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Intravascular Coagulation in Fulminant Meningococcemia

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ACUTE MENINGOCOCCAL INFECTION in man pursues a variable course; usually the patient survives a severe illness characterized by a petechial skin eruption, meningitis, and a rapid response to appropriate antimicrobial therapy. However, an occasional unfortunate victim may die in profound and unresponsive shock hours after the onset of illness despite prompt and "adequate" treatment. Intravascular deposits of fibrin have been found at autopsy in such patients (1, 2), which suggests that diffuse intravascular coagulation could contribute to the clinical manifestations of meningococcal infection.

Intravascular coagulation produces characteristic platelet and clotting factor changes. Therefore, we have measured platelet and clotting factor levels in 19 patients with acute meningococcal infection in an attempt to delineate during life the type of patient in whom diffuse intravascular coagulation occurs and the clinical manifestations of the condition.

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MATERIALS AND METHODS

All patients were studied on the Communicable Disease Service in the Los Angeles County General Hospital. The diagnosis was confirmed by recovering *Neisseria meningitidis* from the blood or the cerebrospinal fluid. Two patients had negative cultures obtained after antimicrobials were started, but diplococci were seen within neutrophilic granulocytes on their blood smears.

Venous blood for coagulation studies was obtained with "silicone technique" as soon as possible after the patient's admission to the hospital and serially in some patients. We tried to count platelets (3) and to measure fibrinogen * (4, 5), factor V (6), and factor VIII (7) on all samples, since reduced levels of these factors are characteristic of an episode of diffuse intravascular coagulation. Factor VII (8) was also measured since this "serum factor" has been reported to fall during intravascular coagulation in experimental animals (9) and man (10). Prothrombin (7), factors IX (11), X (12), XI (13), and XII (7) were assayed on a few samples. Specific factor assays were expressed in percent of a pooled normal plasma standard; the normal range for these assays is approximately 60 to 150%. In addition to these specific assays, three screening tests—the Quick prothrombin time (14), the kaolin-activated partial thromboplastin time (PTT) (15), and the thrombin time (14)—were performed on many samples in the hope that these relatively simple but less specific procedures would identify the patient with intravascular coagulation.

Tissue sections obtained at autopsy from multiple organs were stained with hematoxylin-eosin and phosphotungstic acid-hematoxylin (PTAH) and examined for fibrin thrombi by light microscopy.

* Fibrinogen concentration was determined by one of two methods that correlate well over a wide range of values.

TABLE 1. Summary of Clinical Data*

Case	Age	Sex	Onset of Illness Before Admission	Temperature on Admission	White Peripheral Count	*Neisseria meningitidis* Recovered from†	Hypotension	Outcome
	yr		*hr*	*F*	*/mm³*			
1	8	F	24	104	9,000	Blood CSF	Deep shock	Death in deep shock 11 hr after admission
2	2	F	8	Not recorded	11,500	CSF	Deep shock	Death in deep shock
3	55	F	36	103	5,500	CSF Throat	Normal; then deep shock	Death in deep shock
4	4 months	F	36	101	10,300	CSF Throat	Deep shock	Death in deep shock 24 hr after admission
5	7 months	M	24	102.6	9,200	Throat; diplococci seen on peripheral smear	Initial deep shock; response to therapy after 1 hr	Death of cardiac arrest 26 hr after admission
6	66	F	24	107	9,500	Blood	18 hr severe	Recovery; course complicated by severe gastrointestinal hemorrhage due to peptic ulcer
7	11	M	12	Not recorded	4,900	CSF	Deep shock after cardiac arrest	Death after prolonged airway obstruction
8	13	M	24	103	24,700	Blood Throat	None	Recovery
9	7	M	24–48	104	12,300	Blood CSF	Transient, mild	Recovery with minimal skin necrosis
10	18	M	24	102	31,500	CSF	None	Recovery
11	49	F	24	99.4	10,800	Blood CSF	None	Recovery
12	15	M	36	102.4	28,200	Blood CSF Throat	None	Recovery
13	4	F	12	101	10,500	Blood	None	Recovery
14	38	M	24	100	9,400	CSF	Transient, mild	Recovery
15	8	M	24	100.4	52,000	Not cultured; diplococci seen on peripheral smear	Transient, mild	Recovery; gangrene of one distal phalanx
16	6	F	48	102	52,800	CSF Throat	Transient, mild	Recovery
17	9	M	12	98.6	25,500	Blood Throat Conjunctiva	4 hr; moderate	Recovery
18	18	M	24	103	28,000	Blood CSF	None	Recovery
19	16	M	48	105	16,800	CSF	Transient, moderate	Recovery; course complicated by arthritis and persistent anticoagulant

