Coagulation Changes in Clinical Shock:

II. Effect of Septic Shock on Clotting Times and Fibrinogen in Humans

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Marked alterations in the clotting mechanism were shown to occur in dogs and rabbits after endotoxin shock. The alterations were attributed to disseminated intravascular coagulation which interfered with perfusion of the vital organs and led to irreversibility and death.

Research in shock has recently shifted from the experimental animal to the human. There is little information on the changes in coagulation in septic shock in humans. This study was undertaken to 1) determine patterns of changes of the clotting mechanism and fibrinogen in the human in septic shock, 2) compare such changes with those occurring in the experimental animal.

Materials and Methods

Forty-two patients were studied. All were in septic shock, characterized by sepsis proven bacteriologically, hypotension with systolic arterial blood pressure below 90 mm. Hg, acidosis, and impaired renal function. Most infections were due to gram negative organisms, specifically Escherichia coli, Pseudomonas and Proteus, though gram positive septicemia occurred in a few. Tables 1 and 2 summarize clinical diagnoses and bacteriologic findings of surviving and fatal cases, respectively. Blood samples were obtained from patients in shock immediately upon admission to the Unit. Determinations were then made every 6 hours until the condition of the patient stabilized; thereafter, blood samples were obtained daily until death or discharge from the Unit. Silicone clotting time was selected as representing the overall process of clotting despite its limitations. The Lee-White method using three tubes was utilized, taking the formation of a solid clot in the third tube as an end point. Clotting time data were expressed in terms of clotting indices.[1] Fibrinogen was determined by the turbidimetric method of Parfentjev.[7] The average mean value of fibrinogen concentration in this method is 250 mg.% (113–380). The fibrinogen concentration data were expressed in terms of fibrinogen index, F, defined as follows:

$$F = \frac{f - fn}{fn},$$

wher f is the observed fibrinogen, and fn is the average normal fibrinogen. A positive fibrinogen index signifies hyperfibrinogenemia, and a negative index corresponds to hypofibrinogenemia. A zero value means that the fibrinogen concentration is the

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TABLE 1. *Clinical Data on Surviving Septic Shock Patients*

Name	Sex	Age	Diagnosis	Bacteriology Culture	Source	Blood Culture
C. S.*	F	28	Septic abortion	Escherichia coli, Clostiridia perfringes	Cervix	—
A. W.*	M	27	Perforated duodenal ulcer	None		None
H. R.*	M	80	Urinary infection, post-transurethral resection	Pseudomonas, Escherichia coli	Urine	None
M. J.*	F	45	Bilateral pneumonia	Hemophilus influenza, Alpha streptococcus, Beta hemolytic streptococcus	Sputum	—
G. L.*	M	31	Bullet wound, abdomen, multiple jejunal perforations	Escherichia coli	Peritoneal cavity	—
L. K.*	M	79	Carcinoma stomach, gastrojejunostomy, pneumonia	Proteus, Klebsiella	Bronchial	—
L. W.*	F	30	Tubo-ovarian abscess	Escherichia coli	Peritoneal cavity	—
O. C.*	M	29	Stab wound of abdomen, peritoneal abscess	Escherichia coli, Pseudomonas	Peritoneal cavity	—
J. P.*	M	30	Acute appendicitis with peritonitis	Bacteroides	Peritoneal cavity	—
E. G.*	F	30	Bilateral pyosalpinx	Escherichia coli	Lochia	—
E. T.	M	58	Pneumonia—Bilateral	D. pneumonia	Sputum	—
J. T.	M	54	Respiratory infection, bronchial asthma	Hemolytic staphyloccus, streptococcus	Sputum	Hem. staph. coagulase negative
W. G.	M	59	Right pyopneumothorax	Staphylococcus aureus	Sputum	+
H. B.	M	61	Carcinoma urinary bladder, peritonitis	Staphylococcus aureus		+
B. S.	F	39	Tubo-ovarian abscess	Proteus, Pseudomonas	Pelvic	—
H. R.	M	44	Intestinal obstruction	Proteus, Escherichia coli	Peritoneal cavity	—
V. S.	F	25	Bilateral pneumonia with abscess—right	Pseudomonas tubercle bacilli	Sputum	—
J. W.	M	68	Bronchopneumonia	Staphylococcus aureus (+)	Sputum	—

* Patients included in the Coagulation Indices Studies.

same as the assumed normal average. The clotting time and fibrinogen indices are plotted against time in Figures 1 to 4.

