Limits of Non-Colloid Solution Replacement in Experimental Hemorrhagic Shock

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ALTHOUGH electrolyte solutions are of proved benefit in resuscitation following acute hemorrhage, there is controversy as to magnitude of blood loss that can safely be replaced solely with balanced salt solution without the need for whole blood transfusion.[1, 2, 7, 11, 14] This study evaluates the administration of balanced salt solution replaced on a 4:1 volumetric basis for progressive amounts of acute blood loss in splenectomized dogs.

Materials and Methods

Splenectomy was performed on 36 adult dogs at least one week prior to study. Blood volume was estimated from body weight by formula.[5] Cardiac output was calculated from oxygen consumption and from oxygen arteriovenous differences using the Fick principle.[6] Under light (25 mg./Kg. BW) Pentobarbital anesthesia, a femoral artery was cannulated after administration of 5 mg./Kg. body weight of heparin. The femoral vein on the opposite side was cannulated for withdrawal of blood samples. A cuffed endotracheal tube was inserted and attached to a respirator and a spirometer for measurement of oxygen consumption.

As indwelling cannula passed through the external jugular vein was used for measurement of central venous pressure. An arterial cannula was used for electronic recording of blood pressure. Hematocrit, pH, total protein, and concentrations of sodium, potassium, chloride and CO_2 determinations were made at 30-minute intervals. Urinary output and volume of the extracellular space (radiosulfate method)[15] was measured prior to bleeding following the administration of saline and 2 hours after saline replacement.

Acute hemorrhage was performed by unclamping the femoral arterial cannula which led into a graduated cylinder maintained at the heart level. Immediately after shedding of the preselected volume of blood, four times this volume of sterile, balanced salt solution * warmed to body temperature was returned into the femoral vein from a reservoir 150 cm. above the heart level.

A control study was performed in 10 unbled splenectomized, anesthetized dogs in which all determinations were observed for 4 hours. A second control study was performed in 4 unbled splenectomized dogs in which the 4:1 equivalent of a 66% hemorrhage was administered intravenously. This amounted to infusion of 20% of the body weight of a balanced salt solution to a normal anesthetized dog.

In pilot studies it was confirmed that the majority of animals would die if 50% of blood volume was removed acutely. There-

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* Na 148 mEq./L.; K 4 mEq./L.; Ca 3 mEq./L.; Lactate 28 mEq./L.; HCO_3 18 mEq./L.; pH 7.4; osmolality 300.

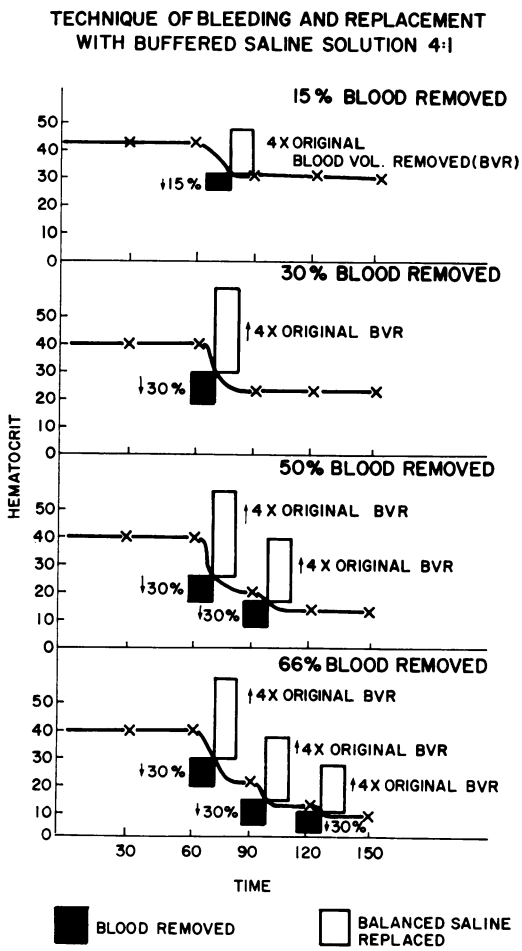

FIG. 1. The pattern of bleeding and replacement. Removal of 50% of estimated blood volume required two bleeding periods; 66% required three bleeding periods. Amount of buffered saline solution replaced was calculated to equal four times the volume of *original* blood removed.

