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US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY 40121

REPORT NO. 902

DISSEMINATED INTRAVASCULAR COAGULATION AND RENAL FAILURE: PRODUCTION IN THE MONKEY WITH AUTOLOGOUS RED CELL STROMA

(Progress Report)

by

MAJ Norman I. Birndorf, MC (M.D.)
and
LTC Harry Lopas, MC (M.D.)

7 October 1970

UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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ACKNOWLEDGMENTS

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In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences - National Research Council.

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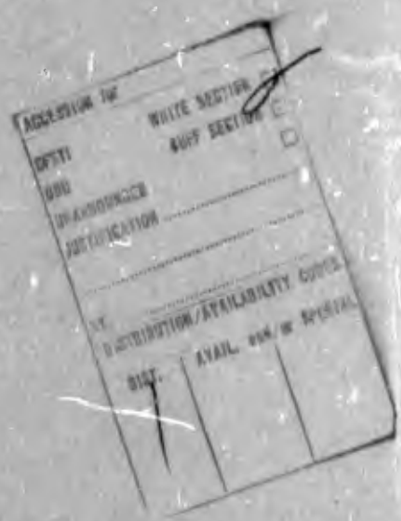

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Blood Transfusion Division
US ARMY MEDICAL RESEARCH LABORATORY
Fort Knox, Kentucky 40121

7 October 1970

Evaluation of Resuscitation and Effects of
Transfusion of Blood and Other Substances
Work Unit No. 175
Combat Surgery
Task No. 00
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ABSTRACT

DISSEMINATED INTRAVASCULAR COAGULATION AND RENAL FAILURE: PRODUCTION IN THE MONKEY WITH AUTOLOGOUS RED CELL STROMA

OBJECTIVE

To evaluate in subhuman primates the role of various constituents of the red cell in the production of a transfusion reaction and to establish a transfusion reaction model for evaluation of therapy and prophylaxis.

METHODS

Red cell sonicates and stroma from red cell ghosts were infused into *Macaca irus* (cynomolgus) monkeys. Blood coagulation and renal function were measured before and after infusion and in a group of control animals infused with 0.85% saline alone.

RESULTS AND CONCLUSIONS

Glomerular filtration was significantly reduced in experimental animals infused with sonicated cells or stroma and evidence of disseminated intravascular coagulation was documented by falls in platelet count, fibrinogen, Factors V and VIII. This work implicates the stromal fraction of the red cell as the cause of intravascular coagulation and renal failure following intravascular hemolysis and establishes an interesting primate model for the study of hemolytic transfusion reactions.

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DISSEMINATED INTRAVASCULAR COAGULATION AND RENAL FAILURE: PRODUCTION IN THE MONKEY WITH AUTOLOGOUS RED CELL STROMA

INTRODUCTION

Transfusion of incompatible blood and the resulting lysis of red cells may lead to disseminated intravascular coagulation (DIC) and renal failure (8,26). In the past, hemoglobinuria and hemoglobinemia have often been blamed for these effects (4,12,13,15). More recently, Rabiner *et al* (23) have shown that if hemoglobin solutions are carefully rendered stroma free, they will not alter blood coagulation or cause renal functional impairment in dogs. We have shown stroma free hemoglobin solution also to be free of these deleterious effects in subhuman primates (2). Infusion of sonicated whole blood which is heavily contaminated with free stroma particles, on the other hand, does initiate DIC ir dogs (24,25). The magnitude of these coagulation changes depends on dose and functional state of the reticuloendothelial system (24,25). The dogs in these reports were not studied from the standpoint of renal function.

The purpose of the present study was to investigate the effect of autologous red blood cell stroma infusions on coagulation and renal functions in subhuman primates. We have found that stroma is strongly thromboplastic and can lead to DIC, and alterations in renal function and architecture, regardless of the presence or absence of free plasma hemoglobin. These studies implicate the red cell stromal envelope as the harmful element in our experiments, as well as in clinical hemolytic states and support the view that renal functional impairment may follow intravascular clotting.

MATERIALS AND METHODS

Preparation of solutions for infusion. Autologous whole blood equal to 25% of calculated blood volume (1) was taken from each experimental animal. The plasma was removed and the red cells washed twice in five volumes of cold 0.85% NaCl. After dilution of the cells in cold saline to 7 g/100 ml hemoglobin concentration, the suspension was sonicated at 31.5 watts/cm^2 for 5 min (Biosonik III, Brownwill Scientific, Rochester, N.Y.); a volume equal to the original volume of shed blood was infused. This energy level was chosen to provide complete hemolysis with minimum heat production. A cooling jacket was not employed since temperature remained below 26°C. The hemoglobin level of 7 g/100 ml was chosen to make this experiment comparable to our previous work with stroma free hemoglobin solutions having this hemoglobin concentration. Autologous stroma from the same volume of blood was prepared by gentle lysis of washed cells in 40 to 50 volumes of 20 mOsm (ideal) phosphate buffer (11) pH 7.41. This suspension was centrifuged at 27,500 g at 4°C for 30 min. The supernatant hemoglobin was decanted and the red cell ghosts were resuspended in cold saline to the original volume and sonicated as

above. Care was taken to minimize bacterial contamination. Sonicated cells or stroma were administered within 90 min of phlebotomy. Preliminary experiments demonstrated a small and transient fall in arterial pressure only during the phlebotomy.

Experimental procedure. Healthy adult *Macaca irus* monkeys weighing between 2.06 and 4.39 kg were anesthetized with intramuscular or intravenous sodium pentobarbital (10 mg/kg); the saphenous or femoral vein was cannulated with a polyethylene catheter for sampling, phlebotomy, and infusion. The bladder was catheterized with a premature infant feeding tube (Sterilon Corp., Baintree, Mass.). Renal clearances of endogenous creatinine (C_{Cr}), inulin (C_{In}) and para-aminohippuric acid (C_{PAH}) were performed according to the method of Pickering and Sussman (22). Clearances were measured four times: clearance I (control clearance) - 60 min in duration just prior to infusion; clearance II - 30 to 60 min postinfusion; clearance III - 60 to 120 min postinfusion; clearance IV - a 30 or 60 min clearance performed 24 hr postinfusion.

