ANNALS OF SURGERY

Vol. 169 April 1969 No. 4

Coagulation Disorders in Combat Casualties:

I. Acute Changes after Wounding
II. Effects of Massive Transfusion
III. Post-Resuscitative Changes

RICHARD L. SIMMONS,* CAPT., MC, USAR, JOHN A. COLLINS,** M.D., CHARLES A. HEISTERKAMP, III, LT.C., MC, USA, DOUGLAS E. MILLS, SP.4, RICHARD ANDREN, SP.5, LOUISE L. PHILLIPS,*** PH.D.

From the Division of Surgery, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. 20012

HEWSON [16] originally observed that venesection was associated with significant alterations in the coagulation mechanism. These observations have been repeatedly confirmed, and it is now generally accepted on the basis of experimental evidence that hemorrhage is followed by a biphasic change in the clotting time.[35, 39, 41] Initially the bleeding induces an acceleration in clotting, but as shock is produced, a state of hypocoagulability results.[13, 35, 39, 41]

Hardaway [13] has pointed out that hemorrhage *per se* does not lead to the development of the hypocoagulable state. However, stagnant blood flow and a state of hypercoagulability prepare the experimental animal for the development of disseminated intravascular coagulation which can be triggered by a variety of stimuli. The coagulation factors may then be consumed in the resulting diffuse response.[31] There are two potential consequences for the patient: the hemorrhage continues because of the depression in clotting factors or irreversible shock or both may be produced by obstructed capillary flow to vital organs.[13]

Most studies of coagulation have dealt with patients who have already developed hemorrhagic diatheses.[20, 21, 40, 43] The present studies represent a survey of the effects of wounding and resuscitation on the coagulation parameters of young, well-conditioned soldiers in Vietnam.

Submitted for publication August 3, 1968.

* Present address: Department of Surgery, University of Minnesota, Minneapolis, Minnesota.

** Present address: Department of Surgery, Washington University, St. Louis, Missouri.

*** Present address: Department of Medicine, Roosevelt Hospital, New York, New York.

Methods

All studies were performed by the U. S. Army Surgical Research Team in Vietnam during two periods: April to October 1966 and June 1967 to January 1968. The patients were 240 American or South Vietnamese soldiers who had sustained missile wounds; patients with burns or head injuries have been excluded. All patients were first studied immediately after helicopter evacuation to the hospital, usually within an hour or two of wounding; no therapy had been given except for emergency dressings and the administration of morphine in some cases. The patients selected for study represent those who appeared to be the most severely wounded.

Fifty-seven of these casualties were followed during resuscitation and operation. Blood was drawn after every three or four units of transfused blood. No patient studied had received any plasma expander other than blood, Ringer's lactate solution, normal saline, or 5% dextrose in distilled water.

In order to determine the dilutional effect of bank blood on the coagulation parameters of transfused patients, samples were drawn from the intravenous tubing of 72 units of blood during transfusion. All the bank blood had been stored (10–21 days) and transported into Fenwal plastic bags containing 67.5 ml. NIH solution A (2.45 Gm. dextrose, 0.8 Gm. citric acid, and 2.2 Gm. sodium citrate/100 ml.). The blood was drawn just prior to reaching the patient, after having passed through the standard infusion filter.

One hundred and twenty patients of the initial 240 were studied for at least 3 days following resuscitation and operation. In 80 of the 120 patients coagulation studies were performed three times daily at 8–12 hour intervals.

Clotting Determinations. Fibrinogen was measured by heat dissolving the precipitate of sodium sulfite and EDTA plasma in sodium hydroxide, reacting with biuret reagent, and reading at 545 mμ.[7, 15] Prothrombin time (PT) was measured by the usual one stage method of Quick.[29] The activated partial thromboplastin time (PTT) was measured at 37° C. using Kaolin-activated platelin, citrated plasma, and calcium.[24] The recalcification time was performed using citrated platelet rich plasma and calcium.[4] The fibrinolysin assay measured the lysis of serially diluted plasma clots, and is reported as the number of tubes showing complete lysis (1–6 plus).[9] Platelet counts were performed by the standard method of Brecker and Cronkite[6]

Arterial pH, P_{CO_2}, P_{O_2}, and blood lactate measurements were performed on admission and at least daily in all patients by methods previously described.[34] Blood volumes were determined in some patients during the post-resuscitative period using simultaneous ^{51}Cr tagged autogenous red blood cells and ^{125}I tagged albumin as tracers.[34]

Shock has been arbitrarily defined as a systolic blood pressure of 60 mm. Hg or less, an arterial lactate content of 20 mg. /100 ml. or more, or an arterial pH less than 7.3.

Results

Normal Values. The mean prothrombin time (PT) of 147 apparently normal patients and personnel was 12.7 ± 0.67 (SD) seconds. The mean activated partial thromboplastin time (PTT) of 210 similar subjects was 47.95 ± 5.22 seconds. Forty normal control volunteers were studied with respect to fibrinogen, recalcification time (RCT), platelet count, or fibrinolysin determinations. The ranges found have been accepted as normal in our laboratories and are noted in Table 1.

Part I. Acute Coagulation Changes after Wounding

Table 1 shows the range of values found in 240 soldiers who were wounded less than

TABLE 1. *Coagulation Parameters in Combat Casualties*

Test and Number of Patients	Number of Patients with Values Listed Normal Range					
Prothrombin Time (sec)	<10	10–11.9	12.0–16.0	16.1–18.0	18.1–20	>20
240	0	31	192	12	6	0
Partial Thromboplastin Time (sec)	<25	25–34.9	35–60	60.1–69.9	70.0–80	>80
239	1	43	179	11	1	1
Recalcification Time (sec)		<80	80–180	>180		
110		28	78	4		
Platelets (/mm³)		<150,000	150,000–450,000	>450,000		
99		7	91	1		
Fibrinogen (mg./100 ml.)	<200	200–249	250–450	450–500	501–600	>600
141	11	11	82	15	17	6
Fibrinolysin			0–2+	3–4+	5–6+	
62			15	29	20	

TABLE 2. *Correlation of Coagulation Factors with Each Other*

	Number of Patients with Values Listed					
	PT (sec)			RCT (sec)		
PTT (sec)	<12	12–16	>16	<80	80–180	>180
<35	9	31	1	11	9	0
35–60	19	156	10	17	63	3
>60	1	6	7	0	6	2
		$p < 0.01$			$p < 0.01$	

2 hours before being admitted to the hospital. Note that in all parameters the values range beyond normal limits in both directions. In particular, there are many patients with very short prothrombin times, partial thromboplastin times, and high fibrinogen levels, but there are fewer patients with high platelet counts. Therefore, the "hypercoagulability" which follows injury does not extend to all factors involved in the coagulation process. It is also striking that fibrinolysin levels are high in a large majority of patients studied. Fibrinogen levels and platelet counts were occasionally depressed, and a few patients had significant prolongations of the prothrombin, partial thromboplastin, or recalcification times.

Cross Correlation of Coagulation Parameters. Table 2 represents the correlation of the six coagulation parameters with each other. From the results we attempted to determine if the factors measured vary independently or whether mass changes in coagulation factors are coincidental with injury and hemorrhage. Only parameters with significant mutual correlations are shown. There was no correlation, either direct or inverse, between platelets, fibrinogen, or fibrinolysin in any combination, i.e., fibrinogen was not depressed when fibrinolysin was elevated, and platelet counts and fibrinogen levels were not simultaneously depressed in a significant number of patients. In contrast, prothrombin time and partial thromboplastin times correlated with one another ($p < 0.01$), but neither measurement could be correlated with platelet count, fibrinogen or fibrinolysin values. Correlation of PTT with RCT val-

TABLE 3. *Effect of Wound Site on Initial Coagulation Parameters*

Wound Site	Number of Patients with Values Listed																	
	Prothrombin Time (sec.)			Partial Thromboplastin Time (sec.)			Fibrinogen (mg./100 ml.)			Platelets ($\times 10^3$/mm.^{3})			Fibrinolysin		
	<12	12–16	>16	<35	35–60	>60	<250	250–450	>450	<150	150–400	>400	0–2+	3–4+	5–6+
Chest	5	34	2	7	33	1	0	9	12	0	16	0	2	6	2
Thoracoabdominal	0	21	3	3	20	1	2	12	2	0	14	0	3	6	1
Abdomen	6	29	4	10	28	1	3	11	8	3	15	0	1	5	2
Extremity & soft tissue	15	91	6	16	84	10	10	41	15	4	22	1	5	6	6
	$p > 0.05$			$p > 0.05$			$p > 0.05$			$p > 0.05$			$p > 0.05$		

ues was excellent, but no correlation occurred between the RCT and the platelet counts. Since the RCT value merely measures the PTT in the presence of endogenous platelet thromboplastin, and the platelets of our patients were seldom low enough to influence the RCT, no further consideration will be given to the RCT value.

Effect of Wound Location on Coagulation Parameters. Table 3 lists the coagulation changes which occurred in association with missile wounds of various body sites. Most patients received multiple wounds of multiple sites; consequently, only the major wound site is listed. Chi square analysis revealed that there was no correlation of coagulation changes with the site of the major wound in these patients.

Effect of Hypoxemia on Coagulation Parameters. A large number of patients were moderately hypoxemic on admission [33] (arterial P_{O_2} less than 80 mm. Hg). Although most of these patients had wounds in the chest, a number of patients with extremity wounds presumably associated with fat embolism [8, 33] also were hypoxemic on admission. Table 4 correlates the degree of hypoxemia with coagulation abnormalities on admission. Only prolonged PT values could be correlated with low arterial oxygen tensions ($p < 0.05$).

Effect of Shock on Coagulation Parameters. Arterial blood pressure, arterial lactate, and pH were determined on admission as indicators of the degree of shock or tissue hypoperfusion and pH. Although these indicators do not correlate perfectly with one another, taken together they form a good basis for determining the degree of injury and perfusion of body tissues after wounding. Table 5 demonstrates relationships between the systolic blood pressure, arterial lactate, and the arterial pH and the coagulation factors measured. Two facts are clear from this table. All the parameters of shock are correlated with prolonged PT and PTT values but not with

low platelets or low fibrinogen values. Secondly, high fibrinolysin titers are present primarily in patients without hypotension, lactatemia, or acidosis.

Although shock is associated with abnormalities of the prothrombin and partial thromboplastin times following wounding, this response was not uniform. Abnormalities were mild in degree and infrequent in occurrence. For example, of 10 patients who had arterial lactate levels greater than 20 mg./100 ml., arterial pH lower than 7.3, and arterial blood pressures less than 80 on admission, only six had any coagulation abnormalities. All coagulation measurements were abnormal in only one patient. Conversely, a large number of patients had PT and PTT values which were clearly shorter than normal. Most of these patients were not in shock, although "hypercoagulable" values are found even in patients with acidosis, hypotension, and lactatemia.

Effect of Coagulation Disorders on Bleeding. Four patients who ultimately bled to death during resuscitation were studied on admission. Table 7 demonstrates the relationship between coagulation defects found on admission with blood transfusion requirements during resuscitation and initial operation. Despite the fact that the PT and PTT were correlated with the degree of shock on admission, there is no statistical correlation between these values and the amount of blood required. In contrast, although platelet counts could not be correlated with the severity of the wound, low platelet counts were significantly related to the volume of blood required for resuscitation.