fore, experiments requiring 50% hemorrhage were performed in two stages interrupted by necessary 4:1 volumetric electrolyte replacement. Experiments requiring loss of 66% of blood volume were performed in three sequential periods of bleeding and immediate fluid replacement. The pattern of bleeding for each volume of hemorrhage is illustrated in Figure 1. Shedding of blood into the reservoir required 2–3 minutes and return of four times this volume of electrolyte approximately 12 minutes. Thus, each cycle of bleeding and vascular refill required 14–15 minutes. Approximately 15 minutes were allowed between bleeding periods for equilibration. In the animals bled 50%, the entire procedure took 45 minutes; with 66% hemorrhage 75 minutes. Following hemorrhage and replacement, serial blood and respiratory gas studies were performed every 30 minutes for 2 to 3 hours.

The animals were then allowed to recover from anesthesia and observed for 7 days. Venous hematocrit determinations and body weights were obtained daily.

Results

Unbled Controls. Anesthesia and mechanical respiration in ten dogs seven days after splenectomy did not appreciably alter ECF volume or other measured factors.

Table 1 documents the changes that occurred when a 4:1 equivalent of 66% of the blood volume was administered to four dogs. This large water and electrolyte load produced a transient 95% increase in cardiac output; a 29% dilutional fall in hematocrit and more than doubling of the oxygen consumption, which, in contrast to the transient elevation in cardiac output, persisted throughout the two hour period of study.

15% Hemorrhage. Table 2 documents the response of two animals to minor hemorrhage and 4:1 salt solution replacement. There is the anticipated evidence of dilution as shown in the hematocrit, osmolality, and hypoproteinemia, but little other change.

30% Hemorrhage. As shown in Table 3, 1:4 volume replacement following 30% hemorrhage not only produced the expected hemodilutional changes but also increased cardiac output 12% and oxygen consumption 17%. Hematocrit at the end of such replacement of blood with salt solution was 25%.

All eight animals survived 30% bleeding and replacement.

TABLE 1. *Infusion 20% Body Weight of Balanced Salt Solution into Normal Dogs (Mean of 4 Dogs)*

Time Min.	Hct. %	Systolic BP mm. Hg.	Temp. °C.	pH	O_2C cc./Kg. min.	C.O. cc./Kg.	CO_2 Vol. %	V.P. mm. Hg.	O.S.M. milli-mol/L.	mEq. Cl^-	mEq. Na^+	mEq. K^+	Total Protein mg./ 100 ml.	Urine cc./ 30 min.	
0	36	145	38.0	7.34	6.96	—	53.47	1.0	309	111	146	3.9	7.0	—	
60	37	150	37.9	7.34	6.83	164	52.52	1.0	314	114	142	3.4	7.0	3.3	
90	38	145	37.6	7.34	6.89	113	51.34	2.2	306	110	138	3.3	6.4	3	Control
120	38	145	37.5	7.33	7.09	122	51.26	3.5	306	113	144	3.2	6.4	20.2	period
150	38	145	37.8	7.32	8.20	126	51.78	3.5	306	112	142	3.4	6.2	5.9	
180	32	150	37.0	7.32	9.48	116	40.86	8.8	306	109	136	3.4	5.2	90	
210	31	154	36.8	7.33	9.99	235	49.01	4.0	304	109	135	3.3	4.6	90	Given 200
240	29	152	36.6	7.32	10.09	194	41.33	3.5	302	108	138	3.4	5.0	90	cc. per
270	27	154	36.8	7.30	11.44	232	55.50	4.5	301	106	137	3.5	4.6	90	Kg.
310	27	150	36.9	7.32	11.49	223	51.26	3.8	294	106	135	3.4	4.8	90	
340	28	151	37.5	7.32	12.65	205	46.34	1.8	297	107	140	3.5	4.8	22	
370	29	146	38.2	7.33	12.10	170	51.36	1.0	297	107	136	3.4	4.8	22	Observa-
410	30	146	38.2	7.32	11.80	155	46.36	2.5	300	107	141	3.6	4.8	22	tion
440	30	142	38.4	7.31	11.54	118	59.54	0.2	303	108	136	3.6	—	22	period
470	29	145	39.4	7.31	14.36	—	—	2.0	—	105	—	—	—	—	

50% Hemorrhage. Data concerning the dogs in which half of the blood volume was replaced with four times its volume of salt solution are shown in Table 4.