In order to establish a patten of behavior for the clotting time indices after septic shock, 23 patients were studied and grouped according to survival (10) or death (13). Clotting time indices of each patient were plotted, neglecting minor deviations from the general pattern. It appeared that clotting time indices followed a certain oscillatory behavior. The average maximal positive and negative values and the distances between the horizontal intercepts were calculated (Fig. 5, Tables 3, 4) for surviving and dying patients. In survivors (Fig. 6), the first change in clotting time was a significant decrease to 47 percent of normal, denoting hypercoagulability. After 10 hours, clotting time indices not only became normal but rose, leading to a hypocoagulable phase. The prolongation in clotting time indices was increased 136 percent over the normal average. Clotting time returned to normal in about 43 hours. The first oscillation was followed by a similar

TABLE 2. *Clinical Data on Expired Septic Shock Patients*

Name	Sex	Age	Diagnosis	Bacteriology Culture	Source	Blood Culture
A. H.*	F	93	Perforated gastric ulcer	Escherichia coli, Staphylococcus aureus (+)	Peritoneal cavity	None
A. C.*	M	58	Pulmonary tuberculosis miliary	Tubercle bacillus	Autopsy	—
H. W.*	M	46	Gastrojejunal fistula with peritonitis	Escherichia coli, Bacillus proteus	Peritoneal cavity	Hem. staph. aureus (+)
J. M.*	M	61	Volvulus sigmoid colon with necrosis	Hemolytic staphylococcus aureus (+)	Peritoneal cavity	None
A. J.*	M	71	Volvulus small intestines	Staphylococcus aureus (+)	Peritoneal cavity	None
E. S.*	F	32	Thermal burns (75%)	Escherichia coli, Staphylococcus aureus (+), Pseudomonas	Skin	—
S. B.*	M	77	Incarcerated inguinal hernia			None
W. B.*	M	76	Urinary tract infection	Bacillus proteus	Urine	+
W. W.*	M	42	Peritonitis, leakage gastrojejunal anastomosis	Staphylococcus aureus (+)	Peritoneal cavity	—
J. K.*	F	20	Thermal burns (60%)	Escherichia coli	Pleural fluid	—
C. D.*	M	63	Internal hernia with gangrene	Pseudomonas	Peritoneal cavity	Staph. aureus (+)
V. S.*	F	39	Jejunal obstruction with peritonitis	Escherichia coli	Peritoneal cavity	None
W. B.*	M	76	Chemical burns pharynx, esophagus and stomach, mediastinitis	Peudomonas, Escherichia coli	Sputum	+
C. R.	F	59	Left middle cerebral artery thrombosis, left lower lobe pneumonia			—
R. H.	M	51	Lung abcess	Escherichia coli	Sputum	—
R. S.	M	69	Perforated duodenal ulcer	Escherichia coli, Streptococcus	Peritoneal cavity	E. coli
N. M.	F	67	Urinary tract infection	Escherichia coli	Urine	+
D. M.	F	63	Pyelonephritis	Escherichia coli	Urine	+
D. M.	F	80	Perforated transverse colon	Escherichia coli, Clostridia perfringens	Peritoneal cavity	None
F. B.	M	80	Urinary tract infection	Escherichia coli	Urine	+
G. B.	F	53	Intestinal fistula	Escherichia coli, Pseudomonas	Peritoneal cavity	+Hem. staph.
J. B.	M	31	Traumatic duodenal rupture, retrocolic abcess	Staphylococcus aureus	Peritoneal cavity	—
O. K.	F	47	Ileal perforation with peritonitis	Escherichia coli	Peritoneal cavity	—
B. M.	M	61	Pyelonephritis	Pseudomonas	Urine	Hem. staph.+
A. N.	F	50	Chronic cystitis bilateral hydronephrosis	Proteus	Bladder	—
J. P.	M	30	Acute appendicitis with peritonitis	Bacteriodes	Peritoneal cavity	—