TABLE 4. *Effect of Arterial Hypoxemia on Initial Coagulation Parameters*

P_{O_2} (mm. Hg)	Number of Patients with Values Listed														
	PT (sec.)			PTT (sec.)			Fibrinogen (mg./100 ml.)			Platelets ($\times 10^3$/mm^3)			Fibrinolysin		
	<12	12–16	>16	<35	35–60	>60	<250	250–450	>450	<150	150–400	>400	0–2+	3–4+	5–6+
<60	2	17	2	2	16	2	2	8	6	0	6	0	0	3	0
50–70	3	44	6	10	37	5	2	21	12	0	15	2	3	9	4
>80	23	111	6	20	117	4	11	43	19	7	43	1	9	11	6
	$p < 0.05$			$p > 0.05$			$p > 0.05$			$p > 0.05$			$p > 0.05$		

Discussion: Part I

A number of investigators have demonstrated that experimental hemorrhagic shock is associated with an increased coagulability of the blood.[16, 35, 39, 41] The initial hypercoagulable phase may be a response to the release of endogenous catecholamines.[18] If shock is uncorrected, how-

TABLE 5. *Effect of Shock on Coagulation Parameters*

Coagulation Parameter		No. of Patients with Systolic Blood Pressures (mm. Hg) of				No. of Patients with Arterial Lactate (mg./100 ml.)			No. of Patients with Arterial pH of		
		<60	60–90	>90		<20	>20		<7.3	>7.3	
PT (sec.)	<12	0	6	19		19	4		1	24	
	12–16	20	34	122	$p<0.05$	117	44	$p<0.01$	19	164	$p>0.05$
	>16	4	5	6		6	9		4	15	
PTT (sec.)	<35	5	6	29		29	4		0	40	
	35–60	15	36	114	$p<0.05$	109	47	$p<0.01$	20	153	$p<0.05$
	>60	4	3	6		4	9		4	12	
Platelets (/mm.^{3})	<150,000	2	0	3		2	3		3	18	
	150–400,000	14	20	43	$p>0.05$	50	24	$p>0.05$	7	51	$p>0.05$
	>400,000	0	2	0		0	0		0	5	
Fibrinogen (mg./ 100 ml.)	<250	4	5	10		11	6		4	12	
	250–450	10	17	52	$p>0.05$	46	24	$p>0.05$	10	64	$p>0.05$
	>450	2	3	30		26	14		3	35	
Fibrinolysin	0–2+	2	2	9		13	1		1	14	
	3–4+	3	6	14	$p>0.05$	13	4	$p>0.05$	2	22	$p>0.5$
	5–6+	1	3	11		8	0		1	11	

TABLE 6. *Initial Coagulation Parameters of Patients Who Exsanguinated*

Patient	PT	PTT	Platelet	Fibrinogen	Fibrinolysin
102	18.2	66.5	144,000	275	6+
162	14.9	61.0	170,000	260	6+
185	14.7	37.1	214,000	—	—
225	14.4	42.7	155,000	355	—

ever, the stage of hypercoagulability is followed by a second phase in which clotting times are prolonged.[13, 30, 35, 39, 41] This stage is associated with depletion of a number of clotting factors, release of endogenous anticoagulants, and secondary activation of fibrinolysin.[13] These effects can be experimentally reproduced by injection of a number of thrombogenic substances into the blood stream.[13] The fact that capillary thrombi can be found both following production of hemorrhagic shock and injection of thrombogenic materials suggested that the mechanism of the late coagulation disorder in hemorrhagic shock involved consumption of coagulation factors by widespread intravascular coagulation.[13]

Hardaway demonstrated that the production of disseminated intravascular coagulation depends on the presence both of stagnant capillary flow and a stimulus to clotting of the blood.[13] The combat casualty may manifest both the stagnant flow plus acidosis, hemolysis, necrotic tissue, and particulate matter in the blood—all of which will precipitate clotting. Thus, coagulation changes in these patients are consistent with those seen in the experimental animal. Patients with moderate wounds, without hypotension, acidosis, or lactatemia usually have normal PT, PTT, platelet counts, and fibrinogen levels. In some, the PT and PTT are shortened and the fibrinogen levels are increased confirming a "hypercoagulable state" in the absence of shock. Fibrinolysin levels seem to be elevated in many patients regardless of the state of shock. Patients with hypotension, acidosis, or lactatemia are more likely to manifest prolongations of PT and PTT sug-

TABLE 7. *Relationship of Coagulation Abnormalities on Admission to Required Transfusions*

		Transfusion Volume Required			
		<4,000 ml.	4,000–8,000 ml.	>8,000 ml.	
PT (sec.)	<12	20	3	1	
	12–16	145	21	2	$p > 0.05$
	>16	10	4	4	
PTT (sec.)	<35	31	5	2	
	35–60	133	29	13	$p > 0.05$
	>60	8	3	2	
Platelets	<150,000	2	4	2	
	150–400,000	61	10	8	$p < 0.05$
	>400,000	1	0	0	
Fibrinogen (mg./100 ml.)	<250	14	5	1	
	250–450	60	10	9	$p > 0.05$
	>450	30	5	1	
Fibrinolysin	0–2	9	2	1	
	3–4	18	4	3	$p > 0.05$
	5–6	10	1	3	

gesting that there is some depletion of the coagulation factors required for both the first and second stages of clotting. However, in these patients there is no evidence that fibrinogen or platelets are consumed with the process which prolongs the PT and PTT. The fibrinogen assay technic utilized in our laboratory unfortunately has been shown to measure non-coagulable protein (which may represent fibrinogen breakdown products) as well as the clottable fibrinogen itself.[27] This might explain the failure of the fibrinolysin titer to correlate with a decreased fibrinogen level. In addition, both fibrinogen and platelets are stored extravascularly and can be rapidly released.[13, 43] The mild degrees of prolongation of PT or PTT might be expected to correlate with significant decreases in this reserve.

A primary activation of the fibrinolytic system could account for some of the coagulation defects since fibrinolysis can destroy a number of coagulation factors in addition to fibrinogen. Fibrinolysin and other proteolytic enzymes can be activated by stimuli such as fear, anxiety, exercise, and the infusion of adrenaline.[5] Fibrinolytic activity was high in most of these patients, however, and was not increased by the presence of shock. It is also unlikely that dilutional factors due to transcapillary refill of the depleted vascular spaces could be responsible for such a rapid fall in coagulation factors.

The results suggest that disseminated intravascular coagulation has been initiated in the most severely wounded combat casualties. The process is not far advanced at the time when even the most severely wounded patient is seen, however. Also, no hemorrhagic diathesis was encountered. In fact, no correlation between the amount of required blood and the preoperative PT or PTT occurred, although such a relationship did exist between platelet counts and the volumes of blood necessary. Since considerable blood loss occurs during debridement of soft tissue wounds, a platelet count greater than 150,000 may be essential to minimize this loss. Other data certainly suggest that a platelet count of less than 120,000 is associated with significantly

TABLE 8. *Effect of Storage on Coagulation Parameters in Bank Blood*

Storage Time (days)	Coagulation Parameters (mean ± S.D.) PT (sec.)	PTT (sec.)	Fibrinogen (mg./100 ml.)
11–13	17.0 ± 1.4	72.3 ± 17.8	497 ± 84
14–16	15.9 ± 2.7	61.5 ± 13.4	426 ± 88
17–19	17.3 ± 2.4	70.0 ± 13.4	412 ± 84
20–22	19.1 ± 3.5	67.6 ± 21.0	419 ± 82
Normal range	12–16 sec.	35–60 sec.	250–450 mg./100 ml.

greater hemorrhage if bleeding has been induced by a surgical procedure.[42]

Hardaway also suggested that disseminated intravascular coagulation may lead to irreversible obstruction of the capillary beds of those viscera necessary for life.[13] In this way, disseminated intravascular coagulation becomes a precursor of irreversible shock. None of the studied patients died prior to receiving a number of transfusions. Only four patients bled to death during operation, and none had pronounced coagulation disorders initially.

It should be emphasized that older debilitated patients, particularly those with preexisting liver disease or coagulation defects, may manifest more severe coagulation disorders under similar conditions. In civilian injuries, evacuation and resuscitation procedures are not as rapidly instituted as in the combat zone. Such patients may remain in shock for prolonged periods of time and develop more extensive intravascular clotting. This may contribute to both uncontrolled clinical bleeding and irreversibility of shock.

Summary: Part I

1. A number of coagulation parameters were studied in acutely wounded combat casualties on arrival at the hospital and prior to administration of any intravenous therapy.

2. Fibrinolysin levels were higher than normal but platelet counts and fibrinogen levels were not consistently abnormal.

3. The prothrombin (PT) and partial thromboplastin times (PTT) could be statistically correlated with the degree of hypotension, acidosis, and lactatemia. Mildly to moderately wounded patients had normal or shortened PT and PTT. Severely wounded patients in shock had normal or prolonged PT and PTT.

4. The findings are consistent with experimental observations that trauma and shock produce an initial phase of hypercoagulability followed by a return to normal and a phase of hypocoagulability. The hypocoagulable phase seems best explained by the onset of disseminated intravascular coagulation precipitated by hemolysis, the release of tissue thromboplastin, acidosis, and the state of hypoperfusion seen in patients in hypovolemic and traumatic shock.

5. The severity of the coagulation defect in these young men is mild. The effect of similar qualitative changes in more debilitated civilian casualties is discussed.

Part II. Effects of Massive Transfusion on Coagulation Disorders

The Effect of Storage and Transport on Coagulation Parameters in Bank Blood. Table 7 illustrates the PT, PTT, and fibrinogen values for 72 units of stored bank blood with respect to the age of the blood. All blood utilized was more than 10 days old because of the delay in transport. Coagulation parameters vary considerably in this bank blood. Mean values for these parame-

ters are only slightly abnormal, however. Platelet counts do not actually represent the number of viable platelets [19] and were not routinely performed on bank blood. Fibrinolysin levels ranged from 2 to 3+ on 12 units of bank blood examined.

The Effect of Transfusion on Coagulation Factors of Combat Casualties. Figures 1 and 2 and Table 9 summarize values for coagulation parameters measured in 57 patients as transfusion progressed during resuscitation and operation. The platelet counts of all patients fell profoundly during the first four transfusions, regardless of the state of shock on admission. The mean platelet count remained about 100,000/mm.[3] after the first 6,000 ml. of blood. The effect of transfusion beyond 20,000 ml. of bank blood could not be determined since most such patients subsequently received several units of fresh ACD blood. Fresh blood generally increased the circulating platelet counts (Table 10).

During sequential transfusions fibrinogen levels in peripheral blood fell slightly (Fig. 1). There was no fall below normal in any patient.

During sequential transfusions, mean prothrombin times and partial thromboplastin times became prolonged. The initial four units of blood appeared to have a greater dilutional effect on patients who were in shock. After 16 units of blood, however, the PT and PTT of both sets of patients were equally abnormal. But these values did not exceed mean values obtained for the bank blood itself.