Collection of samples and laboratory analysis. Blood and urine were assayed by the method of Miller and Miller (21) for creatinine,* that of Brun (7) for PAH, and that of Handelsman and Drabkin (14) for inulin.

After clearing the phlebotomy catheter, blood for coagulation tests was collected in plastic tubes containing 3.8% sodium citrate, V:V, 9:1, citrate to blood. Specifically deficient human substrate plasma was used to measure coagulation factor activity (except Factor II which was assayed using Sietz filtered, $BaSO_4$ adsorbed beef plasma) following previously published methods (3). Platelets were counted directly by phase contrast microscopy (5). Euglobulin clot lysis times, partial thromboplastin times, and prothrombin times were performed by standard methods. Methods for coagulation tests were selected, modified, and normal values in cynomolgus monkeys established in this laboratory (3). The ethanol gelation test gave technically unsatisfactory results (6).

Hemoglobin concentration in blood and urine was determined colorimetrically as cyanmethemoglobin except for levels below 0.25 g/100 ml when the method of Crosby and Furth was used (9).

Maximum sampling volume for any experiment was less than 10% of the calculated blood volume. A control group of animals was established by duplication of the experimental procedure except that 0.85% saline was given as the infusion fluid.

Statistical analysis. Student's "t" test for paired observations was used to compare preinfusion and postinfusion data in the same animals.

*The Jaffé chromogen was not excluded from serum so inulin clearances equaled or exceeded creatinine clearances.

When parallel data in two different groups were compared, the "t" test for unpaired observations was employed.

RESULTS

Plasma and urine hemoglobin. A mean total of 3.2 g of hemoglobin was given in the sonicated red cell suspensions. This raised the control mean plasma hemoglobin of 13 mg/100 ml to 2200 mg/100 ml at 5 min and 890 mg/100 ml at 4 hr after infusion. In the first 4 hr 20% of the infused dose was excreted in the urine which contained concentrations of hemoglobin ranging from 250 to 1200 mg/100 ml.

In the case of the sonicated red cell ghost suspensions, the mean total hemoglobin contamination was 48 mg. The mean plasma hemoglobin of this group rose from a control of 15 mg/100 ml to 58 mg/100 ml 15 min after infusion.

The mean recovery of red cell ghosts (estimated on Coulter Counter) was 26% ± 11 (SD) of the red cell count of the whole blood. After sonication, particles were no longer detectable with the Coulter Counter.

Effects of sonicated red cells and red cell stroma on renal function. Animals infused with saline alone showed no significant changes in glomerular filtration (GFR) from control as measured by C_{cr} and C_{in} (Fig. 1). Statistically significant reductions in GFR, and renal plasma flow (as measured by C_{PAH}) occurred when sonicated red cells were infused (Fig. 2). Renal function was most severely affected at the third clearance period (1 to 2 hr postinfusion). Tremors, convulsions, tachypnea and tachycardia occurred in several animals at this time. Two animals in this group died about 20 hr after infusion. Reductions in GFR were also noted in animals infused with sonicated ghosts (Fig. 3); and the clinical response was similar but less severe. Actual mean values for clearance, and statistical data are shown in Table 1. Postinfusion clearances of these two groups also differed significantly from the same clearance in the saline group, if they changed significantly from their preinfusion values. Mean urine output after infusion remained about the same in all three groups when compared to pre-clearance values.

Coagulation changes. Selected coagulation tests before and after autologous sonicated red cell infusion were performed serially in two animals in a separate experiment. Tests were used which, in our opinion and that of others (18), most accurately reflect DIC: Factor V and Factor VIII activity, platelet count, and fibrinogen concentration. Trends were verified with partial thromboplastin and prothrombin times. Figures 4 and 5 illustrate marked falls in coagulation factors by 1 hr after infusion. Factor V fell faster, but began recovery immediately. Factor VIII fell to very low levels between 1 and 4 hr. Platelet count and fibrinogen fell less markedly.

Two other monkeys were infused with sonicated blood and a more complete but single analysis was done before, and 1 hr after infusion (Table 2). Intrinsic and extrinsic factor concentrations fell as expected; partial thromboplastin time and prothrombin times lengthened, and hyperfibrinolysis as measured by euglobulin clot lysis time appeared in one animal.

The coagulation factor changes in the two main experimental groups are shown in Table 3. The two animals having serial tests and the two having extensive analysis after sonicated red cell infusion are considered in that group for purposes of analysis. DIC, as indicated by significant depression of platelet count, fibrinogen concentration, and Factors V and VIII activity occurred with infusions of either sonicated blood or stroma. Some fall was noted in saline control animals, but was in no case significant by paired "t" test score. When postinfusion values of this group were compared to postinfusion values of the other two groups, there were statistically significant differences in all cases.

Pathologic changes. An autopsy was performed on one animal in the sonicated red cell group which died before completion of the experiment. Grossly, the lungs showed scattered hemorrhagic areas surrounding bronchi and blood vessels (Fig. 6) with occasional small but grossly visible intravascular thrombi. Microscopic sections showed hemorrhagic pneumonia and infarction with fibrin aggregates in blood vessels (Fig. 7.) Petechial hemorrhages were noted on the surface of the kidney and cortical swelling was seen on cut section (Figs. 8 and 9). Microscopic examination of kidney sections showed red cells and fibrinous exudate in Bowman's capsule and renal tubules and postmortem autolysis (Fig. 10). Phosphotungstic acid hematoxylin stains did not demonstrate glomerular fibrin.