* All patients had petechiae noted on or shortly after admission. The amount of purpura varied but was most marked in those patients with severe shock.

† CSF = cerebrospinal fluid.

Results

The clinical data on the 19 patients are summarized in Table 1. We have divided these patients into three groups on the basis of the results of their coagulation tests.

PATIENTS WITH EVIDENCE OF INTRAVASCULAR COAGULATION

This group is comprised of Cases 1 through 6; their platelet counts and clotting studies are summarized in Table 2. Good evidence of diffuse intravascular coagulation was obtained in the first five patients. Severe thrombocytopenia, moderate reduction of fibrinogen, and low levels of factors V and VIII were found in Cases 1 through 3. Factor VII was also low (see discussion below), and the screening tests were markedly abnormal. The studies performed in Cases 4 and 5 were incomplete, but the combination of marked thrombocytopenia and hypofibrinogenemia found in each strongly suggests intravascular coagulation.

The first four patients *died in profound shock* within hours after admission to the hospital. Two of these cases are summarized below.

Case 1: An 8-year-old girl was well until the day before admission when she developed fever. The next morning she was confused, febrile, and had petechiae. She was taken to an emergency hospital at 9:30 AM where a lumbar puncture revealed clear fluid. Her blood pressure was 70/50 mm Hg, and her platelets, counted because of her purpura, were reported as 218,000/mm³. When we first saw her at 11 AM she was critically ill with widespread petechiae, ecchymoses, and an undetectable blood pressure. Blood for our clotting studies was obtained at 11:40 AM, approximately 24 hr after the apparent onset of illness. In addition to the studies recorded in Table 2, the following were found: prothrombin, 48%; factor IX, 50%; factor X, 39%; factor XI, 45%. She was treated with intravenous penicillin, hydrocortisone, plasma, and metaraminol. At 1:20 PM she was given a single 10,000-IU dose of heparin intra-

TABLE 2. Initial Coagulation Studies and Autopsy Findings in the Patients with Evidence of Intravascular Coagulation

Case	Platelets	Screening Tests			Specific Factor Assays				Autopsy Findings
		Quick Time (Normal, 14 to 17 sec)	PTT* (Normal, 36 to 50 sec)	Thrombin Time (Patient/ Control)	Fibrinogen	Factor V	Factor VIII	Factor VII	
	/mm³		*sec*		*mg/ 100 ml*	←——— *%* ———→			
1	51,250	33	90	50/25	168	10	24	11	Adrenal hemorrhage and microthrombi
2	Markedly reduced on smear	30	66	—	203	43	48	37	Adrenal hemorrhage and microthrombi
3	2,500	31	73	24/15	194	14	25	51	Adrenal microthrombi; renal glomerular capillary thrombosis
4	24,000	—	—	—	30	—	—	—	Adrenal hemorrhage and microthrombi
5	44,000	—	—	—	120	—	—	—	Adrenal hemorrhage and microthrombi
6†	180,000	22	56	46/33	380	60	100	23	—

* PTT = partial thromboplastin time.

† As noted in the text, clotting studies in this patient provide only equivocal evidence of intravascular coagulation.

FIGURE 1. Section of the adrenal cortex showing microthrombi in the sinusoids of Patient 1. (Phosphotungstic acid-hematoxylin, × 125.)

venously. She remained in deep shock and died at 10:20 PM after cardiac arrest. Autopsy revealed gross bilateral adrenal hemorrhage. Microscopic fibrin thrombi were not seen when the routine tissue sections were first examined; however, a subsequent review of the PTAH-stained sections disclosed microthrombi in the adrenal sinusoids (Figure 1) but nowhere else.