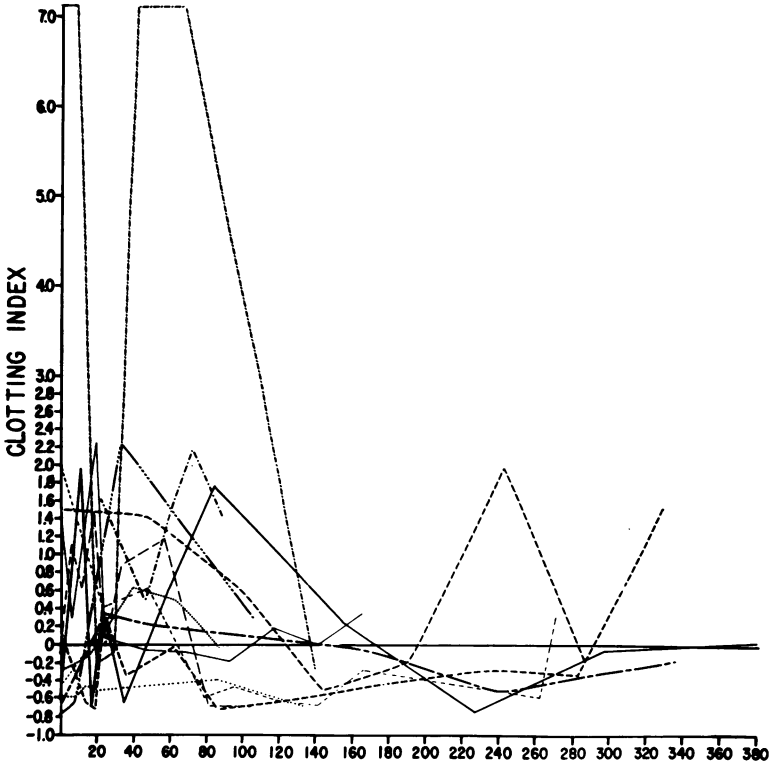

FIG. 1. Graphic illustration of the clotting time indices in surviving septic shock patients. Time "zero" indicates time of admission of patient to the unit and the abscissa represents duration of stay.

second oscillation which was not significantly decreased in amplitude compared to the first. Although our studies were not extended beyond this second oscillation, we assume that the oscillatory behavior continues with a decreasing amplitude and frequency, until the assumed average normal bounds are reached.

In the 13 patients who expired (Fig. 7), a similar oscillatory pattern could be observed. However, the amplitude of the positive deflection of the first oscillation was significantly higher than that in the surviving group. Only eight patients survived beyond the first oscillation and provided enough data to compare with their first oscillation (Fig. 8). The second oscillation was much larger in amplitude than the first and although only two patients survived to the third oscillation, the latter exceeded the previous ones considerably. The oscillatory pattern of clotting time indices, though similar in survivors and non-survivors, is different in amplitude and frequency. In surviving patients in septic shock, oscillations diminished in frequency and amplitude in contradistinction to fatal cases where the response was an increase in amplitude and frequency.

The same method of analysis was applied to fibrinogen indices (Fig. 3). The apparent discrepancy in fibrinogen response to septic shock is not real. A definite pattern can be established in surviving patients studied an extended time which fits the patterns shown in Figure 3. The early response of fibrinogen to sepsis is a sudden rise, the extent of which has not been correlated with the severity of sepsis but with defense mechanisms of the body. This rise is sustained as long as sepsis is present, however, with gradual regression of the septic process, fibrinogen decreases gradually. In this series of survivors, the maximum period of observation was about 3 weeks, at which time fibrinogen levels