Analysis of tissues from other animals completing the experimental protocol did not show changes as striking as those above. Abnormalities at autopsy were seldom noted and microscopy of cut sections failed to show fibrin deposition in glomerular tufts.

DISCUSSION

Incompatible transfused blood has produced renal failure and a bleeding diathesis associated with "defibrination" (consumption of blood coagulation factors resulting from DIC) (8,17,26). Some investigators, using rats, dogs, or humans as experimental subjects (4,12,13,15), have implicated the hemoglobin released from lysed cells as the cause of this syndrome. Others, as early as 1886, have felt the red cell stroma to be the cause (10,24,25,28,29).

If the hypothesis that the released hemoglobin itself was harmful is correct, purified hemoglobin, free of stroma and methemoglobin, could be expected to alter renal function and blood coagulation. The conclusions reached by some investigators that hemoglobin is dangerous were

based on the use of solutions which were not rendered stroma free. In most instances, blood was lysed with distilled water before injection, with the stroma remaining in suspension. Filtration through a filter with very small pores (0.2 μ) is necessary to remove stroma even if precautions are taken to prevent formation of small particles during lysis (23).

The data in this report clearly support the evidence that the stromal envelope of the lysed red cell is dangerous when infused, and that the transfusion need consist only of disrupted autologous cells or hemoglobin free stroma. Although all animals developed DIC, most became ill after infusion, and some died, histopathologic changes were usually unimpressive and fibrin thrombi could not be seen by light microscopy. McKay (19) has shown that DIC can occur in monkeys with considerable deposition of fibrin in the renal vasculature, visible only by electron microscopy, and that, even then, early local fibrinolysis may make detection difficult.

The current evidence that glomerular disease can be secondary to intracapillary fibrin deposition (based on demonstration of platelet thrombi and fibrin in glomerular tufts) (16,27) is also supported by this report despite our failure to demonstrate fibrin. DIC, as defined by commonly accepted laboratory criteria (18,20), was accompanied by rapid and significant decrease in glomerular filtration following infusion of hemolyzed red cells or stroma.

Further investigation may implicate other structures or contents of the red cell as important in this morbid process, but at present it is reasonable to assume stromal lipid and not hemoglobin to be the cause. This model of DIC in monkeys may be helpful in the study of other disease processes altering coagulation.

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Figs. 1, 2, and 3. Clearance I is considered as 100% clearance value for all animals and subsequent clearances are expressed as mean percentage change from control. Saline (control experiment), sonicated autologous whole blood, and red blood cell stroma were infused after the control clearance (arrow). (See text.)