Case 3: A 55-year-old woman was well until 2 days before admission when she developed a sudden shaking chill. The following day she complained of head and neck pain and had fever. The morning of admission she became disoriented. On admission at 11 AM she was incoherent and had a blood pressure of 150/90 mm Hg. The skin showed a pattern described as livedo reticularis, but during the examination petechiae began to appear. Blood for clotting studies was obtained at 3 PM (48 hr after the first sign of illness). Studies other than those recorded in Table 2 included prothrombin, 53%; factor IX, 75%; factor X, 76%; factor XI, 76%; and factor XII, 42%. Initial therapy consisted of antibiotics only (ampicillin, chloramphenicol, and streptomycin). At 4:30 PM her blood pressure could no longer be obtained, and over the next few hours she was given packed red cells, plasma, and dexamethasone. At 5 PM, 5,000 IU of heparin were administered intravenously, and this dose was repeated every 4 hr. Despite these measures she remained in deep shock and died at 6 AM the following day. Gross adrenal hemorrhage was not seen at autopsy, but microscopic sections showed spotty hemorrhage into the cortex of both glands and fibrin thrombi in the sinusoids. The most striking finding, however, was extensive deposition of fibrin in the afferent arterioles and glomerular capillaries of both kidneys (Figure 2) without associated renal cortical necrosis.

The patient in Case 5 was admitted to the hospital in severe shock and with widespread purpura and cyanosis. After initial therapy that included heparin, his blood pressure rose, and his general condition improved. He died suddenly of a cardiac arrest 27 hr after entry, differing from the first four patients in that he did not die of irreversible shock.

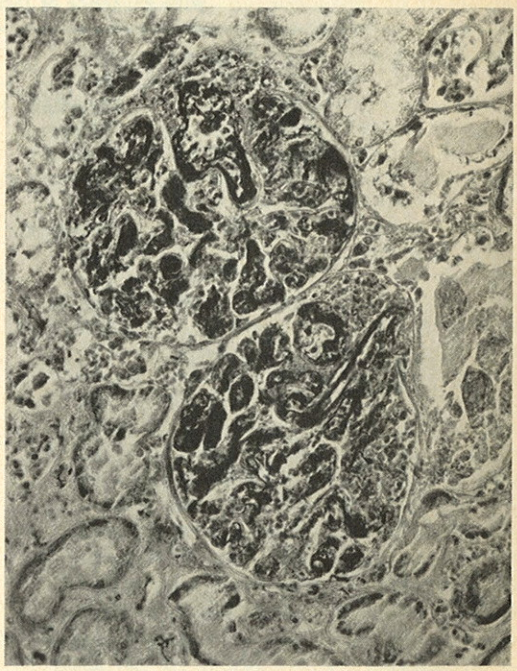

FIGURE 2. Section of the kidney of Patient 3 showing fibrin deposits within the glomerular capillaries. (Phosphotungstic acid-hematoxylin, × 250.)

Case 5: A 7-month-old boy appeared well until 11 PM the evening before admission when he developed fever. At 5:30 AM the parents noticed a skin rash; at 9 AM the infant was seen by a physician who referred him to the hospital. When first seen at 11 AM the child was lethargic, cyanotic, had a barely perceptible pulse, and was covered with petechiae and purpura. An infusion of dextrose and saline was started, and he was given ampicillin intravenously. At 11:20 AM 1,000 IU of heparin and 15 mg of dexamethasone were administered intravenously. In addition he received a small amount of plasma. The blood pressure rose to 90/30 mm Hg, and a blood sample was obtained for a platelet count and fibrinogen determination (see Table 2). Diplococci were seen within neutrophils on the peripheral blood smear and in a smear from one of the petechiae. Over the next few hours his condition seemed to stabilize, and at 5:30 PM he voided 12 ml of urine. The heparin was continued at a dose of 700 IU every 4 hr. Other therapy included packed red cells, chloramphenicol and streptomycin, mannitol, and digoxin. Through the night he continued to put out urine, and his blood pressure remained stable. The following morning he had more labored respirations, but his central venous pressure did not exceed 10 cm of saline. The scheduled 10 AM dose of heparin was omitted because he was steadily bleeding from the cutdown incision. At this time no bacteria could be found on the peripheral smear: the fibrinogen had risen to 460 mg/100 ml, but the platelet count had fallen to 16,000/mm³. The child had an abrupt cardiac arrest at 1:40 PM and died. Autopsy revealed gross bilateral adrenal hemorrhage. The lungs were congested and heavy. PTAH-stained sections showed microthrombi in the adrenal sinusoids. Fibrin thrombi were not seen in other organs.

