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The Hemostatic Defect of Uremia

I. Clinical Investigation of Three Patients with Acute Post-traumatic Renal Insufficiency

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IT HAS BEEN KNOWN for many years that uremia is often associated with a bleeding tendency. According to Riesman,[24] Morgagni, early in the eighteenth century, described a woman in whom "though she already had the odor of urine in her breath, vomiting of blood and bleeding from the nose proved beneficial." A number of cases of bleeding tendency in chronic uremia[21, 16, 4] and more recently in acute uremia[19, 29, 5] have been reported. However, the importance of bleeding in uremia has often been overlooked. In one recent comprehensive review of the management of uremia,[28] bleeding is not even mentioned as a possible complication. In a few cases there were significant thrombocytopenias, probably secondary to the toxemia,[21, 18, 7] but this is an unusual finding in uremia with hemorrhage. None of the coagulation tests have shown consistent abnormalities. There have been reports of abnormalities of clotting time in glass,[8] bleeding time[16] and capillary fragility.[16, 19] However most investigators have reported these tests to be normal. Others have attributed the bleeding tendency to capillary fragility,[24, 16, 8] but their evidence is not good. Uremic enterocolitis is a frequent cause of gastrointestinal hemorrhage in uremia, but this cannot explain the purpura, epistaxis or other clinical manifestations of a hemorrhagic tendency. Furthermore, the enterocolitis itself may be a manifestation of a hemorrhagic tendency.

With improvements in the management of fluid and electrolyte balance, patients with acute uremia now survive long enough to develop a bleeding tendency. For example, Teschan et al.[29] found a bleeding tendency in 15 of 55 cases of acute post-traumatic renal insufficiency. In post-traumatic uremia a bleeding tendency is the more significant because these patients have injuries which are potential bleeding sites and because they may require surgery.

The purpose of the present investigation was to obtain information on the pathogenesis of bleeding in acute uremia. Three consecutive patients with acute renal insufficiency were studied from this point of view.

METHODS

In the tests requiring thromboplastin, an acetone extract of human brain was used. It was prepared in a manner similar to Quick's technic for the preparation of rabbit-brain thromboplastin.[22] Coagulation time of whole blood in glass tubes was determined by a

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modified Lee and White technic;[23] the normal range was 5 to 10 minutes. The coagulation time in silicone-coated tubes was done by the method of Jaques et al.;[11] the normal range was 25 to 40 minutes. Prothrombin activity of plasma was measured by the one-stage method of Quick.[22] Prothrombin time was converted to percentage of normal prothrombin activity by comparison with the prothrombin times of normal plasma mixed in measured proportions with calcium-phosphate-adsorbed normal plasma. Platelet counts were done by the method of Brecher, Schneiderman and Cronkite;[3] the normal range was 200,000 to 300,000 per cu.mm. Bleeding time was determined by the method of Duke;[6] the normal values were 3 to 5 minutes. Prothrombin consumption was determined by the one-stage technic of Stefanini and Crosby;[26] normal results were above 25 seconds. Labile factor was measured by Quick's technic[22] and was expressed as a percentage of normal. Fibrinogen was determined by Cullen and Van Slyke's tyrosine method as described by Quick.[22] Normal values varied from 250 to 400 mg. per 100 ml. of plasma. Fibrinolytic activity was determined by comparing the fibrin content of diluted, thrombin-treated plasma with the fibrin content of a similarly clotted mixture measured after 24 hours' incubation. Comparisons were made with controls run simultaneously.[1] Capillary resistance was determined by the method of Madison[17] using a blood-pressure cuff. Stable factor was measured by the method of Köller et al.[15] and was expressed as a percentage of normal. Antithrombin activity of plasma was determined by the method of Johnson and Seegers.[13] Clot retraction was determined by visual estimation of the degree of retraction one hour after clotting of whole blood in glass and was recorded as 0 to 4 plus. The thromboplastin-generation test was that of Biggs and Douglas;[20] the platelets, adsorbed plasma, serum and substrate plasma were all obtained from the patient. The heparin activity of blood was determined by a protamine-titration test described by Freeman.[9] The heparin-tolerance test was that of van Creveld and Paulssen;[30] controls were run simultaneously. The coagulation time of recalcified

TABLE 1
(Patient #1)