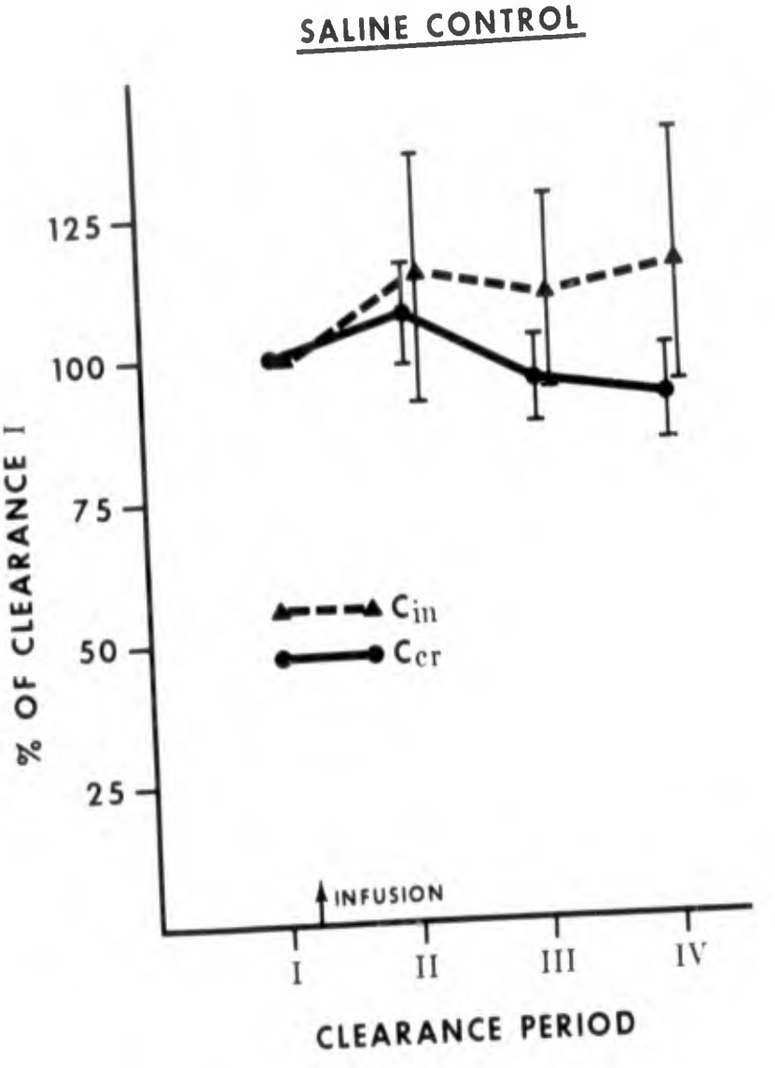

Fig. 1

SONICATED AUTOLOGOUS RED CELL INFUSION

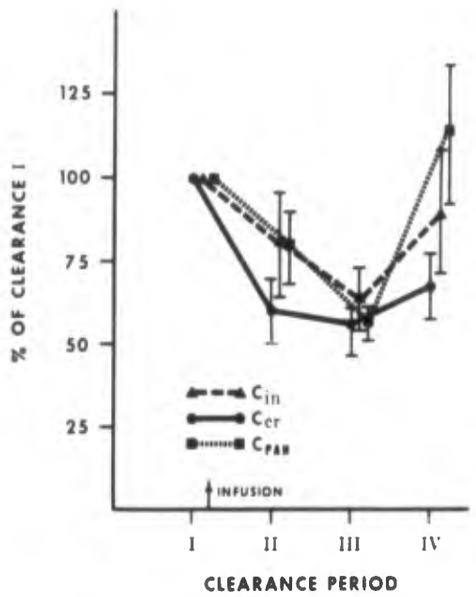

Fig. 2

SONICATED RED CELL STROMA INFUSION

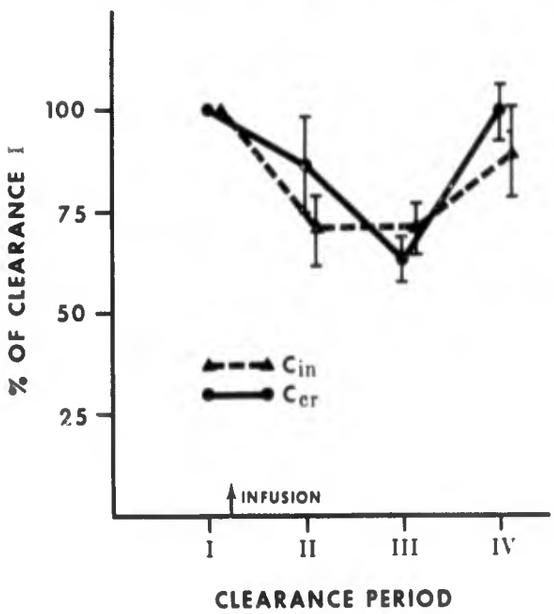

Fig. 3

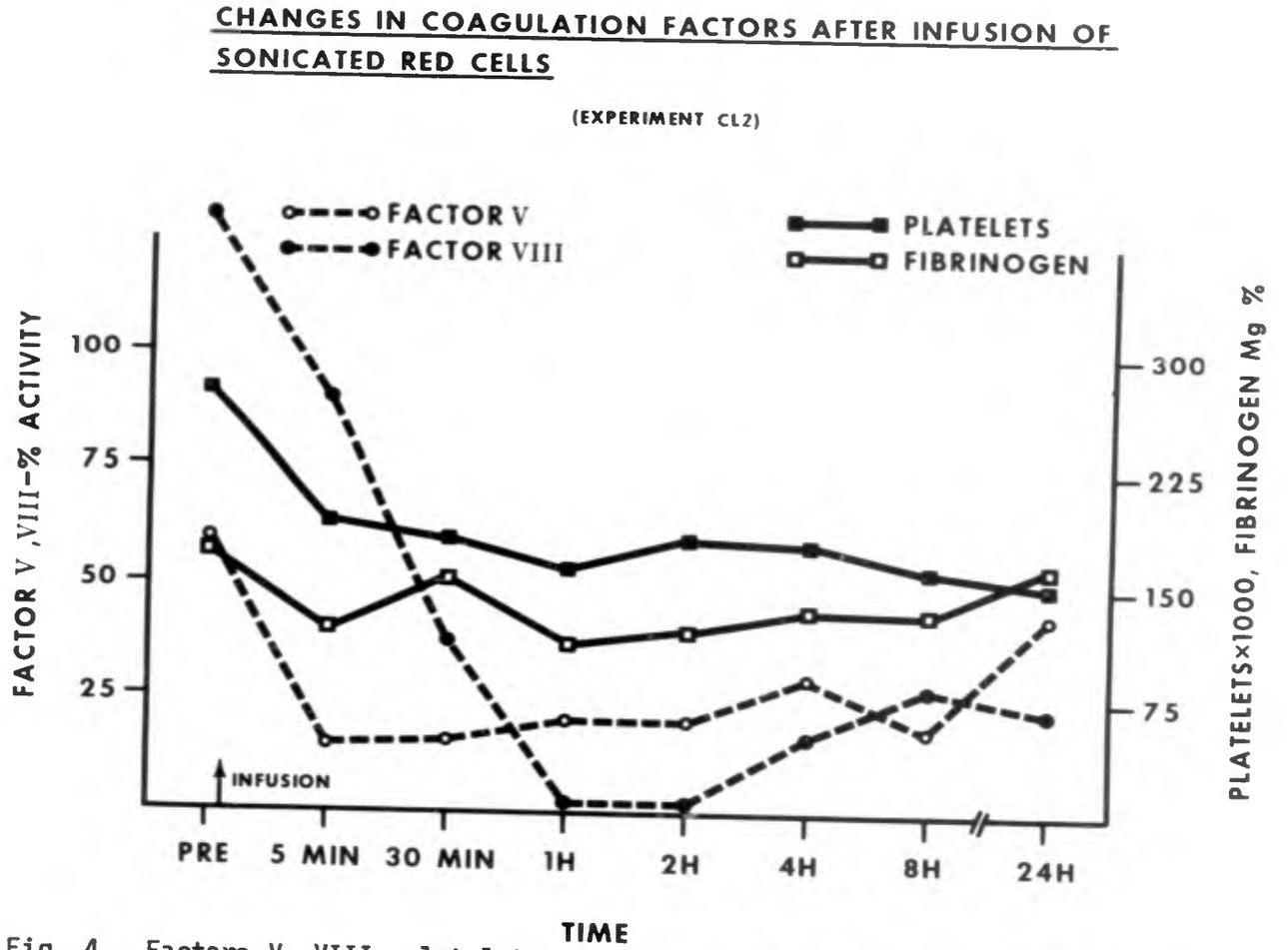

Fig. 4. Factors V, VIII, platelets, and fibrinogen were assayed at measured intervals (ordinate) following infusion of sonicated blood (arrow). Note marked fall in all factors except fibrinogen which fell slightly. Complete recovery had not occurred at 24 hr after infusion. Convulsions occurred at 8 hr.