Figure 2 demonstrates the effect of transfusion on PT and PTT of patients whose values were normal, shortened, or prolonged on admission. In general, multiple transfusions of all patients resulted in a similar degree of dilution regardless of the coagulation parameters on admission. PT and PTT values which were prolonged on admission tended to return toward normal and to stabilize somewhat below the levels in the bank blood itself. Conversely, PT

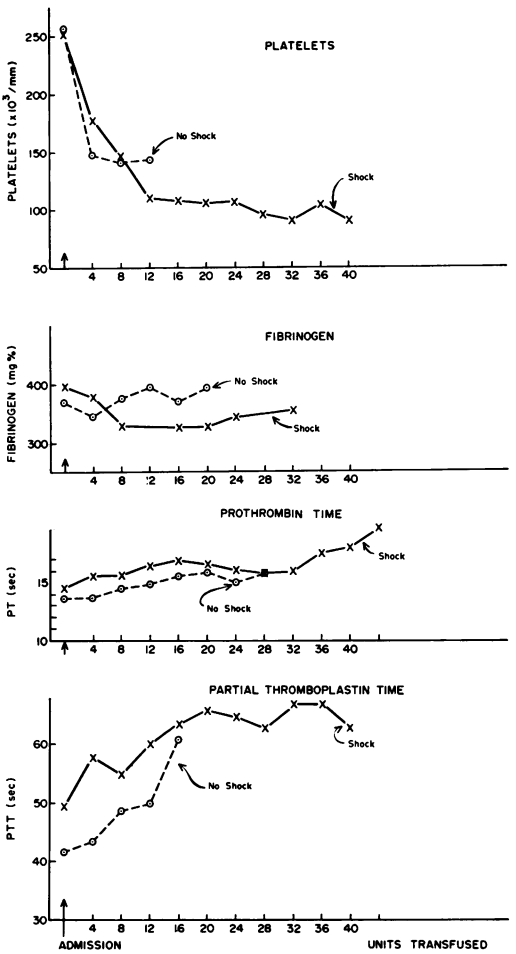

FIG. 1. Mean coagulation parameters of combat casualties during transfusion with stored bank blood. Patients admitted with a systolic blood pressure of 60 mm. Hg or less, an arterial blood lactate greater than 20 mg./100 ml., or an arterial blood pH less than 7.3 are designated as patients admitted in shock. Note that the changes do not exceed those seen in bank blood.

and PTT values which were normal or hypercoagulable on admission showed dilution to the same level if similar amounts of blood were given (Fig. 2).

The mean values presented in Figures 1 and 2 present the overall effect of transfusion but cannot depict the range of variation observed in individual patients. Several examples of the interaction between the coagulation mechanism of specific patients and large volumes of bank blood are presented in Figures 3–8.

TABLE 9. *Effect of Transfusion on Development of Prolonged PT and PTT*

Units of Blood	Total No. of Patients Studied*	% of Patients with Prolonged Values	
		PT >16	PTT >60
0	57	7.0	8.8
4	57	12.2	21.1
8	44	22.7	38.6
12	32	31.2	40.6
16	21	52.3	52.3
20	14	50.0	64.2
24	7	42.9	57.1
28	6	33.3	66.7
32	6	50.0	83.3
36	6	66.7	83.3
40	3	100.0	66.7

* All patients excluded after receiving fresh blood.

Figure 3 illustrates coagulation changes in a patient during two operations 4 days apart. At each of these operations a similar quantity of bank blood was administered. This patient sustained a thoracoabdominal wound with perforation of the right lobe of the liver. On admission, his systolic blood pressure was 80, arterial lactate 5 mg./100 ml. and arterial pH 7.29. Initial normal coagulation parameters became abnormal after 8 units of blood. Twelve units of blood were given at the first operation, but immediate reoperation was required to control continued bleeding from the hepatic wound. Four days later, gastrointestinal bleeding necessitated pyloroplasty and vagotomy. The blood pressure, arterial pH, and lactate remained normal throughout this second hemorrhage. During this operation, 14 units of blood were administered with no accompanying coagulation disorders. The findings in this patient suggest that the combination of trauma, hemorrhage, and shock may act to exaggerate

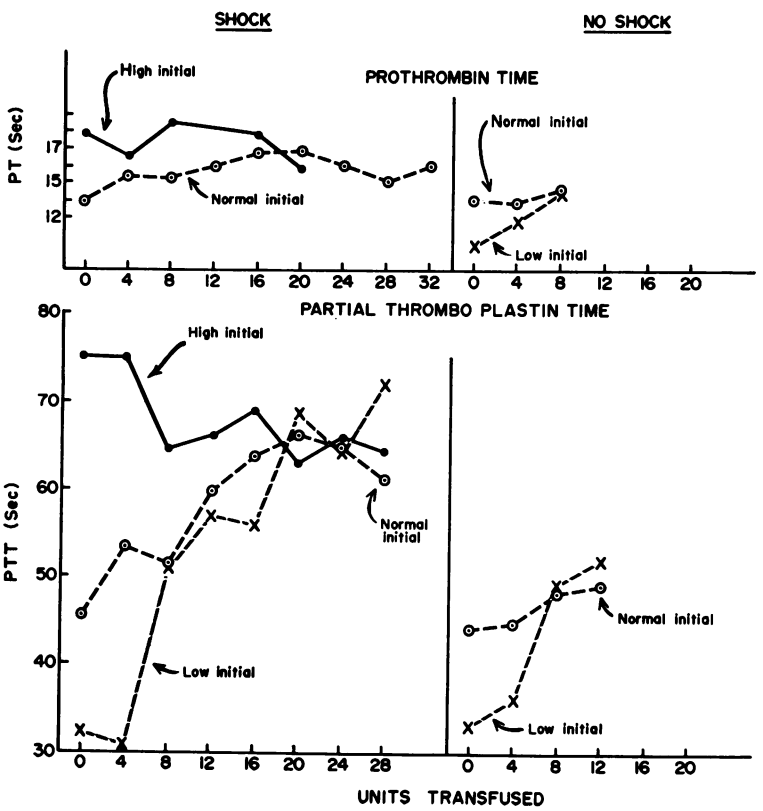

FIG. 2. Effect of transfusion on the mean prothrombin and partial thromboplastin times of combat casualties. Note that multiple transfusions with stored bank blood result in similar defects regardless of the initial status of these factors in combat casualties after wounding.

TABLE 10. *Effect of Fresh Blood on Coagulation Defects During Transfusion*

Pt. No.	Units Bank Blood	Units Fresh Blood	Prothrombin Time (sec.) Pre-fresh	Prothrombin Time (sec.) Post-fresh	Partial Thromboplastin Time (sec.) Pre-fresh	Partial Thromboplastin Time (sec.) Post-fresh	Platelets (/mm³) Pre-fresh	Platelets (/mm³) Post-fresh
162	20–25	4	16.9	14.4	76.5	60.0	83,000	186,000
188	36–44	4	21.7	17.9	81.4	17.9	76,000	83,000
195	16–20	2	24.0	14.3	77.7	59.3	76,000	82,000
255	36–46	4	21.9	21.6	78.5	61.0	86,000	192,000
285	44–48	3	17.8	17.5	60.7	70.1	101,000	141,000

dilutional changes which may occur with rapid transfusion.

Figure 4 illustrates coagulation changes in a patient who received 57 units of blood during his course which terminated when fatal pulmonary edema developed in the postoperative period. The patient was admitted in shock with a penetrating missile wound. During operation he had repeated episodes of hypotension. The coagulation changes observed were consistent with those in patients with similar degrees of transfusion—dilution of platelets to levels of 75,000 to 80,000, and elevations of PT to above 20 seconds, and PTT to more than 80 seconds. These levels were slightly greater than those found in stored blood. When the transfusion rate was slowed after bleeding had been controlled, however, both the PT and PTT rose to extremely high values. Possibly, coagulation changes which might have appeared in a patient with a comparable degree of shock were masked or even corrected by the rapid transfusion of bank blood which contained an adequate level of coagulation factors. Fresh blood only temporarily corrected the deficiencies.

Coagulation factors of two patients who exsanguinated are illustrated in Figures 5 and 6. One (Fig. 5) developed a severe coagulation abnormality after only 8 units of blood and suffered a cardiac arrest. The patient was resuscitated briefly and administered an ampule of calcium gluconate (1 Gm.). Immediately thereafter his PTT returned rapidly toward normal; however,

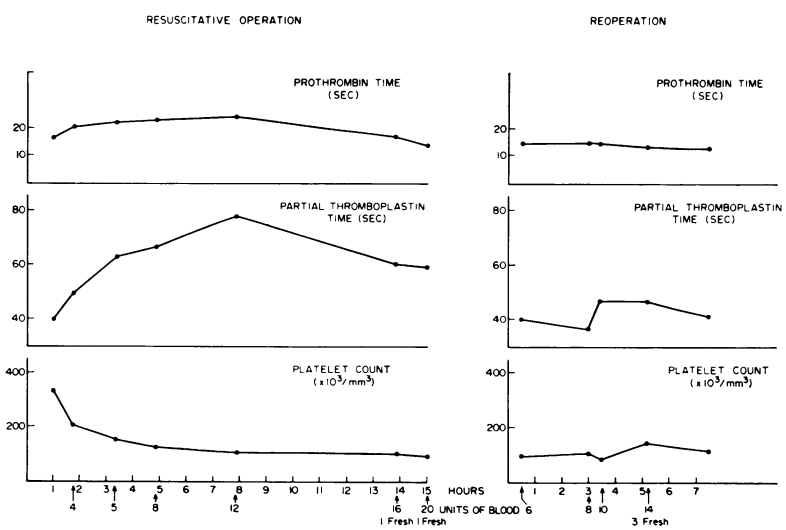

FIG. 3. Effect of transfusion on the coagulation parameters of patient number 195. During resuscitation after wounding, a dilutional effect of bank blood on these parameters is seen. Reoperation and transfusion 4 days later with similar volumes of blood did not result in dilution of the coagulation factors.

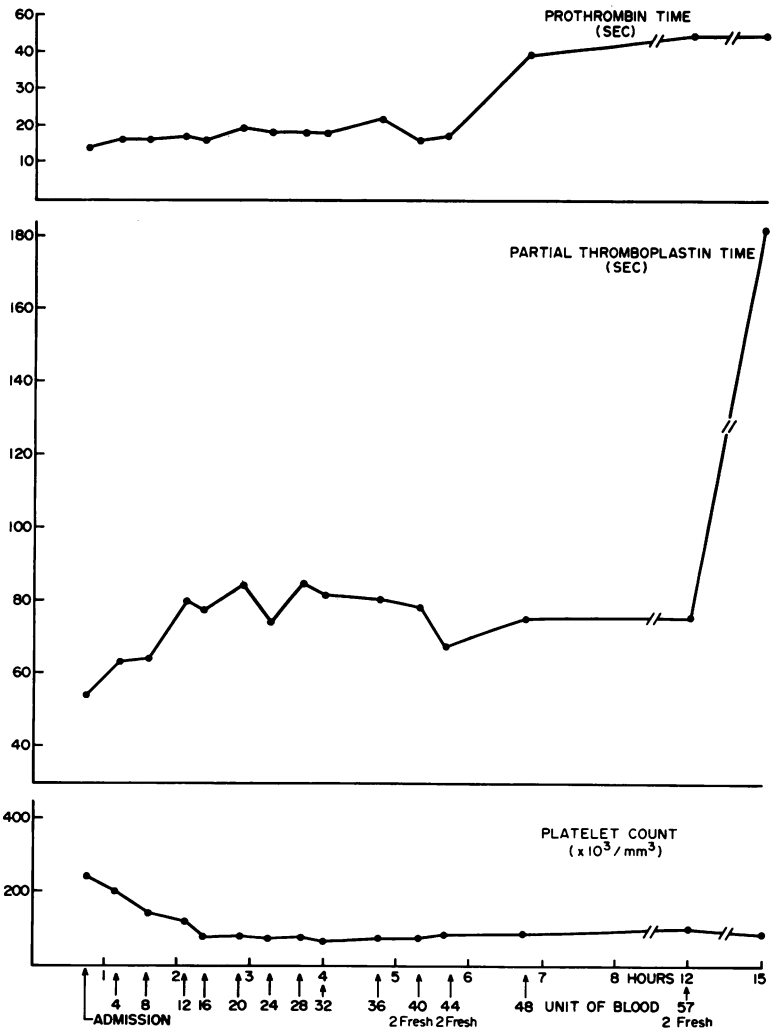

FIG. 4. Effect of transfusion of the coagulation parameters of patient number 188. The dilutional effect of bank blood is seen after 8 units of blood. Fresh blood administration resulted in a shift of the PT and PTT toward normal. Slowing of the transfusion rate was accompanied by severe prolongation of PT and PTT which were unaffected by subsequent transfusion of fresh blood. The patient died in the immediate postoperative period with massive pulmonary edema despite a normal blood volume and cardiac output.

the patient died following a second cardiac arrest and persistent bleeding. The hemorrhage could not be attributed primarily to the coagulation defect but rather to uncontrollable bleeding from the lacerated pulmonary vessels.

