labile factor (accelerator globulin) appears to have been deficient after massive transfusion. The labile factor of stored plasma was not well corrected by the addition of the plasma from patients who had just previously received massive transfusions. At the same time the depression in prothrombin activity of the six patients could be corrected by the addition of deprothrombinized plasma which contains labile factor but not stable factor or prothrombin. The lack of labile factor, following resuscitation with stored blood, may have been due to the large transfusions of this labile deficient, stored blood. All of the blood used for transfusion was at least ten days old, and it has been shown that blood stored in ACD solution becomes relatively deficient in labile factor.[22]

Smith[32] demonstrated that the administration of ACTH will cause a fall in labile factor activity followed by a slow rise. It is possible that the stress of injury and release of adrenal substances could contribute to the labile factor deficiency demonstrated shortly after injury and resuscitation.

It should be stated, however, that the depression in prothrombin activity was not so great as to cause a serious fault of hemostasis. The oozing tendency that occurred among battle casualties after transfusion of 20 or more pints of blood was probably not on the basis of the labile factor deficiency. It was also not due to fibrinolysis or a deficiency in fibrinogen or platelets.

The secondary fall in prothrombin activity presents a problem we cannot completely explain. At this stage of recovery, the depression in prothrombin activity was often corrected by the addition of heated serum that was free of fibrinogen, labile factor, stable factor, prothrombin and thrombin. The depression was also corrected by deprothrombinized plasma, which indicates that the deficient factor was not absorbed by tricalcium gel. The factor or factors that

corrected the "secondary fall" in prothrombin activity, was stable in oxalated serum heated to 58° C. for 30 minutes. Its heat stability and its failure to be absorbed by tricalcium phosphate gel are two characteristics that eliminate all of the known clotting factors excepting Platelet Factor III.[33]

It is worthy of note that at this phase of recovery the patients were producing excessive numbers of platelets, many of which were large and "immature." It is entirely possible that, because of rapid production of platelets, a deficiency of Platelet Factor III could exist. This defect may not have been apparent earlier, immediately after the transfusion, because of the contribution of platelet materials from the large numbers of nonviable platelets in the transfused blood or because the production mechanism of this factor had not as yet failed. There appeared to be no deficiency of labile factor during the secondary fall. The patient's plasma was usually more than adequate to correct the labile factor deficiency of stored plasma. There appeared to be no lack of prothrombin in the patient's plasma as the addition of heated serum or deprothrombinized plasma restored the prothrombin times that were prolonged more quickly than normal.

Fibrinolysin was not encountered in these patients during the period of shock, following transfusion or during recovery. Previous work had demonstrated that cold increases the titer of antifibrinolysin in the blood.[20] It should be pointed out that this study was conducted during the winter months and the casualties, therefore, had been chilled prior to admission. The cold may have accounted for the absence of fibrinolytic activity in these patients.

CONCLUSION

Stress in the form of battle injury, resuscitation and operation produces a response which is similar to the response of the body following other forms of stress. This response is characterized by a rise in platelets, plasma fibrinogen, a shortening of the clotting time with subsequent rise and a decrease in prothrombin activity. None of these alterations was responsible for a hemorrhagic or thrombotic tendency of major clinical significance. Postoperative oozing of blood was not a major clinical problem, and did not result from a known systemic deficiency.

In the most severely injured casualty there appeared to be an adequate response of the coagulation mechanism to meet the threat of prolonged continued oozing from the innumerable open surfaces.

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