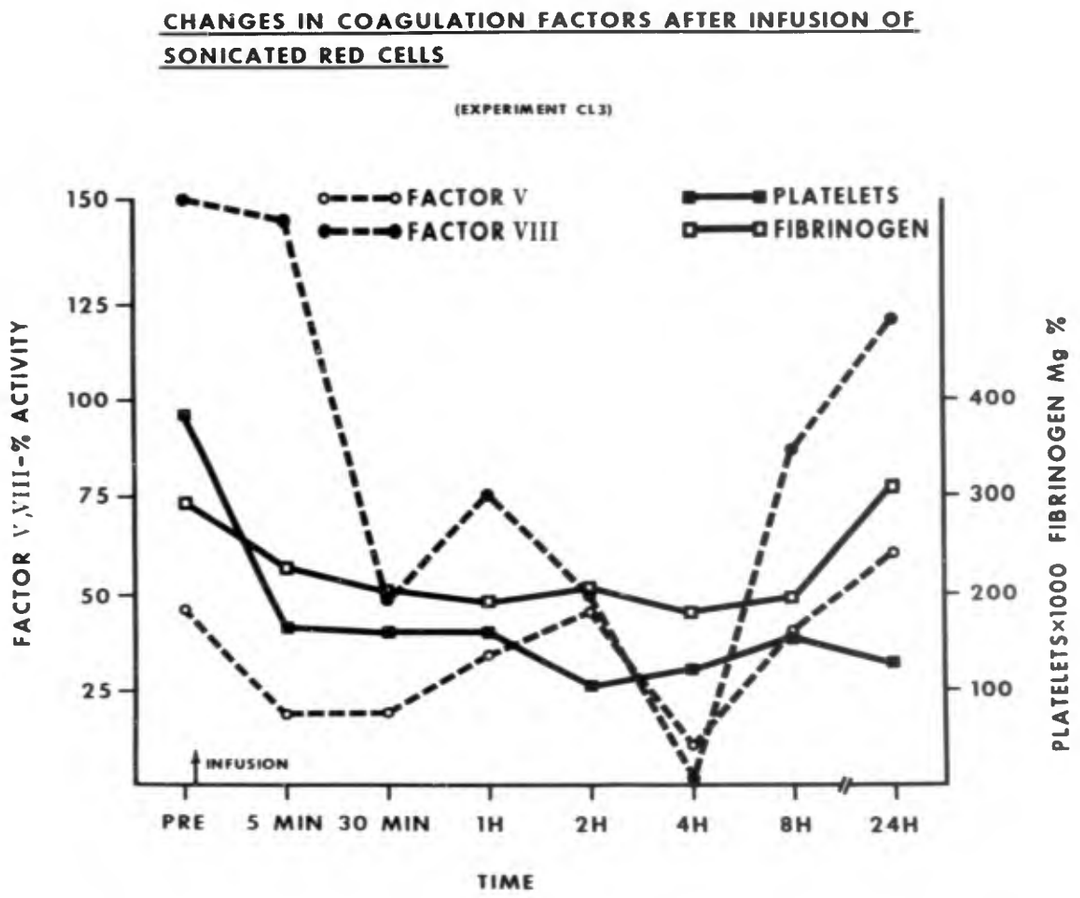

Fig. 5. A sharp fall in Factors V and VIII was noted at 4 hr, but almost complete recovery (except platelets) by 24 hr.