The second patient (Fig. 6) exsanguinated from a gunshot wound that involved the retroperitoneal plexus after 28 units of blood. During transfusion only moderate dilutional changes appeared in his PT and PTT. Any alterations attributable to shock were possibly masked by the rapid transfusion rate.

Figures 7 and 8 demonstrate the variable effect of tranfusions in patients who developed coagulation abnormalities before treatment was instituted. As pointed out above, the mean PT and PTT values generally tend to return toward normal during transfusion. In one patient, a 3 unit transfusion produced a prompt return to normal PTT values (Fig. 7), while in another patient 8 units were required (Fig. 8). These results suggest that re-establishment of a normal circulating blood volume may play as large a role in the return of coagulation factors to normal, as does infusion of coagulation factors in bank blood.

Effect of Fresh Whole Blood on Coagulation Disorders During Transfusion. Table 10 illustrates the effect of fresh

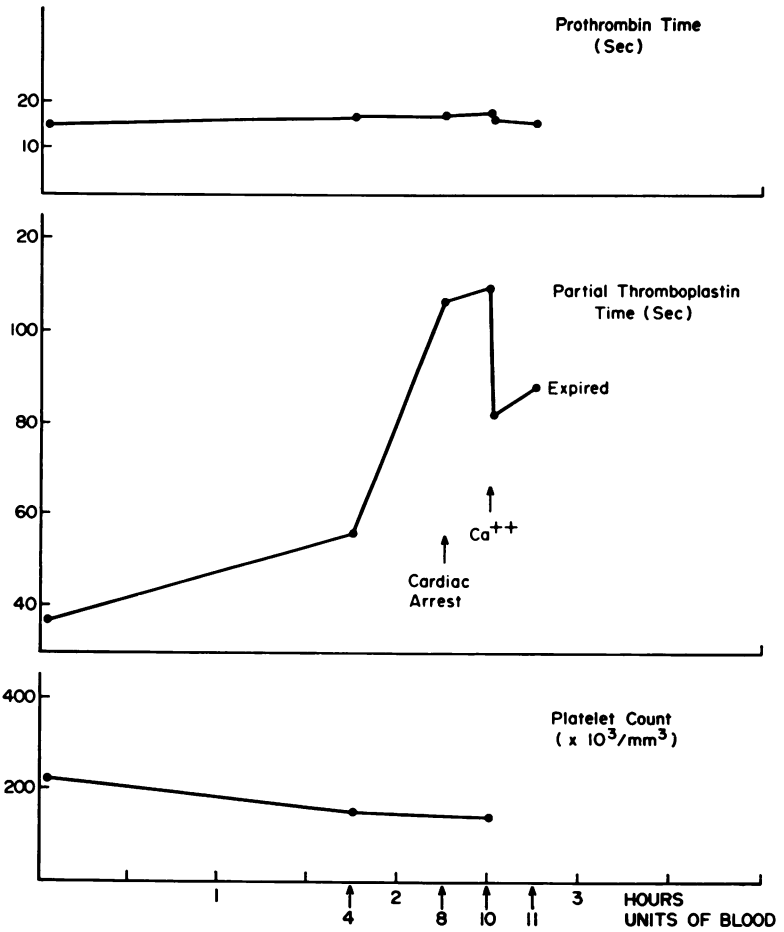

FIG. 5. Effect of transfusion on the coagulation parameters of patient number 162. Prolongation of PTT appeared at about the time of cardiac arrest. Calcium infusion returned the PTT toward normal within seconds.

whole blood in patients who have coagulation defects accompanying massive transfusion therapy with stored bank blood. The fresh blood was transfused into the patient within 1 hour of withdrawal. Platelet counts improved somewhat and the PT and PTT returned toward normal. In patient #188, however (Fig. 4), when administration of fresh blood coincided with slowing of the transfusion rate, the PT and PTT values rose again soon after transfusion of fresh blood. Table 11 demonstrates that the PT and PTT return to normal in the vast majority of patients within 24 hours even if fresh blood is not given.

Discussion: Part II

Massive administration of stored bank blood can adversely affect the coagulation mechanism in several ways. (1) Incompatible transfusion can precipitate disseminated intravascular coagulation leading to consumption of coagulation factors.[14, 79] (2) Citrate intoxication can occur with de-

TABLE 11. *Effect of Transfusion Volume on Return of PT and PTT to Normal after Transfusion*

No. of Units Bank Blood	No. of Patients	% Patients Studied Attaining Normal Levels in First 24 Hours	
		PT	PTT
4–12	24	100	100
12–24	25	72*	76*
24–40	8	62.5**	75**

* 1 death included who never attained normal levels.
** 2 deaths included who never attained normal levels

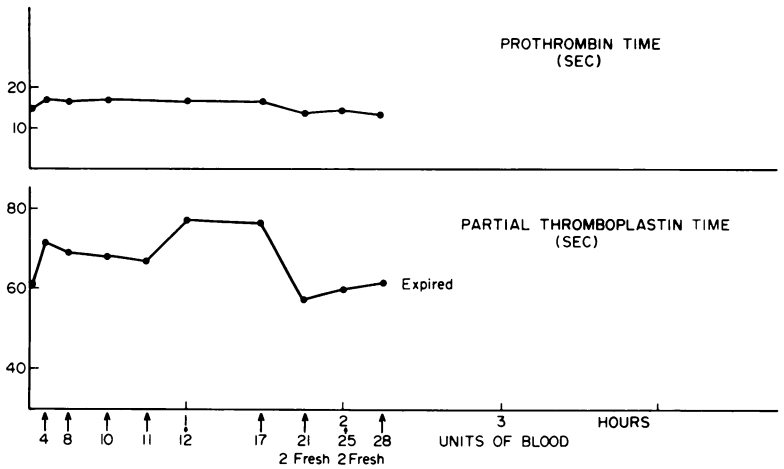

FIG. 6. Effect of transfusion on the coagulation parameters of patient number 225, who bled to death due to uncontrolled hemorrhage from the retroperitoneal space. The dilutional effect of bank blood on the PT and PTT is shown. These parameters returned to normal after 4 units of fresh blood but bleeding continued.

pletion of ionic calcium necessary for normal clotting.[25] (3) The thromboplastic substances which accompany hemolysis and platelet death during storage may trigger disseminated intravascular coagulation in patients with a stagnant capillary circulation.[13] (4) Thrombocytopenic factors may be present in normal plasma.[37] (5) The

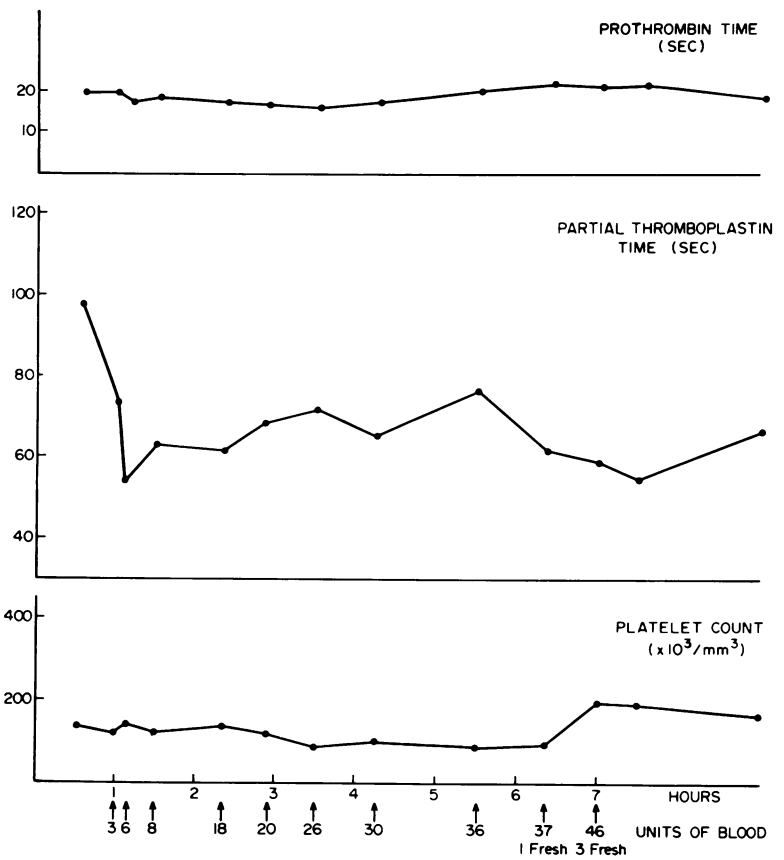

FIG. 7. Effect of transfusion on the coagulation parameters of patient number 255, who was admitted in severe shock with prolonged PT and PTT. The infusion of bank blood returned the PTT to normal followed by a secondary dilutional effect. Although no significant coagulation problem was present, fresh blood improved the PTT and platelet count.

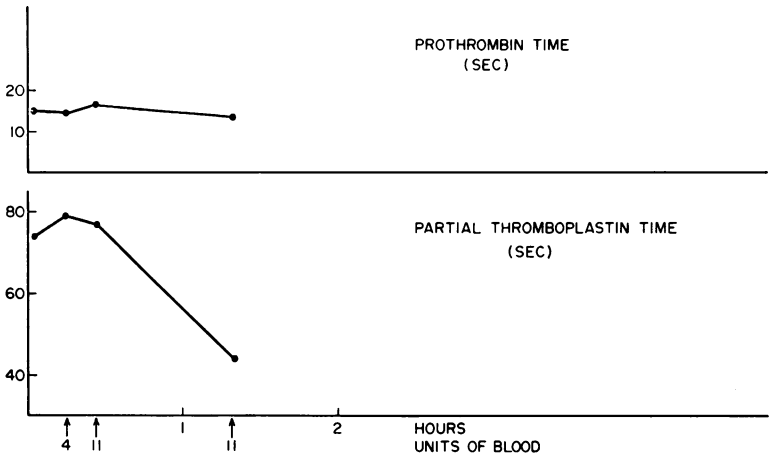

FIG. 8. Effect of transfusion on the coagulation parameters of patient number 151, who was admitted in severe shock with prolonged PTT. Transfusion with bank blood was not accompanied by any change in PTT until shock was controlled.

instability of factors V, VIII, and platelets during storage may lead to a significant degree of dilution of coagulation parameters and thus produce hemorrhagic diatheses.[17, 19, 22, 23, 28, 38]

In general, recipients of large quantities of bank blood did not exhibit greater clotting abnormalities than those already present in the bank blood. The initial more rapid dilutional effect seen in patients in shock is consistent with the fact that these patients had lost a greater amount of their own blood. Levels of clotting factors in patients who already had developed coagulation abnormalities prior to transfusion generally returned toward normal with increasing transfusions, although the rapidity of the response was variable. The fall in platelet count was rapid but never fell below 75,000/mm.^{3} in any patient. In short, no gross evidence of incompatible transfusion was encountered, hemolysis and the release of thromboplastic substances into bank blood did not precipitate detectable degrees of intravascular coagulation, and no evidence was obtained for a thrombocytopenic factor in plasma.