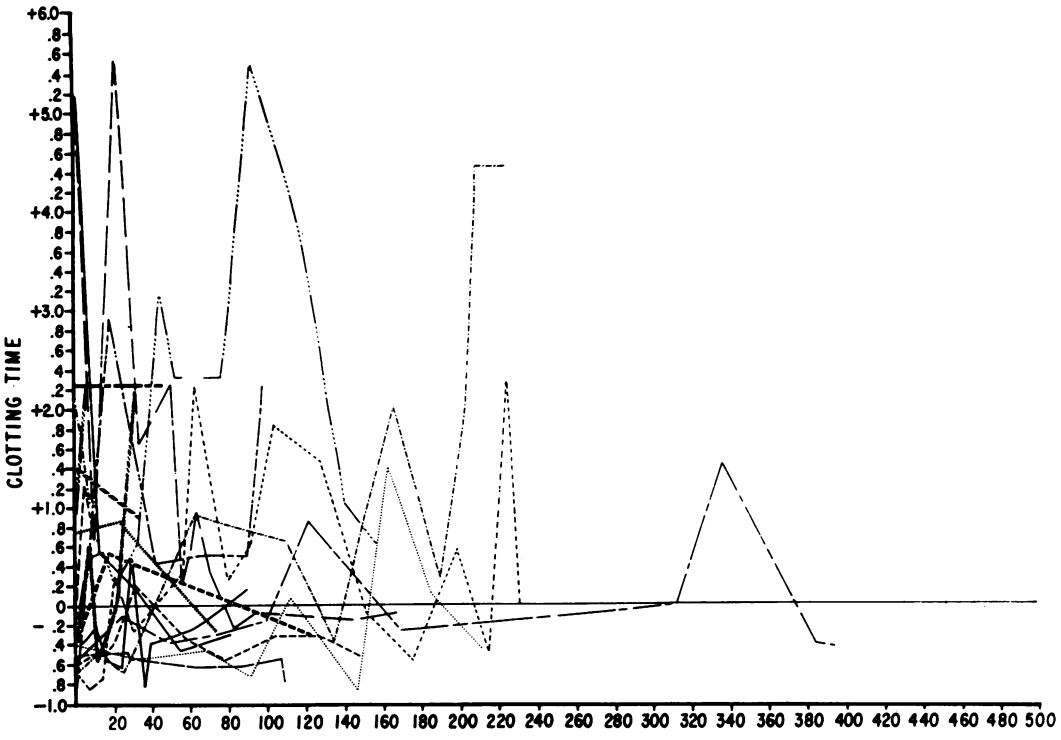

FIG. 2. Graphic illustration of the clotting time indices in eight expired septic shock patients.

had not yet returned to normal. With this general pattern in mind, it is possible to account for variations observed in the following manner:

1) Individual variations.

2) Variations related to time of observation. These patients are seen at variable periods after the onset of septic shock intervals which change the part of the graph to which their responses fit best.

3) Age of patients. Response of older patients has been minimal. This is illustrated in patients L. W. and E. G. who were 80 and 79 years old, respectively.

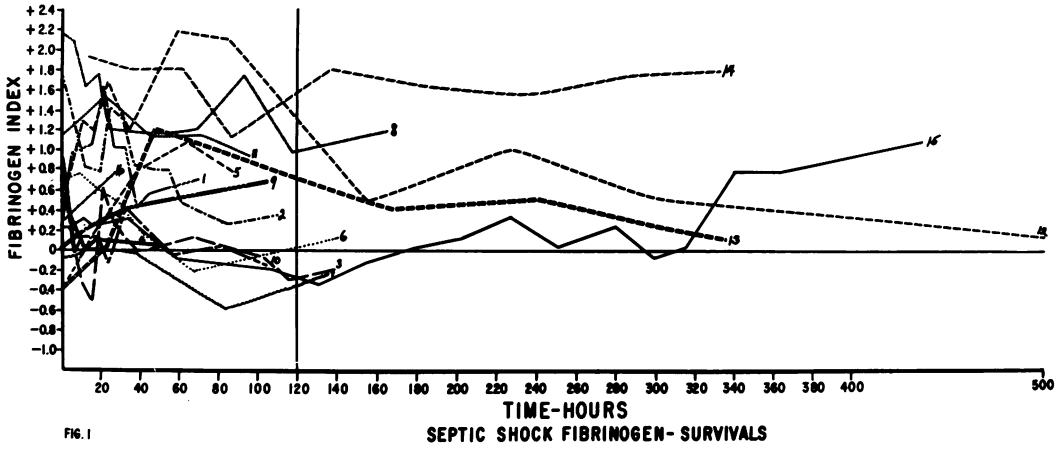

FIG. 3. Fibrinogen indices versus time in surviving patients.