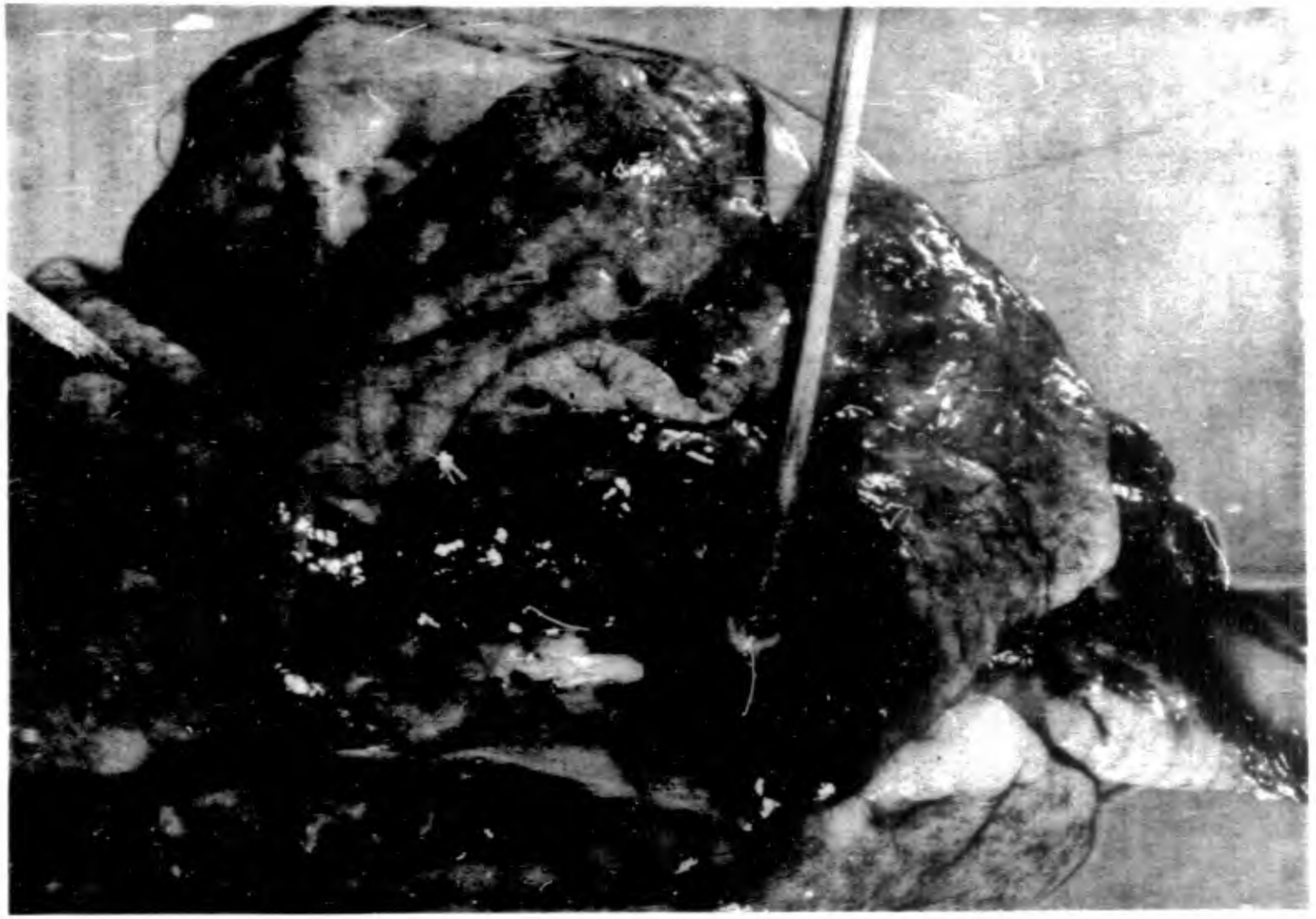

Fig. 6. Lung, surface, and section through bronchus and blood vessel.

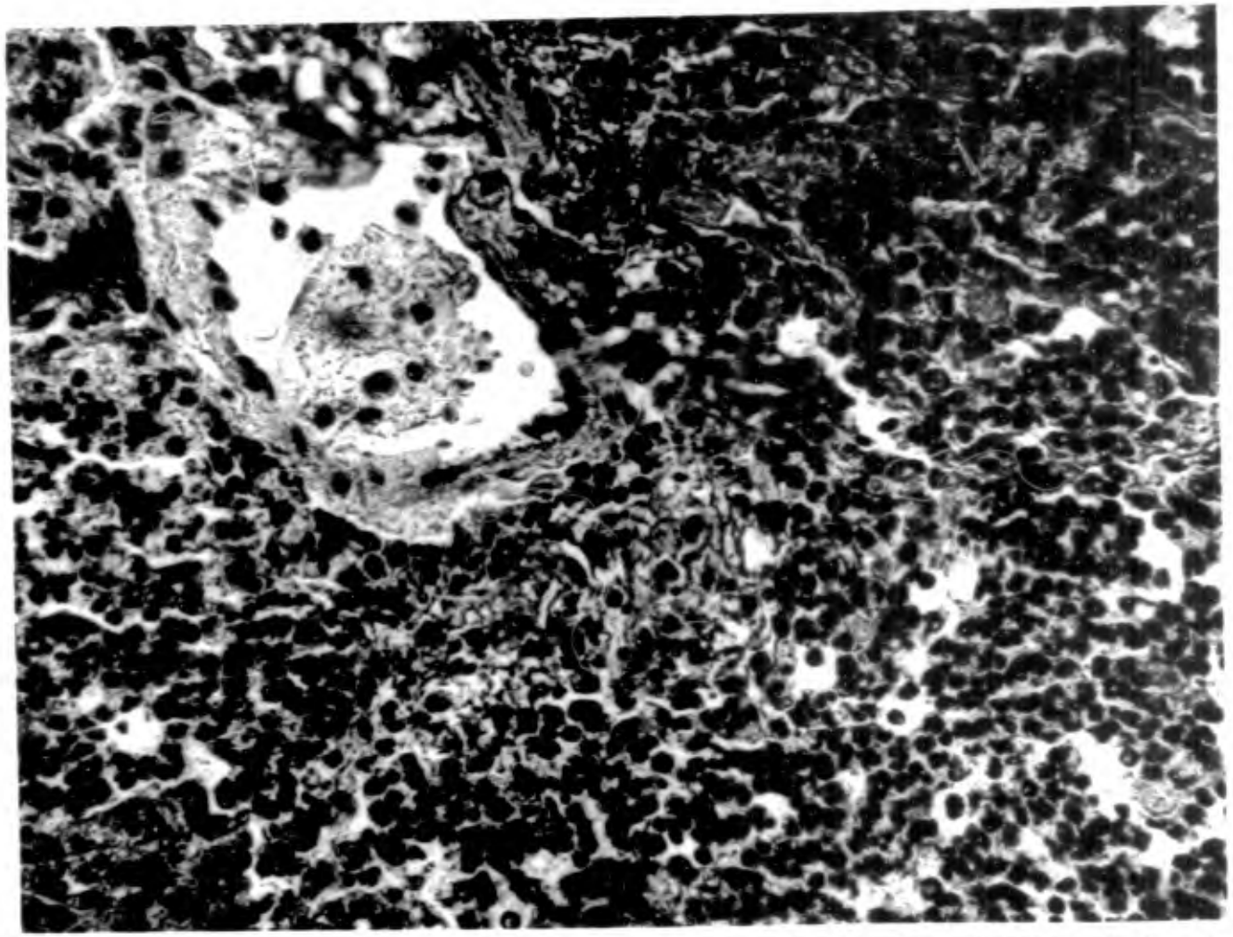

Fig. 7. Lung, x600. Marked hemorrhage and polymorphonuclear infiltration surround an arteriole containing an antimortem thrombus. This area taken from the section in Figure 6.