The use of fresh blood to counter dilutional effects of bank blood has frequently been suggested.[12, 38] Mean platelet counts of about 100,000 after 12 units of bank blood is considered adequate for normal hemostasis, however Voorhees and Phillips point out that such levels may be inadequate when surgical bleeding has been induced.[42] The rather mild dilutional effects on PT or PTT probably do not represent a clinically significant deficit. The use of fresh blood leads to some improvement in platelet counts, PT, and PTT. A few units of fresh blood cannot be expected to correct marked deficits in coagulation, however, when these are the result of disseminated intravascular coagulation, fibrinolysin activation, the release of endogenous anticoagulants, or citrate intoxication. In the patient who had marked coagulation defects after 57 transfusions, fresh blood had no permanent effect on these changes. The actual defect observed in this patient resembles the course of disseminated intravascular coagulation during shock and tissue injury.

In a patient who consumes coagulation factors at a rapid rate, the infusion of clinically tolerated amounts of fresh whole blood, obviously would have little effect on coagulation parameters. In fact, the early rapid administration of bank blood may mask changes in the patient's own coagulation mechanism, since coagulation disorders become apparent only after the transfusion rate has slowed.

Fresh ACD blood also would not be ex-

pected to have beneficial effects in a patient with citrate intoxication. This patient developed a prolonged PT and PTT just prior to cardiac arrest. Following administration of calcium ion, the PTT returned dramatically toward normal before reestablishment of circulation. It is commonly stated that citrate intoxication is not a problem until levels of ionic calcium are sufficiently low to interfere with cardiac action.[25] The rapid infusion of ACD blood into patients with deficient detoxifying mechanisms, which results from stagnant circulation, could permit the appearance of citrate intoxication. Prophylactic ionic calcium infusions into patients in shock receiving large quantities of citrated blood may be indicated.

Individual differences in dilutional effect of bank blood probably depend not only on the variable depletion of coagulation factors during storage, but also upon intrinsic events within the patients. One patient (Fig. 3) responded to 12 units of blood differently on two different occasions. A distinct dilutional effect of the bank blood was seen during transfusion after a period of hypotension and acidosis following wounding. Four days later the dilutional effect was not seen during gastrointestinal hemorrhage at which time hypotension and acidosis had been avoided.

No clinical evidence of hemorrhagic diatheses appeared in any of these young men despite large volumes of transfused blood. The patients who bled to death did so on a basis of inadequate surgical control. The pattern of dilution of coagulation factors due to massive transfusions, and the deviations from the pattern suggest that hemorrhagic diatheses result from changes within the patient in response to trauma and shock rather than effects of transfusion.

It should be emphasized that these studies were carried out in patients with traumatic wounds who were otherwise healthy and normal. Dilutional effects of massive transfusion and intrinsic effects of trauma and shock may be exaggerated in elderly debilitated or cirrhotic patients frequently seen on a civilian surgical service. Coagulation changes of such patients should be carefully followed and fresh blood used if indicated.

Summary: Part II

1. Transfusion of combat casualties is accompanied by dilutional coagulation defects compatible with levels of coagulation factors in stored bank blood. Platelet levels fell rapidly during transfusion to about 100,000/mm.[3] The prothrombin times, partial thromboplastin times, and fibrinogen levels were less severely affected.

2. Significant operative bleeding was not encountered in conjunction with these mild dilutional coagulation changes.

3. The administration of stored bank blood to casualties who have developed coagulation defects secondary to shock results in a partial return of coagulation factors toward normal. Pre-existing coagulation defects were not aggravated by thromboplastic substances in bank blood.

4. Transfusion with stored bank blood may mask the appearance of endogenous coagulation disorders which develop in patients in prolonged shock.

5. The use of fresh whole blood will partially counteract the dilutional effect on coagulation parameters but is rarely necessary in young, previously healthy men. In the presence of coagulation defects associated with presumed disseminated intravascular coagulation, fresh whole blood was not associated with any permanent improvement in coagulation parameters.

Part III. Coagulation Changes in the Post-resuscitative Period

Alterations of Prothrombin Time and Partial Thromboplastin Time in the Post-resuscitative Period. Of the original 240

TABLE 12. *Effect of Preoperative Shock, Postoperative Hypoxemia and Postoperative Blood Volume on Occurrence of Abnormal PT or PTT in the Convalescent Period*

	Number of Patients with					
	Preoperative		Convalescent		Convalescent	
Convalescent Values	Shock	No Shock	Po_2 <80	Po_2 >80	Normal Blood Volume	Low Blood Volume
Abnormal PT or PTT	31	26	42	10	6	6
Normal PT or PTT	31	46	37	12	9	2
	$p < 0.01$		$p > 0.05$		$p > 0.05$	

patients, 120 were studied 1–3 times a day for at least 3 days following admission to determine the stability of the coagulation parameters in the immediate post-resuscitative period. Fifty-seven developed abnormal prolongations of prothrombin times (PT) or partial thromboplastin times (PTT) or both. The others developed no prolongations of these parameters, although occasional patients had shorter than normal times.

Of 57 patients who developed PT or PTT abnormalities in the post-resuscitative period, 46 had normal values in the immediate postoperative period. This indicates that development of abnormalities in these parameters in the post-resuscitative period were not continuations of dilutional changes which appear with transfusion.

Table 12 represents a correlation of the development of prolonged PT or PTT values with shock on admission to the hospital after wounding. It is apparent that the presence of hypotension, lactatemia, or acidosis after wounding predisposes to development of coagulation abnormalities in the post-resuscitative period ($p < 0.01$).

Blood volume determinations were performed on 23 patients in the immediate postoperative period. Two groups of patients were found: those who had blood volume deficits of 15% or less, and those who had deficits of more than 15%.[34] Table 12 shows that undertransfusion is associated with a greater number of patients who developed coagulation abnormalities in the post-resuscitative period, although the relationship is not statistically significant ($p < 0.02$).

Arterial blood gas determinations were performed daily on most of these patients. Moderate to severe hypoxemia was common.[8, 33] Arterial oxygen tension less than 80 mm. Hg appeared at the same time as abnormal prolongation of the PT or PTT in 38 of 53 patients in whom simultaneous determinations were performed. In these same patients, however, there were periods in which hypoxemia did not accompany prolongation of PT or PTT. Table 12 illustrates the relationship between development of hypoxemia at some time during the course, and development of coagulation abnormalities. Hypoxemia occurred without development of coagulation abnormalities at approximately the same rate as in patients with coagulation disorders ($p > 0.05$). The relationship between hypoxemia and postoperative PT or PTT abnormalities is not altered by controlling for the preoperative presence of shock or requirements for large volumes of blood.

Tables 13 a and b correlate volumes of transfused blood during resuscitation and operations with development of prolonged PT or PTT in the early post-resuscitative period. There is a significantly increased chance of developing these abnormalities

TABLE 13a. *Effect of Volume of Blood Required During Resuscitation on Occurrence of Abnormal PT or PTT in Convalescent Period (Patients in Shock on Admission)*

	No. Patients Requiring Volume (ml.) Blood		
Convalescent Values	<1500	2000–4500	>5000
Abnormal PT or PTT	3	8	21
Normal PT or PTT	6	7	5
	$p < 0.05$		

TABLE 13b. *Effect of Transfused Volume on the Occurrence of Abnormal PT or PTT in the Postoperative Period (Patients Not in Shock on Admission)*

	No. Patients Requiring Volume (ml.) Blood		
Convalescent Values	<1500	2000–4500	>5000
Abnormal PT or PTT	15	6	5
Normal PT or PTT	28	14	1
	$p < 0.10$		

TABLE 14. *Effect of Abnormal Pre-Transfusion PT or PTT on the Occurrence of Abnormal PT or PTT Convalescent Period*

	No. Patients with Pre-Transfusion	
Convalescent Values	Abnormal PT or PTT	Normal PT or PTT
Abnormal PT or PTT	9	1
Normal PT or PTT	45	58
	$p < 0.01$	

TABLE 15. *Effect of Wound Location on the Development of Prolonged PT or PTT in the Convalescent Period*

	No. Patients with	
Wound Site	Prolonged PT or PTT	Normal PT or PTT
Chest	10	18
Thoraco-abdominal	11	13
Abdominal	14	14
Extremities and Soft tissues	22	18
	$p > 0.05$	

if large volumes of blood have been required in patients in shock ($p < 0.05$). The trend is similar in patients not in shock on admission, but the difference is not statistically significant ($p < 0.10$).

Table 14 demonstrates that an abnormal PT or PTT on admission to the hospital prior to any treatment is almost always followed by prolongations of these parameters in the post-resuscitative period. Since most of these patients were in shock on admission, this correlation might be expected.

Table 15 shows that there is no correlation between sites of major wounds and development of prolonged PT or PTT in the post-resuscitative period.

Most (41/57) abnormal PT or PTT values appeared in the first 24 hours following the resuscitative operation. Table 16 lists the time of first appearance of these abnormalities. There is no tendency for the abnormalities to appear earlier in patients who were in shock on admission or in patients who received the most blood.

Forty-two of 57 patients developed PT greater than 16 seconds, and 38 developed PTT greater than 60 seconds some time following resuscitation. Only 24 patients developed abnormalities of both parameters, however, and in only 13 did these abnormalities coincide.

After development of the first abnormal values, the PT or PTT always became normal for a period of time. Twenty-four patients subsequently developed further abnormalities in PT and/or PTT. Table 17 illustrates the number of separate abnormal peaks of PT or PTT which appeared in these patients. Each abnormal peak was followed at varying intervals by some normal values. Mean time intervals between

TABLE 16. *Effect of Pre-Transfusion Shock and the Volume of Transfused Blood on the Time of Appearance of Abnormal PT or PTT*

Time of First Appearance of Abnormal PT or PTT	No. Patients with				
	Preoperative		Volume Transfused		
	Shock	No Shock	<4,000 ml.	4,000–8,000 ml.	>8,000 ml.
24 hours or less	20	21	15	15	11
24–48 hours	6	3	4	3	1
More than 48 hours	5	2	4	1	2
	$p > 0.05$		$p > 0.05$		

each peak value and the previous peak are also listed in this table. At first glance Table 17 suggests a regular recurring abnormality appeared at approximately 2-day intervals. Standard deviations of these time intervals between subsequent peaks are very large, however, which indicates that no one pattern of peak sequence can be predicted. Similarly, there is no relationship between the number of peaks and the degree of shock on admission, the volume of blood transfused during resuscitation and operation, the degree or duration of hypoxemia, the presence of abnormal coagulation parameters in the immediate post-wounding period, or the time of appearance of the first peak. Apparently, the number of abnormal peaks can best be correlated with the number and significance of serious surgical complications which occurred in the postoperative period. Table 18 lists nine patients who developed four or more separate abnormal PT or PTT peaks in the post-resuscitative period, the wounding agent, the site of major wound, and the complications which coincided with the development of the cyclic abnormalities which appeared. Note the wide variety of complications. In only two patients (#234 and #237) were these complications not deemed life-threatening at the time. Two patients ultimately died.

Table 19 lists coagulation studies performed prior to death in these two patients and in two others dying more than 24 hours after wounding. All four developed coagulation disorders although in only one were they severe enough to cause rebleeding in the immediate pre-terminal phases. Coagulation defects in patients who died in the first 24 hours after wounding have been discussed in the preceding sections.