TABLE 3. *Clotting Indices Versus Time in Surviving Septic Shock Patients*

Name	h_2	h_1	XM	XL	X_1	h_0	X_k	h_1	XO	X_j	X_1'	ho'	X_1	XO'	L_1''	X_A	Lo''	X_1''
C. S.	−0.76	+2.24	14½	18½	—													
A. W.	−0.30	+0.62	19½	20½	66	−0.03												
H. R.	−0.52	+1.9	2	9	16½	−0.68	1½	+1.8	20	48	136	−0.73	55	169				
M. J.		+2.24		19	35	−0.2	57	+0.2	75	11	35	—	—	—	+0.35	24		
G. L.	−0.68	+0.32	16	8	87	−0.52	137	—	—	—								
L. K.	−0.1	+1.1	1	10	—	—	—	1.4	—	7	23	−0.06	0	1	+1.2	32	−0.7	48
L. W.	—	+0.15	—	0	2	−0.7	17	+0.36	21	3	21	−0.74	42	133	+1.46	150		
O. C.	—	+1.5	—	0	108	−0.52	36	+1.9	56	79	120	−0.18	3					
J. P.	—	+1.9	—	0	61	−0.58	17	+0.35	141	68								
E. G.		+1.62	—	—				+2.2	—									
Total	−2.36	+13.59	53	85	375.5	−3.23	265.5	+8.21	313	216	335	−1.71	100	303	+3.01	206	−0.7	
Aver.	−0.47	+1.36	10.6	9.44	53.64	−0.46	44.25	+1.17	62.6	36	67	−0.43	33.3	101	+1.00	68.6		

TABLE 4. *Clotting Indices Versus Time in Expired Septic Shock Patients*

Name	h_2	X_M	X_L	h_1	X_1	X_K	h_0	X_1	X_J	h_1'	X_1'	X_A	h_0'	X_0'	X_B	h_1''	X_1''
A. H.	−0.8	4	14	+2.92	—	—	+0.42	—	55	+2.24							
A. C.	−0.32	10	17	+0.54	77	37	−0.34										
H. W.	−0.58	103	18	+0.86	55	11	−0.28	155	18	+1.44	61	21	−0.44				
J. M.	—	—	—	+5.49	—	17	−0.46										
A. J.	−0.24	3	41	+3.2	—	—	+2.31	—	40	+5.49	—	—	+0.62				
E. S.	—	—	—	+5.49	—	—	+0.7	—	13	+5.5	67	5	−0.2				
S. B.	−0.04	0	6	+1.3	—	—	+0.6	—	—	—	—						
W. B.	−0.6	4	3	+0.62	5	2	−0.58	8	19	+2.24							
W. W.	−0.74	109	2	+0.20	10	28	−0.86	35	10	+1.42	40	18	−0.44				
J. K.	−0.81	27	3	+0.48	5	4	−0.8	43	15	+0.26							
C. D.	−0.68	43	16	+0.92	80	8	−0.36	13	26	+2.1	—	—	+0.26	—	19	+4.44	
V. S.	−0.6	26	5	+0.22	14	38	−0.56										
W. B.	−0.84	36	20	+2.24	—	—	+0.26	—	24	+1.84	71	25	−0.36	37	38	+2.24	44
Total	−6.35	365	145	+24.38	244	148	+0.61	254	220	+22.53	239	69	−0.56		57	+6.68	44
Aver.	−0.57	33.2	13.2	+1.88	35	18	+0.05	50.08	24	+2.5	60	17	−0.09	37	28	+3.34	44