All of the eight animals survived the immediate posthemorrhage period, but three died within 7 days. Final hematocrit following such dilution was 16%. Cardiac output transiently rose a maximum of 78%, but during most of the study was elevated only about 30%. Oxygen consumption was not significantly changed.

In the days following bleeding the mass hematocrit of these animals fell to 12% but by the fourth post-hemorrhage day began to rise.

66% Hemorrhage. All of the four animals bled 65 to 70% of their blood volume died within 12 hours.

Data on the four animals bled two-thirds of their blood volume in three stages and replaced with four times the volume with electrolyte solution is shown in Table 5.

Final mean hematocrit was 10%. Despite the massive volume of replacement intravenous fluid, central venous pressure fell to a mean of 1.5 mm. Hg. Central venous CO_2 rose a maximum of 41%. Oxygen consumption rose erratically to a maximum of 24%, but fell almost to the control level by the end of the experiment. Cardiac output more than doubled, but by the end of the experiment cardiac output was obviously insufficient. General deterioration was

TABLE 2. *Response Following Hemorrhage of 15% Blood Volume and 4:1 Volumetric Replacement with Balanced Salt Solution (Mean of 2 Dogs)*

Time Min.	Hct. %	Mean BP mm. Hg.	Temp. °C.	pH	O_2C cc./Kg. min.	C.O. cc./Kg.	CO_2 Vol. %	V.P. mm. Hg.	O.S.M. milli-mol./L.	mEq. Cl^-	mEq. Na^+	mEq. K^+	Urine cc./30 min.	
30	44	133	38.6	7.36	8.76	—	32.36	−1.0	297	113	128	3.7	2	Control period
60	43	130	38.0	7.37	8.76	102.76	22.96	−1.0	294	117	133	3.8	2	
														Bleeding and replacement
90	32	125	37.2	7.37	9.89	116	37.48	−1.0	296	110	130	3.6	42	
120	32	117	37.1	7.33	8.80	179	43.00	−0.5	290	109	131	3.4	42	
150	32	113	37.1	7.30	8.62	134	40.12	−1.0	288	109	132	3.4	17	Observation
180	30	95	36.4	7.32	7.77	84	36.86	−1.0	292	116	132	3.3	16	period
210	34	95	36.8	7.36	8.05	103	39.31	−1.0	289	117	134	3.4	4	
225	34	100	37.0	7.35	8.19	74	37.50	−1.0	296	108	132	3.4	4	

TABLE 3. *Response Following Hemorrhage of 30% Blood Volume and 4:1 Volumetric Replacement with Balanced Salt Solution (Mean of 8 Dogs)*

Time Min.	Hct. %	Systolic BP mm. Hg.	Temp. °C.	pH	O_2C cc./Kg. min.	C.O. cc./Kg.	CO_2 Vol. %	V.P. mm. Hg.	O.S.M. milli-mol/L.	mEq. Cl^-	mEq. Na^+	mEq. K^+	Total Protein mg./ 100 ml.	Urine cc./ 30 min.	
0	39	133	38.2	7.326	7.49	—	49.82	3.5	306	112	138	3.9	6.0	—	Control
60	39	147	38.0	7.325	7.75	134.08	42.00	5.5	309	111	139	3.6	6.3	14.8	period
90	26	131	37.8	7.318	8.15	184.78	50.19	8.0	306	108	139	3.6	2.7	—	
120	26	128	37.7	7.296	8.80	146.15	46.43	7.5	310	110	137	3.4	3.5	95.2	Observa-
150	27	122	37.6	7.274	9.08	139.86	51.76	6.2	304	112	137	3.2	3.8	—	tion
180	26	118	37.4	7.263	8.32	124.98	52.18	5.1	301	116	135	3.2	3.7	45	period
210	26	115	37.3	7.266	7.71	145.29	46.86	3.0	300	111	132	3.2	3.8	—	
240	24	111	37.5	7.275	8.64	151.00	53.18	3.5	299	110	132	3.2	4.1	18.3	

reflected in acidosis (mean pH 7.17) and systolic hypotension of 60 mm. Hg.