	November						
	4	7	9	12	16	17	24
One stage proth. time (% of normal)	54	57	39	60	—	70	—
Labile factor (% of normal)	100	100	100	—	—	100	—
Stable factor	100	100	100	100	—	75	—
Glass clotting time (min.)	—	6	6	—	7	8	—
Silicone clotting time (min.)	34	100	80	80	70	75	50
Bleeding time (min.)	12	7	11	4	—	—	—
Capillary fragility	neg.	neg.	neg.	neg.	—	—	—
Prothrombin consumption (sec.)	25	19.7	16.8	16	16.5	28	15
Platelet count (× 1000/cu. mm.)	—	205	200	106	200	—	—
Clot Retraction	4+	4+	4+	4+	—	4+	—
Fibrinogen (mg./100 ml.)	—	800	830	—	555	800	—
Fibrinolytic activity	—	normal	normal	—	—	normal	—
Antithrombin activity of plasma	—	normal	normal	normal	—	normal	normal
Clotting time of recalcified plasma	—	—	—	normal	—	—	—
Heparin-protamine-titration	—	—	—	normal	—	—	—
Heparin tolerance test	—	—	normal	—	—	—	—

	November						
	1	4	6	8	11	14	19
Blood urea nitrogen (mg./100 ml.)	290	330				350	
Dialysis			*		*	*	
Urinary output (ml. 24 hours)	<100	<100	<100	<100	<100	<100	<100
Clinical	Ecchymoses	Large hematomas; bloody stools				New Ecchymoses	Hematomas right arm; tarry stools

TABLE 2
(Patient #2)

	November		December	
	24	27	1	2
One stage prothrombin (% of normal)	—	100	—	70
Labile factor (% of normal)	—	66	—	—
Stable factor (% of normal)	—	80	—	100
Glass clotting time (min.)	7	8	—	—
Silicone clotting time (min.)	—	120	70	—
Bleeding time (min.)	—	14	—	15
Capillary fragility	—	negative	—	—
Prothrombin consumption (sec.)	39.3	22.4	15.7	20.1
	40	18.4	17.6	23.9
Platelet count (× 1000/cu.mm.)	—	155	—	363
Clot Retraction	normal	normal	normal	—
Fibrinogen (mg./100 ml.)		800		470
Fibrinolytic activity of plasma		normal		normal
Antithrombin activity of plasma		normal		normal

	November			December		
Dialysis	24	26 •	28 •	2	3 •	8 •
Blood urea nitrogen (mg./100 ml.)	176	200		360		
Urinary output (ml./24 hrs.)	100			150		
Clinical Bleeding	None	None	None	None	Hemorrhage into right pleural cavity	

plasma was measured by the technic of Quick;[22] the normal range was 120 to 150 seconds. In one case an experiment was performed in which the patient's blood was mixed with normal blood. Whole blood was drawn from the patient using the two-syringe technic and silicone-coated glassware. Simultaneously and with the same technic blood was drawn from a normal subject. With silicone-coated pipettes the two bloods were mixed in a series of tubes in the proportions shown in table 4. The tubes were incubated at 37 C. and the clotting times of the mixtures were measured. The methods used for chemical determinations of the patients' blood have been described elsewhere.[14]

CASE SUMMARIES*

Case 1 (table 1). A 40 year old man developed acute renal insufficiency following ingestion of bootleg alcohol and cigaret-lighter fluid. He was oliguric for 23 days and during this time hemodialysis was carried out three times. He developed many large superficial ecchymoses and subcutaneous hematomata, bleeding from his mouth, hematemesis and bloody stools. After the onset of diuresis, severe gastrointestinal bleeding continued. Radiologic examination revealed gastric and duodenal ulcers. A subtotal gastrectomy was performed; the excised portion of the stomach had two large acute ulcers. Bleeding vessels in the base of a duodenal ulcer were ligated. Postoperatively no further bleeding occurred and the patient recovered from his renal disease.

Case 2 (table 2). On November 20, 1954, a 20 year old man was injured in an

* The cases will be reported in detail elsewhere.[25]

automobile accident, rupturing his right kidney so that nephrectomy was necessary. Postoperatively the patient was oliguric and developed azotemia. Hemodialysis was carried out four times. Two weeks after the accident the patient developed pain in the right lower chest and on December 3 a thoracentesis demonstrated a bloody empyema. Several days later thoracentesis was repeated. Several hours afterward the patient developed severe, intractable hypotension and died. At autopsy the right chest was found filled with blood. The site of thoracentesis was marked by a hematoma 8 x 10 cm., but the intercostal vessels had not been injured. There were many small perivascular hemorrhages in the brain and myocardium.