The peak values of PT and PTT in patients who developed prolonged values in the postoperative period may be quite high (PT range 16.1–24 sec; PTT range 61 sec-infinity). The range of these values far exceeds the range either in the immediate post-traumatic period or during resuscitation. No correlation can be made between the degree of abnormality and the presence of shock on admission, the volume of blood transfused, or the presence of PT or PTT abnormalities on admission.

TABLE 17. *Multiple Abnormal PT or PTT Peaks in Post-resuscitative Period*

No. Separate PT or PTT Abnormal Peaks	No. Patients Developing Peaks	Time Interval Between Peak and Preceding Peak (mean ± S.D.)
1	33	31.0 ± 36.2 hours
2	12	53.6 ± 34.8
3	3	54.1 ± 30.2
4	7	51.3 ± 30.5
5	1	63.5
6	0	54
7	1	48

TABLE 18. *Course of Patients with More than Four Abnormal PT or PTT Peaks*

Patient No.	Wound*	Complications
171	Mfw abd, extrems	Persistent anemia Pulmonary edema Necrotizing pneumonia Death
205	Gsw abd	Wound disruption Intestinal obstruction
228	Gsw chest, abd	Disruption ileocolic anastomosis Gastric ulcer Cardiac arrest Intraperitoneal sepsis Death
232	Mfw chest, extrems	Atelectasis and contusion entire right lung
234	Gsw chest, abd	Rebled from hepatic laceration requiring reoperation
237	Gsw chest, abd	Fever, hypoxemia
240	Mfw chest, extrems	Atelectasis and contusion entire left lung
241	Mfw chest	Extensive atelectasis and pneumonia right middle and lower lobes
256	Gsw abd	Pneumonia Intestinal obstruction

* Mfw—multiple fragment wounds.
Gsw—gunshot wounds.

Thirteen patients developed PT values greater than 20 sec. or PTT values greater than 120 sec. Nine of these are listed either in Table 18 or Table 19 which include all deaths occurring after 24 hours, and those patients who had multiple peaks associated with severe complications. Of the remaining four, one peak appeared following development of postoperative pulmonary edema. The other three appeared in the immediate post-resuscitative period. Only one of these patients had been in shock or had received more than 4,000 ml. of blood.

Figures 9–11 illustrate the course of these changes in three patients. Figure 9 depicts coagulation changes in patient #244 who received multiple fragment wounds of both lower extremities and required 1,000 ml. of blood during resuscitation and operation. The mildly hypercoagulable values on admission rose to abnormal levels on the first postoperative day (PTT = 65.5) but promptly fell to the normal range. The PTT oscillated within this range for the next week and then stabilized between 40–45 sec. A peak in the PT occurred on the third postoperative day, and it too returned to normal with slight cyclic variations. The variations in each of the parameters did not precisely parallel each other.

Figure 10 illustrates coagulation parameters in patient #228, who suffered a gunshot wound of the chest and abdomen and required 4,000 ml. of blood during resuscitation and operation. Postoperatively he developed pulmonary edema with severe

TABLE 19. *Coagulation Parameters Prior to Death*

Patient No.	Time Prior to Death	PT (sec.)	PTT (sec.)	Platelets (/mm.^{3})	Fibrinogen (mg./100 ml.)
	15 hours	14.2	41.0	—	—
163	1½ hours	14.5	51.2	—	—
	½ hour	22.1	125.9	81,000	210
	70 hours	18.5	60.7	285,000	400
171	45 hours	15.2	51.3	—	410
	18 hours	14.5	49.3	122,000	480
	24 hours	16.4	72.3	144,000	630
228	18 hours	17.1	68.9	161,000	660
	20 minutes	18.6	56.5	165,000	—
	7 hours	20.7	69.9	71,000	240
266	5 hours	21.8	76.3	87,000	240
	2 hours	22.0	70.1	44,000	250

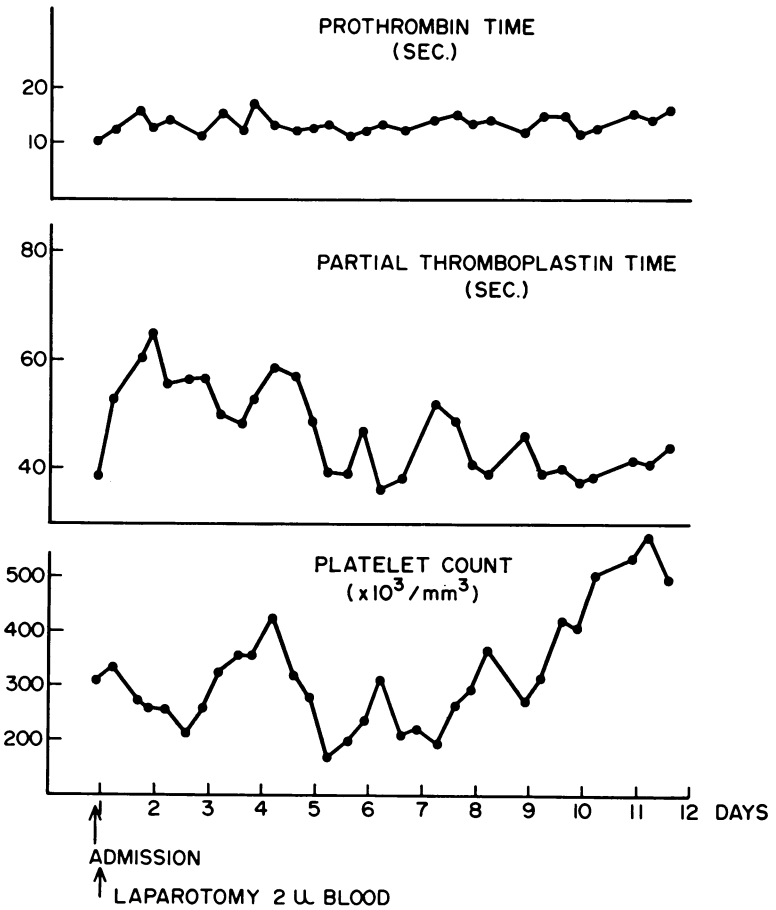

FIG. 9. Post-resuscitative coagulation parameters in patient #244. Minimal transient defects were seen in the PT and PTT, but a cyclic pattern of variation in the normal range was present for the first postoperative week.

TABLE 20. *Coagulation Parameters in Patients Reoperated for Bleeding*

Patient No.	Site	PT (sec.)	PTT (sec.)	Platelets (/mm.³)	Fibrinogen (mg./100 ml.)	Lysis
99	Neck internal jugular vein (day 1)	11.4	30.5	—	—	4+
100	Post-tibial artery (day 0)	15.9	60.1	—	250	4+
195	Liver wound (day 0)	17.2	60.0	103,000	280	0
195*	Gastric ulcer (day 3)	13.3	45.1	130,000	420	0
228	Gastric ulcer (day 9)	15.2	44.8	216,000	—	3
247	Soft tissue (day 0)	14.1	43.8	160,000	—	—
298	Liver wound (day 0)	13.1	41.5	149,000	390	—

* Second bleeding episode.

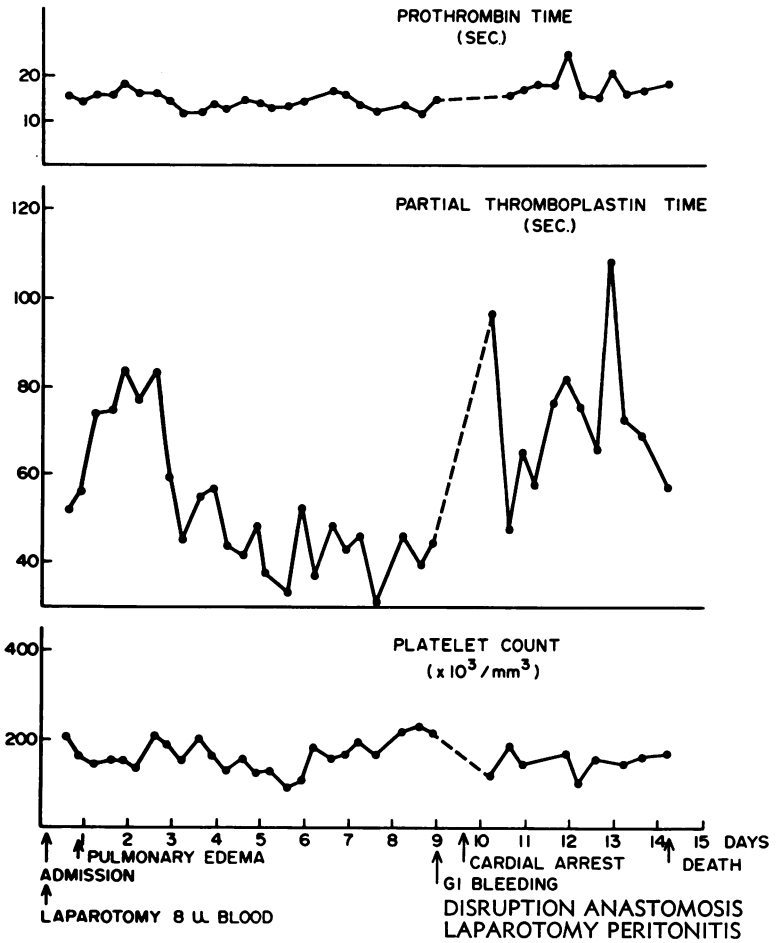

FIG. 10. Post-resuscitative coagulation parameters in patient #288. The patient was admitted in shock and developed pulmonary edema 12 hours after operation. This episode was accompanied by abnormal prolongations of the PT and PTT which returned to normal, although the cyclic pattern was present. Disruption of the intestinal anastomosis, GI bleeding, and cardiac arrest appeared on the 9th postoperative day. At the time of bleeding coagulation parameters were normal, but they became abnormal in a recurrent cyclic pattern during the septic course which followed reoperation.

hypoxemia despite normal blood volume and cardiac output. During the first and second postoperative days, PTT and PT were both prolonged but returned to normal as the pulmonary edema was controlled. Cyclic variation within the normal was present in both PT and PTT during this otherwise stable period. On the 8th postoperative day there was evidence of both upper gastrointestinal bleeding and disruption of an ileo-colic anastomosis which had been performed. Coagulation parameters were in the normal range at this time. During operation cardiac arrest occurred. Postoperatively cyclic oscillations between normal and abnormal coagulation parameters recurred and only terminated with the patient's death due to septicemia and respiratory insufficiency. Autopsy confirmed the presence of severe peritonitis.

Figure 11 illustrates the course of patient #205, who was wounded by a single high velocity missile which perforated his abdominal wall. Despite 6,000 ml. of blood and moderately severe shock, coagulation parameters remained within normal ranges for the first few days except for a transient elevation of PT to 16.9 sec. on the second postoperative day. On the fifth postoperative day, however, his abdominal wound disrupted. This was accompanied by severe prolongation of both the PT and PTT. A course consisting of cyclic recurrent abnormalities then ensued with gradual return to normal range as intestinal ileus resolved.