Discussion

The proper role of balanced salt solution as a resuscitative fluid following acute blood loss is a topic of current debate. Some maintain that electrolyte solutions by reason of quick leakage from the intravascular space are only suitable as emergency measures until intravascular fluid volume can be volumetrically replaced with whole blood.[2, 3, 5, 8] Shires [10-12] and Dillon *et al.*[1, 2] believe that given in sufficient volume, such electrolyte solutions are of definitive value because they restore depleted interstitial fluid and sodium mass. Much of the argument revolves around the degree of interstitial fluid depletion that accompanies hemorrhage. Shires maintains that there is an inappropriate decrease of E.C.F., a depletion far beyond that which can be accounted for by the volume of shed blood.[10, 12] Moore [9] maintains that the apparent depletion of E.C.F. following bleeding is small and attributable mainly to insensible fluid losses during and after the shock period. He reports only small changes of E.C.F. following bleeding when the space is measured with radiobromine.

Regardless of the mechanism, or details of fluid shift, electrolyte solutions are of clinical value in the resuscitation of patients following massive hemorrhage.[7, 12, 14] Pragmatically, the argument is reduced to defining the maximum blood loss that can safely be replaced by non-erythrocyte-containing balanced salt solution. Moderate hemodilution is well tolerated and even beneficial so long as the intravascular and

TABLE 4. *Response Following Hemorrhage of 50% Blood Volume and 4:1 Volumetric Replacement with Balanced Salt Solution (Mean of 8 dogs)*

Time Min.	Hct. %	Systolic BP mm. Hg.	Temp. °C.	pH	O_2C cc./Kg. min.	C.O. cc./Kg.	CO_2 Vol. %	V.P. mm. Hg.	O.S.M. milli-mol./L.	mEq. Cl^-	mEq. Na^+	mEq. K^+	Total Protein mg./ 100 ml.	Urine cc./ 30 min.	
0	40	140	37.8	7.389	7.74	—	43.08	3.8	315	111	137	3.3	6.7	8	Control
60	41	150	37.6	7.353	7.37	128.32	48.73	3.1	313	115	137	3.4	6.5	8.4	period
90	21	142	37.6	7.333	7.43	225.30	53.99	7.1	301	115	136	3.3	2.4	12.6	Bleeding and re-placement
120	16		37.6	7.288	7.99	186.02	50.41	7.8	303	113	138	3.2	2.2	126.3	
150	16		37.6	7.274	7.51	159.27	52.14	3.5	307	114	137	3.2	2.4	66	Observa-
180	16		37.6	7.263	7.18	182.31	52.97	2.8	306	113	137	3.1	2.6	65.9	tion
210	16		37.5	7.281	6.94	151.84	51.72	5.4	302	114	136	3.0	2.8	34	period
240	16		37.5	7.259	7.30	171.33	52.30	5.1	304	115	136	3.1	2.8	34.6	

TABLE 5. *Response Following Hemorrhage of 66% Blood Volume and 4:1 Volumetric Replacement with Balanced Salt Solution (Mean of 4 Dogs)*

Time Min.	Hct. %	Systolic BP mm. Hg.	Temp. °C.	pH	O_2C cc./Kg. min.	C.O. cc./Kg.	CO_2 Vol. %	V.P. mm. Hg.	O.S.M. milli-mol L.	mEq. Cl^-	mEq. Na^+	mEq. K^+	Total Protein mg./100 ml.	Urine cc./30 min.	
0	39	138	38.5	7.360	7.12	—	42.50	3.0	324	—	141	3.5	6.9	5	Control
60	41	145	38.6	7.330	7.46	122.13	42.05	3.0	325	—	142	3.4	6.6	5	period
90	21	138	38.3	7.278	7.77	126.99	48.96	4.5	314	—	146	3.3	2.9	22	Bleeding
120	14	124	38.6	7.210	8.98	138.32	53.04	5.0	322	—	144	3.3	2.0	22	and replacement
150	10	078	38.8	7.210	9.16	273.63	59.00	6.8	318	—	143	3.2	1.7	22	
180	10	073	39.0	7.213	8.07	255.72	56.90	5.0	312	—	141	3.2	1.9	20	Observation
210	8	073	39.1	7.203	7.24	213.15	46.59	3.7	316	—	141	3.5	1.9	20	period
240	10	063	39.5	7.195	8.19	174.60	57.25	3.7	314	—	142	3.5	2.0	20	
270	10	060	38.7	7.170	7.77	69.48	—	1.5	306	—	141	3.3	1.8	—	

extracellular volume is maintained. A point is ultimately reached, however, when the oxygen carrying capacity of the blood is insufficient to maintain the tissues. At this point erythrocytes must be added for resuscitation. The current experiments are designed to delineate this critical point, which heretofore has not been accurately defined.