The sixth patient in this group also had severe shock but survived with therapy that included heparin. *Evidence of intravascular coagulation was equivocal,* consisting of a moderately prolonged thrombin time, a slightly prolonged partial thromboplastin time, and a factor V level at the lower limit of our normal range.

Case 6: A 66-year-old woman was admitted to the hospital 24 hr after she became ill with a shaking chill. The morning of admission she became obtunded and had a high fever. When first seen at 11 AM she was acutely ill, with a temperature of 107 F but a normal blood pres-

TABLE 3. Initial Coagulation Studies on the Patients Without Evidence of Intravascular Coagulation

Case	Platelets	Screening Tests			Specific Factor Assays			
		Quick Time (Normal, 14 to 17 sec)	PTT* (Normal, 36 to 50 sec)	Thrombin Time (Patient/ Control)	Fibrinogen	Factor V	Factor VIII	Factor VII
	/mm³	*sec*			*mg/ 100 ml*	←——*%*——→		
7	181,000	21	—	25/30	209	85	165	25
8	225,000	19	—	22/24	316	68	—	29
9	126,000	25	—	29/26	296	75	180	14
10	170,000	24	—	28/26	365	90	115	10
11	142,500	—	—	26/26	620	110	250	52
12	250,000	26	46	22/25	570	45	195	23
13	260,000	23	46	23/25	410	75	170	21
14	75,000	22	—	34/33	520	70	100	17
15	95,000	—	—	—	510	75	75	17
16	160,000	—	—	—	670	94	325	40
17	152,500	25	48	26/23	620	70	290	14
18	296,250	21	46	24/26	650	100	290	50
19	7,500	21	120	28/26	750	100	120	72

* PTT = partial thromboplastin time.

sure and no petechiae. Shortly thereafter, as she was being examined by a second physician, her blood pressure fell to 65/40 mm Hg, and crops of petechiae began to appear. A blood sample taken at 2:45 PM revealed a platelet count of 180,000/mm³; the peripheral blood smear showed diplococci within neutrophils. Despite the normal platelet count, the prolonged thrombin time and the PTT (see Table 2) were taken as presumptive evidence of intravascular clotting, and, because of this and her rapidly deteriorating condition, heparin therapy was started at 3:30 PM (5,000 IU intravenously every 4 hr). She remained severely hypotensive and oliguric for 18 hr; she also received antibiotics (ampicillin, streptomycin, and chloramphenicol), digoxin, hydrocortisone, and isoproterenol. The heparin was stopped after 24 hr because her condition seemed to stabilize and because of steady bleeding from a cutdown incision. Significantly, her platelet count fell to 118,000/mm³ while she was still on heparin and to 61,000/mm³ on the third hospital day. She survived a stormy course characterized by azotemia and by two late episodes of gastrointestinal bleeding attributed to a peptic ulcer.

PATIENTS WITHOUT EVIDENCE OF INTRAVASCULAR COAGULATION

The coagulation studies of Cases 7 through 19 did not reveal clear-cut evidence of intravascular coagulation (see Table 3). All but one of these patients survived. The exception, Patient 7, had meningococcal meningitis and died from central nervous system damage after a prolonged period of apnea after obstruction of his airway. Patient 19 is included in Table 3, but his findings are unique and will be considered separately. The findings in Cases 7 through 18 demonstrated a fairly constant pattern which is summarized as follows:

Platelets: Severe thrombocytopenia was not seen. The platelet count was normal in eight patients, between 100,000 and 150,000/mm³ in two patients, and between 75,000 and 100,000/mm³ in two others.