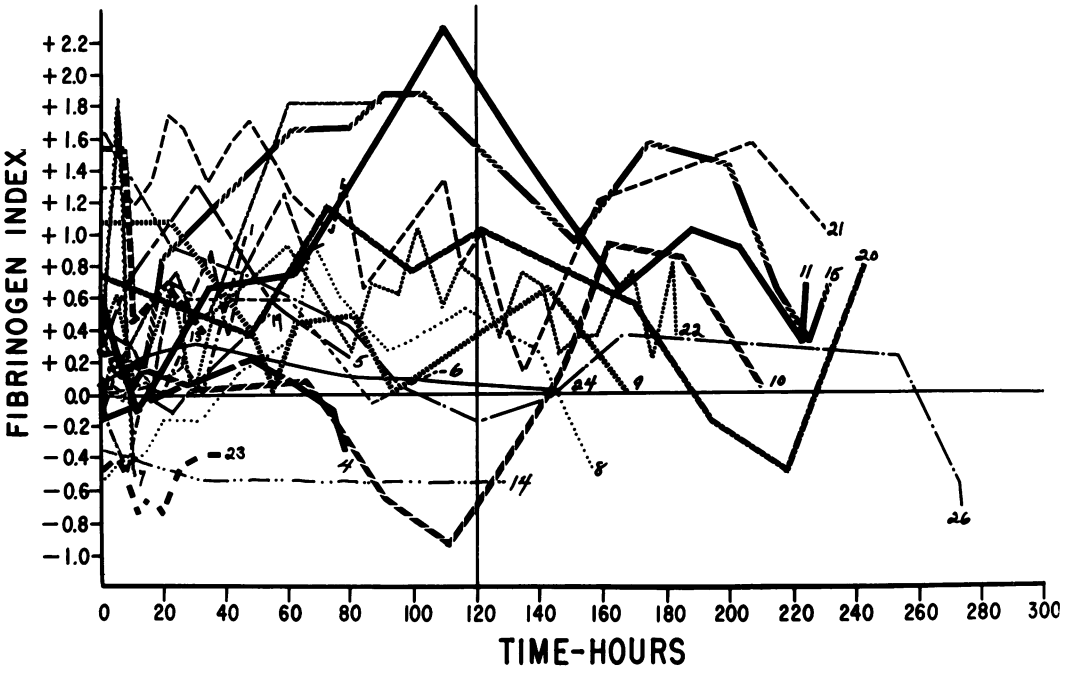

FIG. 4. Fibrinogen indices versus time in expired patients.

4) Severity of sepsis. Patients who are severely debilitated by sepsis leading to shock have minimal fibrinogen response.

5) Type of infection. Most patients had gram negative infections, predominantly Escherichia coli and Pseudomonas. There were two (H. R., M. J.) with Staphylococcus aureus septicemia who had a rapid return of fibrinogen levels to normal, in sharp contrast to the gradual return to normal observed in gram negative infections.

Fibrinogen indices of 26 non-survivors are plotted in Figure 4. It is difficult to define any specific pattern from the composite graph. Further study of these patients helped us classify them in two groups:

1) Shock complicating acute sepsis. There were 12 patients in this group, with

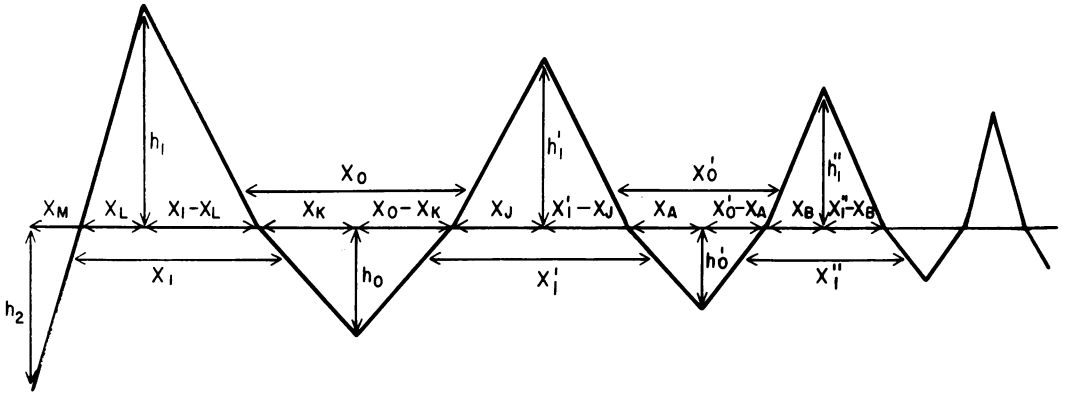

FIG. 5. Graphic illustration of the various letters shown in Tables 3 and 4.