Shires empirically recommends that patients in hemorrhagic shock or at operation be given 5% of their body weight of balanced saline solution before or with blood transfusions. Trudnowski[14] suggests that a loss of 700 cc. of blood by a healthy adult can safely be replaced with a 3:1 ratio of buffered saline.[11] Mefzerot[7] estimates that a loss of 20% of blood volume can satisfactorily be replaced with saline. Takaori and Safar achieved 24-hour survival in 10 dogs when they were bled to a hematocrit of 10% and replaced with equal volumes of Dextran and saline.[13] According to our data, this would equal removal of more than two-thirds of the blood volume.

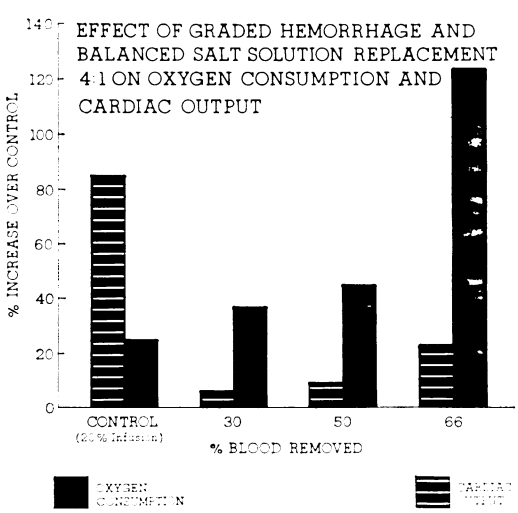

FIG. 2. Changes in oxygen consumption and cardiac output in treated animals immediately following completion of fluid replacement.

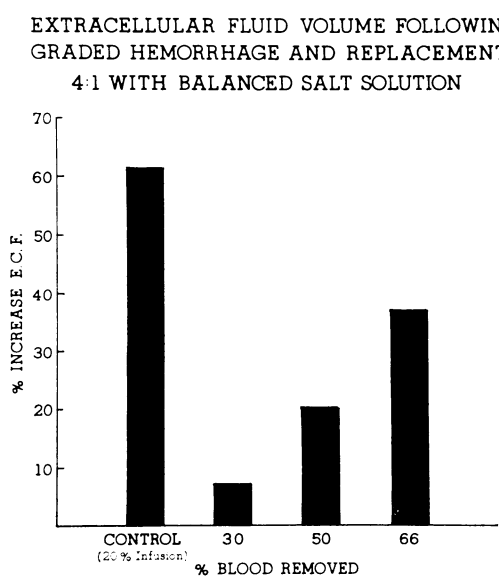

FIG. 3. Change in extracellular fluid volume (radiosulfate method) in treated animals immediately following hemorrhage and fluid replacement.

The current studies demonstrate that loss of 50% of blood volume can safely be replaced for an acute period with four times the volume of balanced salt solution with immediate but not universal long-term survival. Hemorrhage in excess of this amount apparently imposes an intolerable acute metabolic burden. Bleeding 65% of the blood volume with 4:1 balanced salt solution replacement uniformly killed the splenectomized dogs.

The critical value of blood loss that can safely be replaced with salt solution according to this experimental model is between 50% and 65% of blood volume.

The numerous measurements performed on these animals are in keeping with the known reactions to hemorrhage and to hemodilution. Hematocrits of 16% were well tolerated in animals bled 50% of blood volumes, but the 8 to 10% hematocrits resulting from acute hemorrhage and replacement in the animals bled two-thirds of blood volume were not tolerated. Hypotension, metabolic acidosis, rise in central venous carbon dioxide content and oliguria appeared in the animals bled most severely. Despite the enormous water load of four times the volume of shed blood, the central venous pressure was not elevated even in the animals that had lost two-thirds of their blood volume and were replaced with almost three times their total blood volume.

Cardiac output rose as expected following hemorrhage and hemodilution as the heart compensated for the decreased oxygen capacity of the dilute blood. In the animals bled most severely, cardiac output more than doubled. The appreciable rise in oxygen consumption (maximum of 23%) in the animals bled 66% of blood volume presumably reflected the simultaneous increase in cardiac output.

Summary

1. Response of splenectomized dogs to graded volumes of acute blood loss with a 4:1 volumetric replacement with balanced salt solution was performed in order to determine the maximum hemorrhage that can be tolerated using only this means for resuscitation.