Screening Tests: The Quick prothrombin time was prolonged in all patients on whom it was performed, reflecting the low levels of factor VII (see below). However, the Quick times were not as long as in the patients with intravascular coagulation, who in addition to low factor VII also had low levels of factor V. The partial thromboplastin time (PTT) was normal in the few samples checked. The thrombin time was consistently normal, an indication that fibrin-split products were not present in the circulation in sufficient concentration to interfere with the thrombin-fibrinogen reaction (16).

Specific Assays: Fibrinogen and factor VIII levels were elevated in most patients in agreement with Egeberg's observation (17) that endotoxin causes rapid elevation of these factors. Possibly, therefore, the normal levels of factor VIII found in Cases 10, 14, and 15 represented some degree of increased utilization.

Factor V levels were within the normal range except for one unexplained low value (Case 12). Egeberg (17) has shown that factor V also rises after an injection of endotoxin but later than the acute elevations of fibrinogen and factor VIII.

Factor VII was low in all patients, with values ranging between 10 and 52% of normal. In two patients low levels were still present after 6 days, but in a third patient factor VII had returned to normal by the fourth day. We found no correlation between the initial factor VII level and either of the following: the duration or severity of the illness or the levels of fibrinogen, factor V, or factor VIII.

A PATIENT WITH A CIRCULATING ANTICOAGULANT

Patient 19 had an endogenous circulating anticoagulant probably due to autoimmune disease. This patient represents nature's own experiment on anticoagulant therapy in meningococcemia.

Case 19: A 16-year-old boy was admitted to another hospital approximately 24 hr after the onset of fever and headache. A lumbar puncture yielded purulent fluid that contained gram-negative intracellular diplococci. He was treated initially with antibiotics and hydro-

cortisone. Because of persistent hypotension and the onset of upper gastrointestinal bleeding, he was given a unit of whole blood and an injection of vitamin K. When first seen in our hospital (48 hr after the onset of illness), he was still hypotensive and bleeding slowly. Clotting studies showed a slightly prolonged Quick time and a normal thrombin time. However, the PTT was markedly prolonged to 120 sec and was not shortened by adding an equal volume of normal plasma to his plasma. The platelet count was 7,500/mm^3, fibrinogen was elevated, and factors V and VIII were normal. With platelet and whole blood transfusions the bleeding stopped; his blood pressure rose, and he made a satisfactory recovery. Subsequently, we established that he had a circulating anticoagulant that appeared to inhibit the activity of the intrinsic prothrombin activator. It was associated with an elevated gamma globulin, a weakly positive test for antinuclear protein and deoxyribonucleic acid antibodies, and a biological false-positive test for syphilis. This anticoagulant has persisted* and presumably was present before his acute meningococcal infection.

Discussion

Each of the four patients with *irreversible* shock (Cases 1 to 4) demonstrated on coagulation studies clear-cut evidence of diffuse intravascular clotting. A fifth patient (Case 5) also had profound shock and good evidence of diffuse intravascular coagulation; his shock responded to treatment that included heparin, but he later died of a cardiac arrest. Patient 6 had equivocal evidence of intravascular clotting at a time when she was still normotensive. Shortly thereafter, her blood pressure dropped precipitously, she was promptly treated with measures that included heparin, and she eventually recovered. Thus, of the six patients in this series with profound endotoxin shock, five had definite evidence and one had equivocal evidence of diffuse intravascular clotting. We suspect, therefore, that intravascular coagulation occurs in every patient with fulminant meningococcemia and severe shock. In contrast, as the remaining cases in this series illustrate, patients with meningococcemia who do not experience severe endotoxin shock do not exhibit definite evidence on coagulation factor assays of extensive intravascular coagulation.