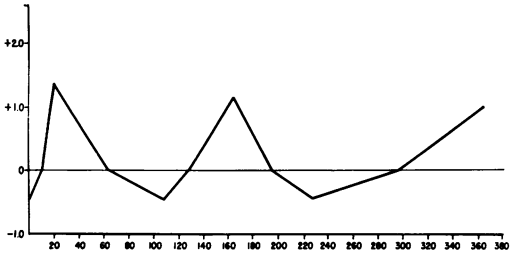

FIG. 6. Graph illustrating oscillatory behavior of clotting indices in surviving septic shock patients.

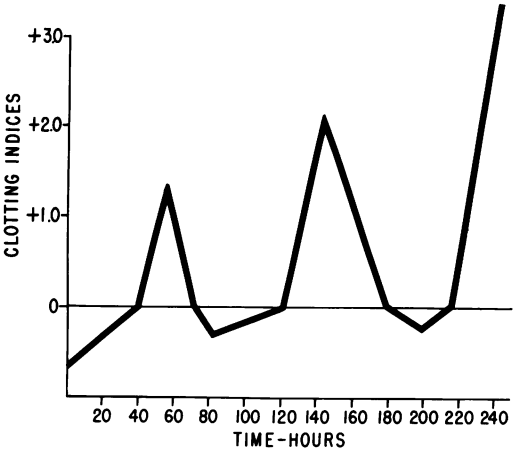

FIG. 7. Graph illustrating overall oscillatory behavior of clotting indices in 13 expired septic shock patients.

three patterns: A) In five, levels rose sharply soon after shock but this rise was temporary; within a few hours there was a terminal acute drop to normal or hypofibrinogenemic levels. B) In three the rise was gradual, and the patients died with elevated fibrinogen levels. C) In four, fibrinogen levels remained normal or low until death.

2) Shock complicating chronic sepsis (six patients). A persistently marked hyperfibrinogemic response was observed, with a tendency to return to normal or subnormal values terminally. Two patients developed septic shock terminally due to peritonitis following postoperative recovery from hemorrhagic shock. Six other patients were excluded from this study because few determinations were made during a short survival period in the Shock Unit.

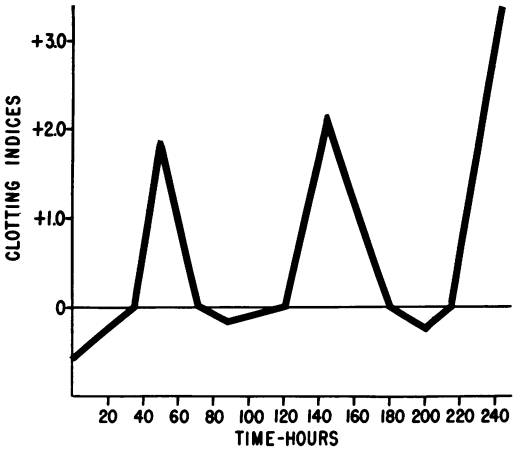

FIG. 8. Graph illustrating clotting indices in expired septic shock patients surviving the first oscillation.

From these observations, it became apparent that patients in fatal septic shock, whether complicating acute or chronic sepsis, have an initial normal or low fibrinogen index which rises to a maximum but returns terminally to normal or subnormal. To establish a common pattern for these patients who died, it was decided to calculate average values for maximal fibrinogen indices and the distances between the horizontal intercepts (Table 5, and Fig. 9). Only 15 patients provided enough data to be included in this composite graph. The average curve indicates an initially low fibrinogen level (29% below normal) which reaches normal within 12 hours. This is followed by an acute rise over a 42-hour period to a maximum averaging 118 percent above normal. A steep fall to normal occurs after 12 hours.