Alterations in Fibrinogen, Platelets,

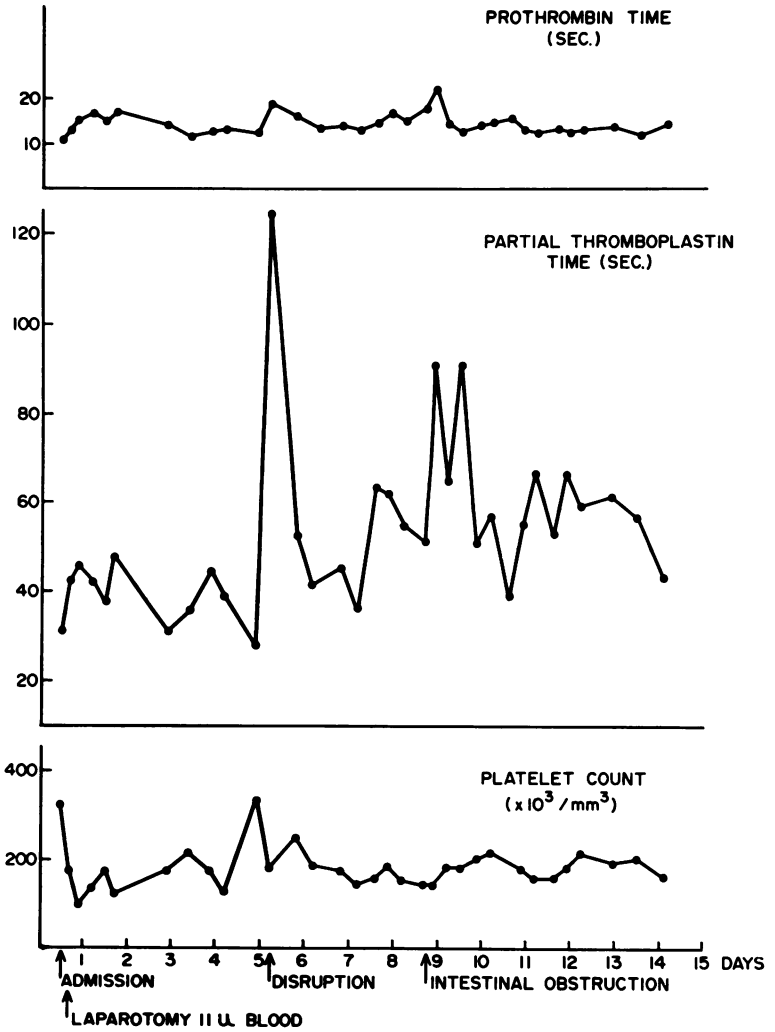

FIG. 11. Post-resuscitative coagulation parameters of patient #205. Despite initial shock and multiple transfusions the PT and PTT remained near normal although they varied cyclically. At the time of wound disruption the coagulation parameters became abnormal and continued a spiking cyclic course until the abdominal complications resolved.

and Fibrinolysin in the Post-resuscitative Period. Figure 12 illustrates the change of fibrinogen values in these patients. The mean fibrinogen value was consistently lower in patients who were in shock at admission, and who developed abnormalities of PT and PTT in the postoperative period. Since the general trend was toward hyperfibrinogenemia with time, these findings suggest that manufacture and release of fibrinogen was delayed or that fibrinogen was being consumed.

Similar findings can be shown for platelet counts and fibrinolysin values during the post-resuscitative period (Figs. 13, 14). All platelet counts remained low for several days after injury; however, platelet counts were lower in patients who received the most blood, who developed PT and PTT abnormalities in the post-resuscitative period, and who were in shock immediately after wounding.

Fibrinolysin titers generally fell in the first few days after injury and resuscitation, although they remained above normal (Fig. 14). The titers were significantly higher ($p < 0.05$) in patients who developed abnormally high PT and PTT values in the postoperative period.

Effect of Postoperative Coagulation Disorders on Postoperative Hemorrhage. Table 20 lists clotting parameters of six

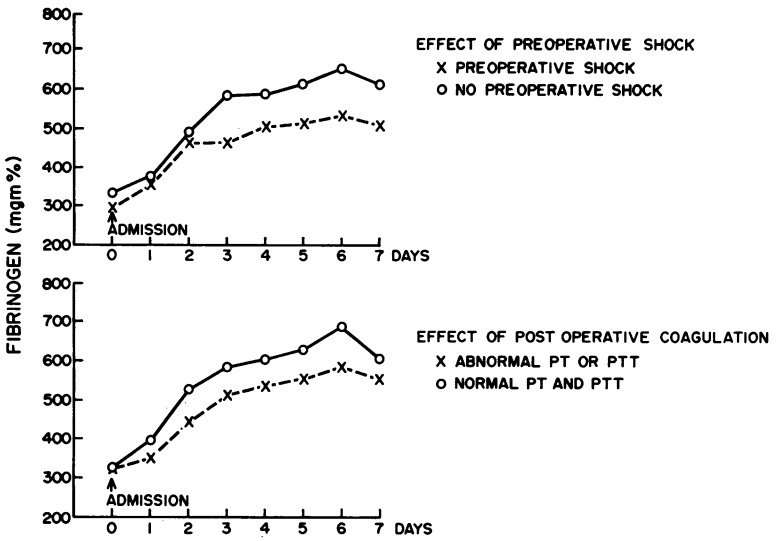

FIG. 12. Mean post-resuscitative fibrinogen levels in combat casualties: Patients with shock after wounding and those developing abnormal PT and PTT during the post-resuscitative period are slower to develop hyperfibrinogenemia. The differences are not statistically significant.

convalescent patients at the time that re-operation was required for hemorrhagic episodes. The coagulation defects were minor in all cases. No other bleeding epi-

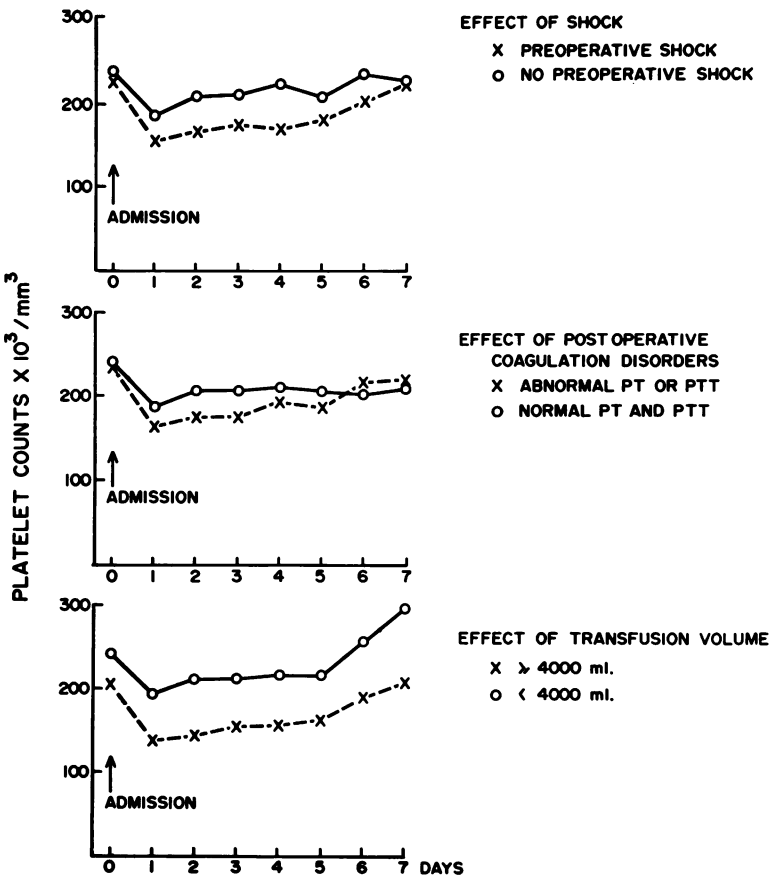

FIG. 13. Mean post-resuscitative platelet counts in combat casualties. Patients who were in shock after wounding, and who received more than 4,000 ml. of blood during resuscitation are significantly slower ($p < 0.05$) in returning platelet counts to normal. This trend is present but not statistically significant in patients who have developed prolongations of PT or PTT in the post-resuscitative period.

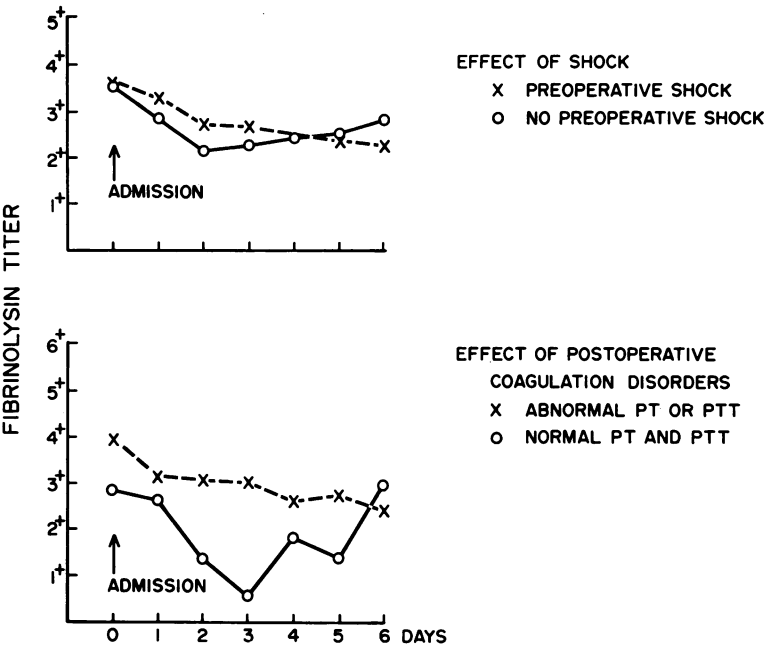

FIG. 14. Mean post-resuscitative fibrinolysin titers in combat casualties. Patients who develop prolongations of PT or PTT during this period maintain significantly higher fibrinolysin titers than those whose PT and PTT remains within the normal range ($p < 0.05$).

sodes requiring reoperation were encountered in these 120 patients or in more than 1,000 other patients seen who were not studied intensively.

Discussion: Part III

Coagulation defects which appear in the postoperative patient have been studied by a number of authors and a variety of defects have been described.[2, 11, 30] Our own preliminary studies showed a considerable variation in clotting parameters on daily specimens. Therefore, blood samples for coagulation studies were drawn three times daily on many patients during their first week of convalescence. A distinct pattern of response was found. A series of cyclic prolongations in PT or PTT or both appeared, which could be correlated with the severity of injury and the volume of blood transfused during the resuscitative and operative periods. These abnormalities almost always appeared if prolongations in PT or PTT were found at the time of admission to the hospital prior to the institution of treatment. The range of variation within individual patients was very great, since each peak was maintained for only a short period (usually less than 8 hours) and promptly returned to normal. The abnormalities were rarely a continuation of dilutional changes which appeared with rapid transfusion, since most patients had returned to normal levels prior to developing secondary prolongations. The frequency and height of recurrent peaks could only be correlated with the presence of life-threatening complications but could never be correlated with the occurrence of hemorrhagic complications. Coincidentally, there were significant depressions of platelet counts, fibrinogen levels and elevations of fibrinolysin in these patients, although cyclic changes seldom coincided precisely in any two parameters.