Intravascular deposits of fibrin have been described in some but by no means all autopsy reports of fulminant meningococcemia. In our series all five patients with profound endotoxin shock who died had microthrombi in the adrenal sinusoids, and one patient also had extensive deposits of fibrin in glomerular capillaries and arterioles. Fibrin thrombi were not identified in other organs. In the four patients with only adrenal sinusoidal microthrombi, associated adrenal hemorrhage obscured the microthrombi, and they were not noticed until sections were reexamined for fibrin with the phosphotungstic acid-hematoxylin stain. Thus, coagulation studies appear to be a more reliable indicator of diffuse intravascular clotting in meningococcemia than routine histological examination of hemotoxylin-eosin-stained tissue sections.

The low levels of factor VII found in every patient except Patient 19 surprised us. Experimental intravascular clotting triggered by tissue thromboplastin increases the clearance of factor VII from plasma (18), and intravascular coagulation in meningococcemia could produce low factor VII levels by this mechanism. However, this does not account for the low factor VII levels found in patients (for example, Patients 8, 9, and 15) without other evidence of intravascular coagulation. Since the normal intravascular half-life of factor VII is only about 6 hr, a cessation of synthesis at the onset of illness could lower plasma levels within hours. Yet, if this were the principal explanation, comparable but later falls would be expected in the related vitamin K-dependent clotting factors with longer intravascular half-lives. This was not

* This patient was first seen in January 1966. The anticoagulant was still present in February 1967.

found in one patient (Figure 3) in whom serial factor VII, prothrombin, and factor X levels were measured. Furthermore, incubation with endotoxin does not reduce the synthesis of factor VII by liver slices (19). Whatever its mechanism, the low factor VII levels may persist for several days, and, since the patients usually cannot eat and are receiving antibiotics, the administration of vitamin K is reasonable.

Thrombocytopenia in meningococcemia could result from at least two effects of the bacteremia: first, direct damage to platelets by endotoxin or bacteria (20, 21), a reaction not blocked by heparin or warfarin in the experimental animal (22); and secondly, intravascular coagulation with resultant destruction of platelets by thrombin. The thrombocytopenia that developed in Patient 6 while she was receiving heparin and the thrombocytopenia of Patient 19, the boy with the circulating anticoagulant, probably resulted from direct damage to platelets by bacteria or endotoxin. These cases illustrate that severe thrombocytopenia may occur without extensive intravascular coagulation. But, when an anticoagulant is not present, the liberation of clotting activity from endotoxin-damaged platelets may well then trigger intravascular coagulation (23, 24). Thus, severe thrombocytopenia in meningococcemia probably means that large numbers of bacteria (or large amounts of endotoxin) have entered or are entering the circulation and warns of the likelihood of intravascular coagulation. As Case 1 illustrates, a sudden fall in the platelet count may have dire prognostic significance.

Therefore, we believe that an examination of a stained peripheral blood smear for platelets should be part of the initial evaluation of all patients with meningococcemia and of subsequent evaluations of critically ill patients. Other coagulation studies may also help in identifying the overwhelmingly ill patient as quickly as possible. Because measurements of fibrinogen and factors V and VIII are usually not quickly available, one must rely on simpler screening tests. The Quick prothrombin time will not be useful for it is prolonged in all patients due to the fall in factor VII. However, when the combination of thrombocytopenia on a peripheral blood smear, a prolonged PTT (reflecting low factor V and factor VIII levels), and a prolonged thrombin time (reflecting fibrin-split products in the circulation) is found, one may infer that the patient has experienced enough endotoxemia to trigger diffuse intravascular coagulation. If it is not already present, one may anticipate imminent severe endotoxin shock. Although these conclusions are based on our experience with meningococcemia, they also apply to other types of septicemia with gram-negative organisms (25).

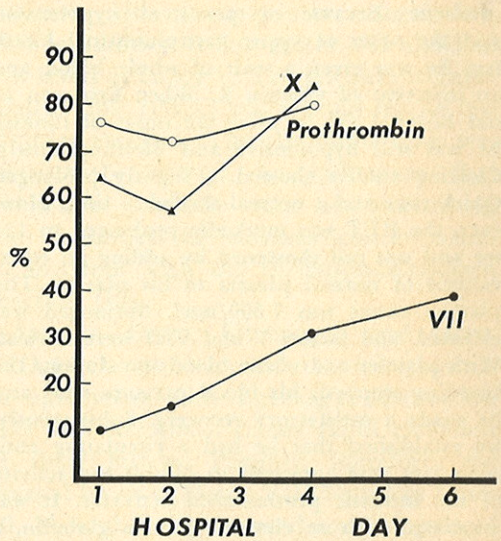

FIGURE 3. Serial prothrombin, factor VII, and factor X levels found in *Case 10*.