Case 3 (table 3). On December 5, 1954, a 21 year old man sustained a crushing injury of back and chest with multiple fractures, retroperitoneal hematoma and left hemothorax. He developed acute renal insufficiency and twice required hemodialysis. On December 9 he had multiple ecchymoses, bleeding from the gums and gastrointestinal hemorrhage. Later there was spontaneous epistaxis. The gastrointestinal bleeding was severe and over a period of three weeks the patient was given transfusions of 111 units of blood. Bleeding continued throughout the period of diuresis and early phases of recovery from uremia. While he was still bleeding gastroscopic and radiologic examinations revealed a hiatus hernia, probably traumatic in origin, but no mucosal lesion of stomach or bowel

TABLE 3
(Patient #3)

	December						
	6	13	14	16	20	22	27
One stage proth. time (% of normal)	55	5	50	80	35	—	67
Labile factor (% of normal)	100	100	—	—	50	—	—
Stable factor (% of normal)	90	10	82	—	60	80	—
Glass clotting time (min.)	14	15	11	—	—	—	—
Silicone clotting time (min.)	75	360	95	—	30	25	25
Bleeding time (min.)	13	13	—	—	4	—	2.5
Capillary fragility	negative	negative	—	—	—	—	—
Prothrombin consumption (sec.)	23	29.1	21.6	22.1	20.4	45.7	—
	27	31.3	22.6	22.3	22.9	45.7	—
Platelet count (× 1000/cu. mm.)	267	207	—	—	65	—	—
Clot Retraction	4+	3+	3+	—	3+	—	—
Fibrinogen (mg./100 ml.)	—	460	415	—	365	—	—
Fibrinolytic activity of plasma	—	normal	normal	—	—	—	—
Antithrombin activity	normal	normal	normal	—	normal	—	—
Thromboplastin generation test	—	—	normal				

	December							
Dialysis	5	7 •	9	14 •	16	20	26	31
Blood urea nitrogen (mg./100 ml.)	212	258	284	280	260	320	160	134
Urinary output (ml./24 hrs.)	150	150	200	1470	1500	4500	6000	6000

Clinical Findings: No bleeding on the 5th; bleeding from gums, ecchymoses on arms, gastrointestinal bleeding on the 9th; nose bleed on the 16th; gastrointestinal bleeding on the 20th; gastrointestinal bleeding on the 31st.

TABLE 4.—*Effect of Normal Whole Blood on Silicone Clotting Time of Blood from Patient Number 2 (December 1)*

Tube	1	2	3	4	5	6
Patient (ml.)	1.00	0.8	0.6	0.4	0.2	0
Control (ml.)	0	0.2	0.4	0.6	0.8	1.0
Clotting time (min.)	70	30	20	20	10	10

was demonstrated. The patient spontaneously ceased to bleed and recovered from the renal disease.

RESULTS

Serial studies of the patients' hemostatic mechanisms were performed during the time that hemorrhagic disease was clinically manifest, and the results are catalogued in tables 1, 2 and 3. Results of a test of clotting time in which blood from patient 2 was mixed with normal blood are shown in table 4.

The coagulation studies revealed several consistent abnormalities in all three cases. There was a prolongation of the coagulation time of whole blood in silicone: 100 minutes in case 1, 120 minutes in case 2 and 360 minutes in case 3. Bleeding time was also prolonged to a maximum of 12 minutes in case 1, 15 minutes in case 2 and 13 minutes in case 3. (Even though bleeding time was prolonged in all three patients the tourniquet test of capillary fragility was consistently and repeatedly negative.) In two of three cases, abnormal prothrombin consumption occurred during the process of coagulation: in cases 1 and 2 serum prothrombin time was 16 seconds. This result is especially noteworthy in case 1 because the serum prothrombin time of 16 seconds was the same as the plasma prothrombin time indicating an extremely small utilization of prothrombin during coagulation. In case 3 the slight decrease of serum prothrombin time cannot be considered significant. Plasma prothrombin activity was reduced in two of the three: in case 1 it was 40 per cent of normal, and in case 3 it was 5 per cent but rose to 50 per cent after intravenous administration of vitamin K_1 oxide. In all three cases subnormal platelet counts were recorded: 106,000 in case 1, 155,000 in case 2 and 65,000 in case 3. These platelet counts are not low enough to be thought of ordinarily as disposing a patient to bleed, and it is of interest that the lowest platelet counts in each case did not correspond with the observed abnormalities of bleeding time and prothrombin consumption.