2. Fifty per cent but not 66% of the blood volume can thus be shed without mortality in the immediate hemorrhage period under such a resuscitative regimen.

3. The physiological stress of hematocrits of 16% following major hemorrhage and replacement dilution are well compensated. This hemodilution is accompanied by an increase in cardiac output and oxygen consumption.

4. On the basis of these experimental studies, it would seem safe to use only balanced salt solution on a 4:1 volumetric replacement basis following blood loss of one half the blood volume in normal subjects.

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Discussion

Dr. Jonathan E. Rhoades (Philadelphia): Dr. Mahorner, members and guests. I have enjoyed this fine paper by Dr. Rush and Dr. Eiseman very much, and I believe its emphasis is important.

Dr William Parkins has studied the use of saline in hemorrhage in dogs, and has said that it was very effective on two conditions; first, that it be given promptly, second, that the amount given be two to three times the volume of blood lost. Dr. Eiseman and Dr. Rush have extended this to four times.

More recently Dr. Arthur Baue, Eugene Tragus, and Dr. Sidney Wolfson have joined our shock group and extended these studies with the following results:

(Slide.) First it was shown (to my surprise) that saline, buffered with sodium bicarbonate, corrects the acidosis of shock, as sodium chloride alone does not, and that there were equivalent beneficial effects on cardiac output. This is a slide of Dr. Baue. The bleeding rate was 5 cc./Kg./min., and it carries the pressure down to 30, maintaining it at that level with a reservoir.

Group 1 received lactated Ringer's alone; Group 3, whole blood replacement; the shed blood was put back; and Group 2 had the lactated Ringer's first and then the blood, half of the blood added.

Group 1, you see, had a lower blood pressure, probably reflecting the lower viscosity and therefore the net decrease in peripheral resistance.

(Slide.) Here is the cardiac output. With the infusion, at the end of the hour, Group 1 overshot and went to a higher-than-normal cardiac output, reflecting (as Dr. Eiseman's data showed) increased pumping around of the blood which then had a lowered oxygen-carrying capacity.

But you see that this fell in the succeeding 3 hours in all groups but most in the group restored with the lactated Ringer's.

(Slide.) Here we have the oxygen consumption. At the end of the 4-hour period oxygen consumption was best with the whole blood replacement, but was well maintained with the other two.

So I think that this is consistent entirely with the clinical impression that patients monitored in this way are less resilient and in general not as good risks, for further surgery. This reinforces the strong conclusion reached during World War II (when plasma was used for resuscitation) that whole blood should be given and the oxygen-carrying capacity restored before further surgery is undertaken.

I would like to express my appreciation to Dr. Eiseman and Dr. Rush for a splendid contribution to our knowledge. Thank you.

Dr. Jesse E. Thompson (Dallas): Dr. Mahorner, Dr. Yeager, members and guests. I have enjoyed Dr. Eiseman's and Dr. Rush's paper very much, and I would like to comment on a clinical application of these principles to civilian surgery.

There is a considerable reduction in functional extracellular fluid volume resulting from major trauma, and the same reduction occurs during a major operative procedure, the magnitude of the reduction being directly related to the degree of surgical trauma.

We have applied these ideas to the management of patients undergoing aortic reconstructive surgery and have worked out a fluid therapy regimen which has largely eliminated the hypotensive and renal complications of this type of surgery. May I have the first slide, please.

(Slide.) The essence of the program is the administration of at least three to four liters of dextrose in lactated Ringer's solution during the course of operation, and an additional liter or so in the first 24 hours postoperatively to replace the sequestered ECF. No other adjuncts, such as mannitol, plasma or vasopressors, have been necessary to maintain satisfactory blood pressure levels and adequate urinary outputs. The next slide, please.

(Slide.) This slide shows the urinary output data. During operation this averaged 106 cc./hr. and postoperatively averaged over 80 cc./hr.

The average blood pressure drop at the time of aortic declamping was 12 mm. of mercury.

In over 400 cases of aorto-iliac occlusive disease our operative mortality has been 2.2%, and in the last 5 years, when we have used this regimen extensively, it has been less than 1%. No patient has died of renal complications. No patient has had an acute tubular necrosis since 1956.

We believe that the regimen as outlined has been a major factor in reducing the hypotensive and renal complications and thus lowering the mortality of major aortic surgery.

Again, I enjoyed Dr. Eiseman's presentation very much. Thank you.