Intravascular coagulation with subsequent deposition of fibrin in small vessels clearly plays a role in the pathogenesis of important clinical manifestations of fulminant meningococcemia, for example, the large ecchymotic skin lesions (26), the hemorrhagic adrenal necrosis (2), and, in a rare patient, renal cortical necrosis (2).

However, the crucial question—does intravascular coagulation contribute significantly to the irreversibility of the shock that usually kills the patient with fulminant meningococcemia?—remains unanswered. Hardaway (27) claims that disseminated intravascular coagulation converts reversible shock to irreversible shock in animals. Each patient in our small series with irreversible shock had clear-cut evidence of intravascular coagulation. Nevertheless, this does not prove a causal relationship. Very large doses of meningococcal endotoxin must have entered the circulation in these patients and could have produced irreversible shock and intravascular coagulation as independent phenomena.

The data on the usefulness of heparin in preventing experimental irreversible shock are conflicting (27, 28). Similarly, our limited clinical observations on the effect of anticoagulants are inconclusive. Although heparin was given without noticeable effect to three patients late in their fatal course, heparin may have altered the course in Case 5 even though the patient later died of cardiac arrest. More convincingly, the early administration of heparin in Case 6 and the endogenous anticoagulant in Case 19 may have protected these severely ill patients from diffuse intravascular coagulation, irreversible shock, and death. Therefore, until further clinical experience proves otherwise, we believe that heparin should be given for a trial period of 24 hr to the patient with meningococcemia who has presumptive evidence of intravascular coagulation or who appears to be going into shock.

If heparin does prove of value in treating meningococcemic shock, it will obviously constitute only one part of the management of the patient. Other measures, as clinically indicated, to restore vascular volume, to correct acidosis, and to improve cardiac function must also be taken if these desperately ill patients are to survive.

Summary and Conclusions

Clotting factors and platelets were measured in 19 patients with acute meningococcal infection. Good evidence of extensive diffuse intravascular coagulation was found in five patients and equivocal evidence in a sixth patient. Each of these patients had fulminant meningococcemia with profound endotoxin shock. Twelve patients, with less overwhelming meningococcal infection, exhibited neither severe hypotension nor clear-cut evidence of intravascular coagulation. Finally, a unique, severely ill patient had an endogenous circulating anticoagulant probably secondary to an unrelated autoimmune disorder. He had marked thrombocytopenia suggestive of the release of large amounts of meningococcal endotoxin but no evidence of intravascular coagulation and only moderate hypotension.

Five of the patients with profound shock died. A special stain for fibrin (phosphotungstic acid-hematoxylin) revealed adrenal sinusoidal thrombi in each, a finding not recognized initially on the routine sections in four cases because of extensive associated hemorrhagic necrosis of the adrenal glands. One patient also had extensive deposits of fibrin in glomerular arterioles and capillaries. Fibrin thrombi were not identified in other organs. This experience suggests that coagulation studies may be a more reliable indicator of extensive intravascular coagulation in fulminant meningococcemia than routine examination of hematoxylin-eosin-stained tissue sections at autopsy.

Five of the six patients with profound endotoxin shock received heparin as part of their therapy for shock. Three patients, given heparin late in their course, died in irreversible shock. A fourth patient came out of shock but died later of cardiac arrest. A fifth patient, who received early heparin therapy, survived.

This clinical study establishes that intravascular coagulation and irreversible shock

occur together in fulminant meningococcemia but does not establish whether these are independent or related manifestations of severe endotoxemia. Further clinical experience, especially with heparin, is needed to determine if intravascular coagulation contributes significantly to the irreversibility of shock in fulminant meningococcemia.

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