DISCUSSION

The bleeding phenomena in acute uremia have various characteristics which suggest the existence of several faults in the hemostatic system. Some patients have bleeding gums, commonly a sign of capillary weakness or platelet deficiency, yet the tourniquet test is consistently negative and spontaneous petechiae are not common. Following anticubital venipuncture an unswollen ecchymosis may extend 15 cm. in both directions, as though the subcutaneous spreading of extravasated blood were relatively unimpeded. In injured patients healing wounds may spontaneously commence to bleed as though an effective hemostatic device had been dislodged. These latter two are examples of faulty

"large-vessel hemostasis" in contradistinction to the faulty "small vessel hemostasis" that is manifested by bleeding from the gums and prolongation of the Duke bleeding time. Hemostasis in small vessels does not require normal coagulation and the bleeding time may be normal when blood is completely incoagulable as it is when fibrinogen is absent.

The studies reported above revealed a consistent defect in blood coagulation, but the impediment, whatever its nature, was not a very heavy one. Thus clotting time of blood in silicone was much prolonged, but clotting time in glass was normal, as was the clotting time of recalcified plasma. If the siliconed tubes containing whole blood were rocked very much or were otherwise disturbed the clotting of blood could be made to occur within the normal time. The "mixing experiment" shown in table 4 suggests the presence of a mild anticoagulant; if delayed coagulation had been due to a lack of some plasma or platelet factor one would expect the addition of small amounts of normal blood to bring the clotting time of tube 2 closer to that of tube 6. Taken altogether, the delay in coagulation, the defect in prothrombin consumption and the normal clotting of recalcified plasma suggests a delay in the reaction between platelets and plasma factors that produces thromboplastin. The heparin tolerance test and protamine titration indicate that the anticoagulant effect is not due to heparin.

It is impossible to say what, if any, pathogenic significance should be ascribed to alterations of clotting time. One can give fairly large amounts of heparin and prolong the clotting time of blood for hours without causing any serious disturbance of hemostasis. On the other hand, with small transfusions of plasma one can correct the prolonged clotting time in hemophilia without improving the hemostatic disease.

It may well be that the thrombocytopenia which developed in case 3 on December 20 was a result of the multiple transfusion which this patient received.[10] However, coagulation abnormalities in this patient appeared prior to his transfusions, and indeed prior to his dialysis. The other patients also showed no correlation between dialyses or transfusion, and the appearance of the coagulation defects.

The cause of the hemorrhagic tendency in acute uremia has not been defined by the results of this study. The methods used have failed to reveal any single serious defect. This may indicate a shortcoming of the methods available for the study of hemostasis in that a serious hemorrhagic disease can be present without more of an alteration of these tests. On the other hand it is somewhat reminiscent of the bleeding tendency associated with cirrhosis where multiple minor deficiencies of the measurable clotting factors appear to summate and produce a defect of hemostasis that none of the deficiencies could cause alone.[27] There is a possibility that none of these small changes is related to the cause of the bleeding. Observe the lack of correlation between the actual level of uremia and oliguria and the hemorrhagic defect. In cases 1 and 3, the bleeding continued well into the period of diuresis and fading azotemia, persisting even after the coagulation studies had returned to normal. It may be that once the bleeding disease has been established, it can persist long after the etiologic factors have been removed. Or it may be that the etiologic factors produced by

uremia persist long after the concentration of blood urea and the output of urine have returned to normal.

Summary

The abnormalities of the hemostatic mechanism in three consecutive patients with acute renal insufficiency have been studied. In every case a prolonged clotting time in silicone and a prolonged bleeding time were found. In two cases defective prothrombin consumption was also present. Coagulation studies revealed no significant deficiency of plasma factors, no serious deficiency of platelet numbers or function and no well-defined anticoagulant effect to explain the changes. All three cases developed significant clinical bleeding at some time during the course of the renal insufficiency.

Summario in Interlingua

Esseva studiate le anormalitates del mechanismo hemostatic in tres consecutive patientes con acute insufficientia renal. In omne caso un prolongate tempore de coagulation insilicium e un prolongate tempore de sanguination esseva constatate. In duo del casos il habeva etiam un defecto del consumption de prothrombina. Studios de coagulation revelava nulle significative deficientia del factores plasmatic, nulle serie deficientia in le numero e le function del plachettas, e nulle ben-definite effecto anticoagulante. Omne le tres patientes disveloppava un significative sanguination clinic a un tempore o a un altere in le curso del insufficientia renal.

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