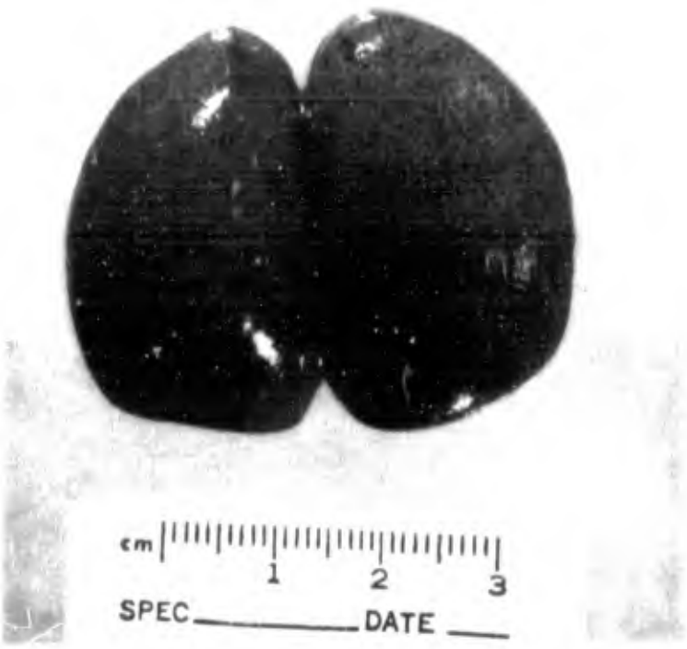

Fig. 8. Kidney surface. Note petechial hemorrhages.

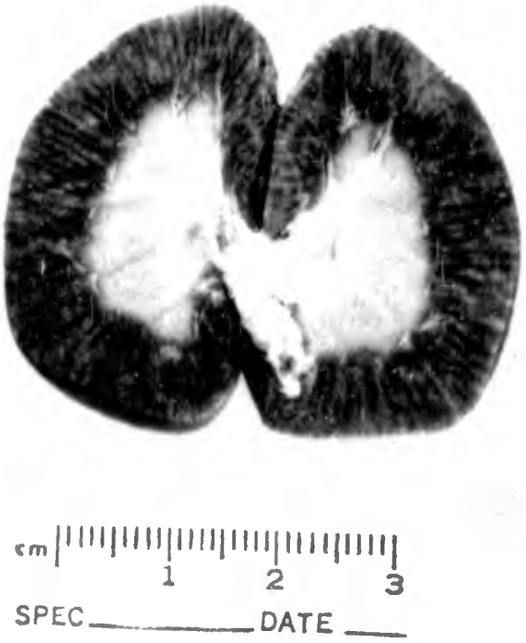

Fig. 9. Kidney, bisected. Cortical swelling is evident.

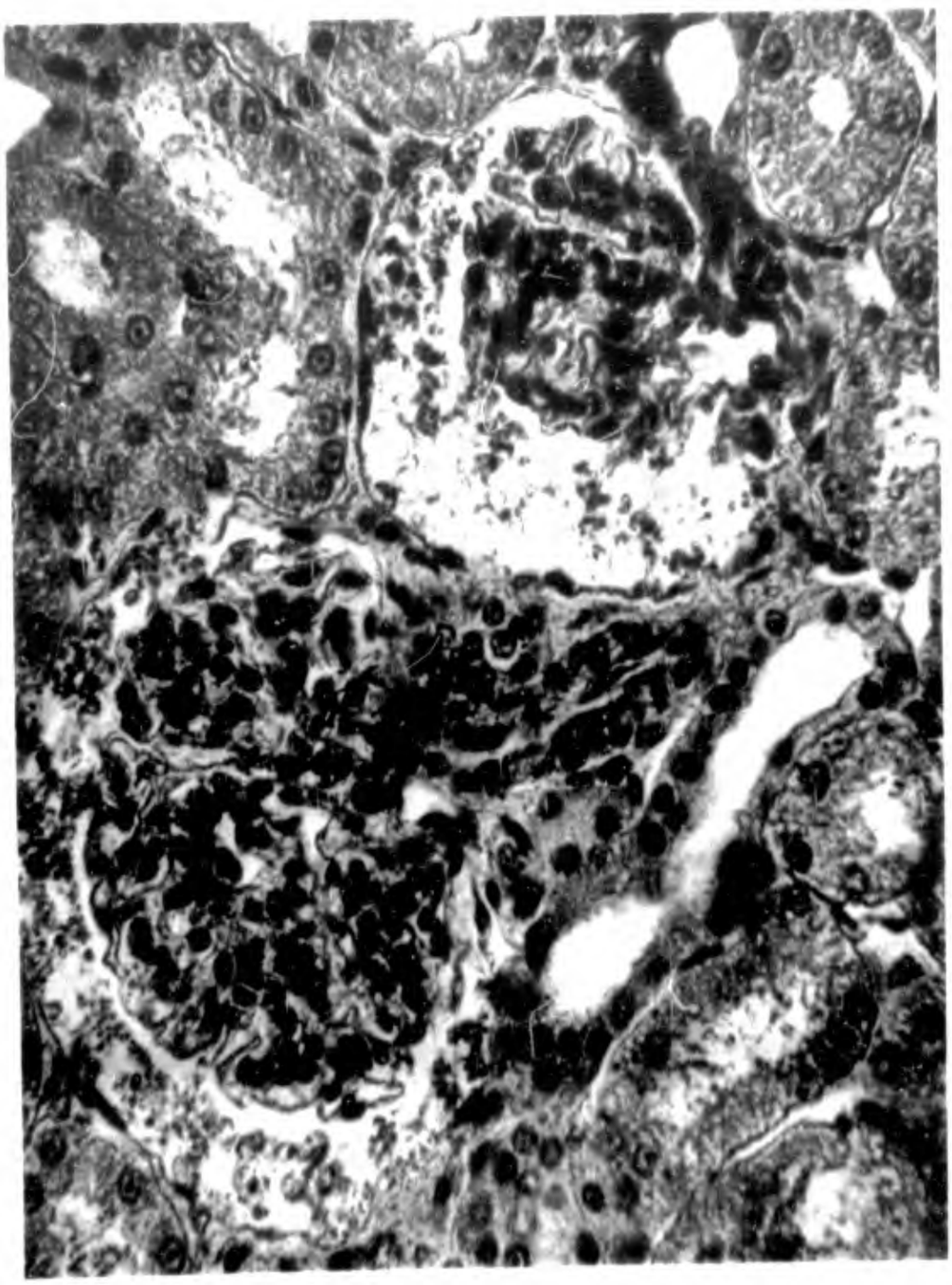

Fig. 10. Kidney, cortical section x600.