Scott and Crosby [30] studied changes in platelet counts, prothrombin times, clotting times, and fibrinogen concentrations in 11 patients convalescing from war wounds. In general, they found clotting times to be shorter than normal and platelet counts and fibrinogen levels to be greater than normal. Prothrombin activity in these 11 patients was diminished during the first

few days, returned to normal, and demonstrated a secondary fall on the fourth day.[30] DeTakats also found variations in clotting times of postoperative patients.[11] These variations were correlated with the generalized stress responses and effects of corticosteroids on the clotting mechanism.[10, 11, 36]

Attar [2, 3] more recently described cyclic variations in silicone clotting times in patients with hemorrhagic and septic shock. Subsequently, he related the progression of these cyclic changes to a poor prognosis.[1] The findings reported here tend to confirm Attar's observations. Patients, who sustain missile wounds with extensive tissue damage and who require many transfusions, develop a series of coagulation disorders which reflect not only the extent of the trauma and blood loss, but also the current state of well-being. These findings are most easily interpreted in terms of a series of episodes of disseminated intravascular coagulation in which coagulation factors are utilized, fibrinolysin activated, and endogenous anticoagulants released.[13, 31] Loss of coagulation factors is reflected in diffuse, though not necessarily severe, abnormalities of screening tests. Such episodes need not be fatal or be associated with irreversible shock. They may occur within the microcirculation of one or more organs which have sustained periods of relative hypoperfusion and which may contain necrotic tissue. In addition, hemolysis of transfused blood, wound contamination with release of endotoxins, and the release of tissue thromboplastin from necrotic tissue can be assumed in these patients. All these factors have been implicated as stimuli for the development of disseminated intravascular coagulation.[13, 31]

That dying patients universally developed coagulation disorders at some time during their course, and that patients with life-threatening complications had the most episodes of PT and PTT elevations agrees with Attar's [1] findings that coagulation changes were associated with a poor prognosis. These results should not be interpreted to suggest that disseminated intravascular coagulation is the terminal mechanism, since the most severe coagulation disorders are seldom present when death is most imminent. Only one patient had incoagulable blood immediately prior to death. This finding was not present an hour previously when he was in the terminal stages of pulmonary edema, but occurred after one cardiac arrest from which he was temporarily resuscitated.

Summary: Part III

1. Coagulation studies were performed as often as three times daily on 120 combat casualties during early convalescence.

2. The prothrombin times and partial thromboplastin times of almost all patients were normal within the first 24 hours after resuscitative operations. Thereafter, abnormalities occurred in either or both parameters in 57 patients. Coagulation abnormalities could be correlated with the presence of shock on admission to the hospital, transfusion of large quantities of blood, and the presence of abnormalities in clotting parameters prior to operation.

3. The degree of prolongation of PT or PTT was much greater than that seen either at the time of admission or during transfusion.

4. In 24 patients a pattern of recurring PT or PTT prolongations appeared in the postoperative period with intervening periods in which these parameters were normal. The presence of four or more of these peaks could be correlated with the appearance of life-threatening complications. All patients who died had abnormalities at some time prior to death. Bleeding episodes which required reoperation, however, were not associated with coagulation abnormalities.

5. Fibrinogen levels were greater than normal in almost all patients. This pattern of recovery was delayed in patients who

had been in shock on admission, or who developed prolongations of PT or PTT during convalescence.

6. Platelet counts returned to normal over the first week in almost all patients. Recovery was delayed in those who had been in shock on admission, who had received large quantities of blood, or who developed prolongations of PT or PTT during convalescence.

7. Fibrinolysin values returned toward normal but remained elevated in most patients during the first convalescent week. The values were significantly higher if prolongation of PT and PTT were present during this period but no correlation could be made with the degree of shock on admission.

8. The coincidence of abnormalities of PT and PTT with thrombocytopenia and fibrinolysis, and a relative deficiency of fibrinogen in most seriously wounded patients is consistent with the idea that nonlethal episodes of disseminated intravascular coagulation occur during recovery from severe trauma and shock.

References

1. Attar, S.: Prognostic Significance of Coagulation Studies in Clinical Shock. Surg. Forum, 17:8, 1966.
2. Attar, S., Kirby, W. H., Jr., Masaitis, C., Mansberger, A. R. and Cowley, R. A.: Coagulation Changes in Clinical Shock. I. Effect of Hemorrhagic Shock on Clotting Time in Humans. Ann. Surg., **164**:34, 1966.
3. Attar, S., Mansberger, A. R., Irani, B., Kirby, W., Jr., Massaitis, C. and Cowley, R. A.: Coagulation Changes in Clinical Shock. II. Effect of Septic Shock on Clotting Times and Fibrinogen in Humans. Ann. Surg., **164**:41, 1966.
4. Biggs, R. and MacFarlane, R. G.: Human Blood Coagulation and Its Disorders. Oxford, Blackwell Scientific Publications, 1957.
5. Biggs, R., MacFarlane, R. G. and Pilling, J.: Observations on Fibrinolysis: Experimental Activity Produced by Exercise or Adrenaline. Lancet, 1:402, 1947.
6. Brecker, G. and Cronkite, E.: Morphology and Enumeration of Blood Platelets. J. Appl. Physiol., 3:365, 1950.
7. Campbell, W. K. and Hanna, M. I.: The Albumin, Globulins, and Fibrinogen of Serum and Plamsa. J. Biol. Chem., **119**:15, 1937.
8. Collins, J. A., Gordon, W. C., Hudson, T. L., Irvin, R. W., Jr., Kelly, T. and Hardaway, R. M., III.: Inapparent Hypoxemia in Casualties with Wounded Limbs. Ann. Surg., **167**:511, 1968.
9. Coon, W. W. and Hodgson, P. E.: Fibrinolysis in Surgery Patients. Surg. Gynec. Obstet., **95**:717, 1952.
10. Cosgriff, A. F., Diffenbach, A. and Vogt, W.: Hypercoagulation of Blood Associated with ACTH and Cortisone Therapy. Amer. J. Med., **9**:752, 1950.
11. DeTakats, G. and Marshall, M. H.: The Response of the Clotting Equilibrium to Postoperative Stress. Surgery, **31**:13, 1952.
12. Goldstein, R., Bunker, J. P. and McGovern, J. J.: The Effect of Storage of Whole Blood and Anticoagulants upon Certain Coagulation Factors. Ann. N. Y. Acad. Sci., **115**:422, 1964.
13. Hardaway, R. M.: Syndromes of Disseminated Intravascular Coagulation with Special Reference to Shock and Hemorrhage. Springfield, Ill., Charles C Thomas, 1966.
14. Hardaway, R. M., McKay, D. G., Wahle, G. H., Tartock, D. E. and Edelstein, R.: Pathologic Study of Intravascular Coagulation Following Incompatible Blood Transfusion in Dogs. Amer. J. Surg., **91**:24, 1956.
15. Henry, R. J., Sabeb, C. and Berkinon, S.: Interferences with Biuret Methods for Serum Protein. Anal. Chem., **29**:1491, 1957.
16. Hewson, W.: *In* the "Works of William Hewson, F.R.S." Ed. by G. Gulliver. London, the Sydenham Society, 1946, p. 55.
17. Howland, W. S., Ochweizer, C. P., Boyan, C. P. and Dotto, A. C.: Physiologic Alterations with Massive Blood Replacement. Surg. Gynec. Obstet., **101**:1478, 1955.
18. Ingram, G. I. C.: Increase in Antihaemophilic Globulin Activity Following Infusion of Adrenaline. J. Physiol., **156**:217, 1961.
19. Ingram, G. I. C.: The Bleeding Complications of Blood Transfusion. Transfusion, **5**:1, 1965.
20. Karlson, K. E. and Lerner, B.: The Coagulation Status of Surgical Patients. Ann. N. Y. Acad. Sci., **115**:315, 1964.
21. Krevans, J. R. and Jackson, D. P.: Hemorrhagic Disorder Following Massive Whole Blood Transfusions. JAMA, **159**:171, 1955.
22. Krevans, J. R., Jackson, D. P., Conley, C. L. and Hartman, R. C.: The Nature of the Hemorrhagic Disorder Accompanying Hemolytic Transfusion Reactions in Man. Blood, 12:834, 1957.
23. Mustard, J. F.: A Study of Changes in Platelets, Antihaemophilic Globulin. Factor V and Factor VII During Blood Collection and Storage by Different Techniques. Brit. J. Haematol., 3:202, 1957.
24. Nye, S. W., Graham, J. B. and Brinkhaus, K. M.: The Partial Thromboplastin Time as a Screening Test for Detection of Latent Bleeders. Amer. J. Med. Sci., **243**:279, 1962.
25. Perkins, H. A.: Postoperative Coagulation Defects. Anesthesiology, 27:456, 1966.
26. Phillips, L. L.: Activation of Plasminogen Following Intravascular Coagulation. Fed. Proc., **24**:606, 1965.
27. Phillips, L. L. and Jenkins, E. B.: Comparison of Two Methods for Determination of Fibrinogen. In preparation.

28. Pitney, W. R.: The Assay of Antihaemophilic Globulin (AHG) in Plasma. Brit. J. Haematol., 2:250, 1956.
29. Quick, A. J.: The Physiology and Pathology of Hemostasis. Philadelphia, Lea & Febiger, 1957.
30. Scott, R. and Crosby, W. H.: Changes in Coagulation Mechanism Following Wounding and Resuscitation with Stored Blood; A Study of Battle Casualties in Korea. Blood, 9:609, 1954.
31. Selye, H.: Symposium on Thrombohemorrhagic Phenomena, Part I. Introduction. Experimental Thrombohemorrhagic Phenomena. Amer. J. Cardiol., 20:153, 1967.
32. Senhauser, D. A.: The Preservation of the Coagulation System in Stored Whole Blood. Cleveland Clin. Quart., 27:125, 1960.
33. Simmons, R. L., Heisterkamp, C. A., Collins, J. A. and Martin, A. M., Jr.: Respiratory Insufficiency in Combat Casualties. III. Arterial Hypoxemia after Wounding. In preparation.
34. Simmons, R. L., Heisterkamp, C. A., III, Moseley, R. V. and Doty, D. B.: Post-resuscitative Blood Volumes in Combat Casualties. Surg. Gynec. Obstet., in press.
35. Smith, J. J., Grace, R. A. and Hussey, C. V.: Coagulation Mechanism and Effect of Heparin in Hemorrhagic Shock. Amer. J. Physiol., 193:593, 1958.
36. Smith, R. W., Margulis, R. R., Brennan, M. J. and Mento, R. W.: The Influence of ACTH and Cortisone on Certain Factors of Blood Coagulation. Science, 112:295, 1950.
37. Stefanini, M. and Chatteujea, J. B.: Studies on Platelets: IV. A Thrombocytopenic Factor in Normal Human Blood, Plasma and Serum. Proc. Soc. Exp. Biol. Med., 79:623, 1952.
38. Strumia, M. M. and Strumia, P. V.: Alterations in Banked Blood, with Special Reference to Hemostasis. Ann. N. Y. Acad. Sci., 115:443, 1964.
39. Tagnon, H. J., Levenson, S. M., Davidson, C. S. and Taylor, F. H. C.: The Occurrence of Fibrinolysis in Shock, with Observations on the Prothrombin Time and the Plasma Fibrinogen During Hemorrhagic Shock. Amer. J. Med. Sci., 211:88, 1946.
40. Todd, J. S. and Phillips, L. L.: Fibrinolytic Hemorrhage in Surgical Patients. Surg. Gynec. Obstet., 114:333, 1962.
41. Turpini, R. and Stefanini, M.: The Nature and Mechanisms of the Hemostatic Breakdown in the Course of Experimental Hemorrhagic Shock. J. Clin. Invest., 28:53, 1959.
42. Voorhees, A. and Phillips, L. L.: Thrombocytopenia in Surgical Bleeding. Ed. by A. W. Ulin and S. S. Gollub. New York, McGraw Hill, 1966.
43. Zucker, M. B.: Unexplained Bleeding in Operations for Neoplasia. Ann. N. Y. Acad. Sci., 115:225, 1964.