TABLE 1

The Effect of Sonicated Red Cells or Red Cell Stroma Infusions on Renal Function

	C_{cr} (ml/kg/min)				C_{in} (ml/kg/min)				C_{PAH} (ml/kg/min)			
Clearance Period	I	II	III	IV	I	II	III	IV	I	II	III	IV
					Saline Infusion Control (8 animals)							
$\bar{X}$	3.56	3.75	3.34	3.10	3.39	3.58	3.44	3.26				
SE	0.20	0.23	0.21	0.13	0.39	0.33	0.44	0.24				
t	-	0.65	0.98	1.45	-	0.41	0.10	0.39				
P	-	NS	NS	NS	-	NS	NS	NS				
					Sonicated Red Cell Infusion (7 animals)							
$\bar{X}$	3.72	2.19	2.08	2.54	4.59	2.82	2.72	3.69	22.9	18.39	13.31	27.29
SE	0.25	0.39	0.29	0.50	1.16	0.35	0.52	0.73	4.20	3.52	2.56	9.75
t	-	3.40	4.03	1.9	-	1.86	2.84	1.42	-	1.67	4.50	0.54
P	-	<.02	<.01	NS	-	NS	<.05	NS	-	NS	<.01	NS
					Sonicated Red Cell Stroma Infusion (9 animals)							
$\bar{X}$	3.06	2.64	2.12	3.01	4.33	2.98	2.26	3.45				
SE	0.27	0.58	0.27	0.39	0.44	0.51	0.32	0.21				
t	-	2.99	4.10	0.20	-	4.43	5.60	3.68				
P	-	<.02	<.01	NS	-	<.01	<.001	<.02				

Actual mean clearance values and standard errors for each experimental group. "t" test and P values are given for each clearance period compared to clearance I, which was performed prior to infusion.

NS = Not Significant.

TABLE 2

Changes in Coagulation Tests and Factors in
Two Animals 1 Hr After Infusion of Sonicated Red Cells

Animal	SC1		SC2	
Test	Pre	Post	Pre	Post
Platelets (x 100)	444	354	549	354
Partial thromboplastin time (sec)	35	45	-	-
Prothrombin time (sec)	10.8	13.8	11.3	12.8
Factor II (%)*	120	80	90	56
Factor V (%)	104	50	60	25
Factor VIII (%)	130	10	170	60
Factor IX (%)	60	12	42	11
Factor X (%)	66	45	70	40
Factor XI (%)	130	100	130	84
Fibrinogen (mg/100 ml)	295	160	311	265
Euglobulin clot lysis time (min)	>90	>90	>90	12

*Coagulation factor values are expressed as percent of standard human reference plasma (Hyland Corp., Costa Mesa, Calif.) to which they are compared.

TABLE 3

Coagulation Changes After Infusion of Sonicated Red Cells or Red Cell Ghosts

	Platelets (x 1000)		Factor V (% activity)		Factor VIII (% activity)		Fibrinogen (mg/100 ml)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
			Saline Infusion Control (8 animals)					
$\bar{X}$	422	368	76	53.4	83	77	357	291
SD	97.4	114	13.4	11.1	18.2	58.5	92.8	56.8
t (p)	1.69 (NS)		1.83 (NS)		0.58 (NS)		2.06 (NS)	
			Sonicated Red Cell Infusion (12 animals)					
$\bar{X}$	389	281	89	24.6	118.1	31.04	249*	184
SD	71.4	56.1	30.9	13.2	37.8	24.8	60.8	47.8
t (p)	3.80 (<.01)		5.77 (<.001)		7.48 (<.001)		3.04 (<.05)	
			Sonicated Red Cell Ghost Infusion (7 animals)					
$\bar{X}$	351	263	81.8	36.2	84.7	29.2	308	233
SD	61	64	23.1	10.7	28.9	15.9	94.5	47.1
t (p)	6.02 (<.001)		4.97 (<.01)		6.16 (<.001)		2.91 (<.05)	

Highly significant falls in mean coagulation test values occurred in both groups infused with autologous blood (paired "t" test).

*Data available for four animals only.

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13. ABSTRACT

Transfusion of incompatible blood may result in disseminated intravascular coagulation (DIC) and renal failure. Recent studies in our laboratories have shown that red cell stroma free hemoglobin infusions are free of these effects. This report is concerned with the role of red cell stroma in the production of these abnormalities.

Sonicated autologous red cells derived from 25% of calculated blood volume were infused into cynomolgus monkeys. DIC, characterized by depression of platelet counts, fibrinogen, and Factors V and VIII occurred in every case. Autopsy of two animals that died after infusion disclosed hemorrhagic pneumonia and alterations in renal architecture.

Sonicated red cell stroma prepared from red cell ghosts obtained from the same volume of blood caused a similar but less severe reaction. Glomerular filtration, as measured by clearance of inulin, and endogenous creatinine fell transiently in both groups. Control animals infused with 0.85% saline exhibited no significant changes in these tests. This study supports the view that DIC and subsequent renal failure following intravascular hemolysis of red cells are due to the stromal fraction of the cell.

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