Discussion

Hardaway [4] demonstrated an immediate prolongation of the clotting time of dogs injected arterially with E. coli endotoxin, with gradual return to normal after 7 hours. In a similar experiment using purified E. coli lipopolysaccharide, Gans [3] found prolonged recalcification time in dogs during the first 15 minutes after endotoxin injection; subsequently, the recalcification

time became shortened, after which gradual prolongation was noted. McKay and Shapiro [5] found shortening of coagulation time in silicone 4 hours following injection of Shear's polysaccharide into the marginal vein of rabbits, and the subsequent return to normal 24 hours after injection. Carozza and Hills [2] demonstrated a trend toward hypercoagulability between the first and second hour after intravenous administration of endotoxin to rabbits.

These results appear conflicting, not only from species to species, but also from the experimental animals to humans. Hardaway [4] attributed the initial prolongation of clotting times in dogs to release of heparin, and the delayed prolongation to the deficiency of coagulating elements secondary to intravascular coagulation. Absence of the initial prolongation of clotting times in the rabbit was attributed to failure of endotoxin to activate heparin endogenously, and to the great sensitivity of rabbits to endotoxin, causing intravascular coagulation.

Our data indicate the cyclic occurrence of hypercoagulability initially after onset of septic shock, followed by hypocoagulability. These findings are similar to those reported in the dog. Interpretation of these changes in humans is difficult, since they represent the interaction of various opposing factors. The initial episode of hypercoagulability can be explained by release of catecholamines and thromboplastic materials following lysis of platelets, plasma dilution of anticoagulant inhibitors,[6] and early manifestations of activated fibrinolytic enzymes. The hypocoagulable phase is as complex to explain as the phase of hypercoagulability. Following the hypercoagulable phase, there is evidence of a decrease of clotting elements, probably due to increased utilization and inadequate production by the liver. There is also experimental evidence of increased anticoagulant and fibrinolytic activity. The latter is mediated through tissue hypoxia and increased catecholamines which activate the plasminogen system.

TABLE 5. *Average Values of Fibrinogen Indices in Fatal Septic Shock*

Name	h_1	h_2	X_1	XL	Xm
C. R.	+0.36	−0.16	13	4	2
R. H.	+0.976	−0.47		31	5
R. S.	+1.25	−0.20		56.5	2.5
A. H.	+0.2	−0.15	47	28	20
J. M.	+1.3				
N. M.	+0.58	0	78	39	
S. B.	+1.86		9.5	6	
A. J.	+0.94	−0.56	107	29.5	38.5
E. S.	+1.07				
W. W.*	+0.94	−0.95	69	19	31.5
C. D.	+2.25	−0.12		94	3.5
W. B.	+1.86	−0.03		82	1.5
H. W.	+1.16				
J. B.	+1.728				
O. K.	+1.02	−0.03		71.50	0.5
Total	+17.47	−2.66	323.5	460.5	105
Aver.	+1.16	−0.29	53.9	41.8	11.6

* Extended to cross the abscissa.

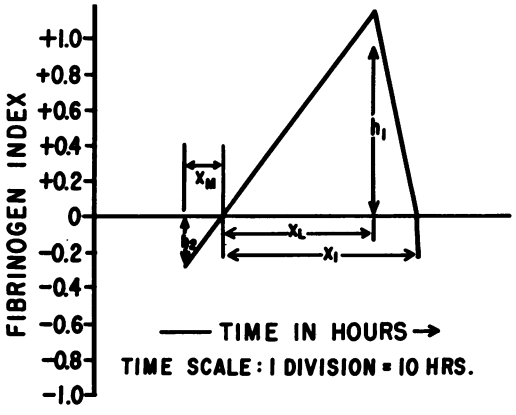

FIG. 9. Graphical representation of the fibrinogen indices in fatal septic shock.

As to experimental fibrinogen changes, McKay and Shapiro [5] demonstrated elevated fibrinogen levels 24 hours after the first injection of endotoxin, and a sharp fall 4 hours after the second injection of endotoxin in rabbits. Hardaway [4] reported a progressive fall in fibrinogen 6 hours after intra-arterial injection of E. coli endotoxin.

Response of fibrinogen to septic shock in man is complicated because it represents the balance between the response of the

body to infection and shock. Since infection preceeds the onset of shock, the body usually has responded by an increase in plasma fibrinogen. This response may be altered by various factors depending on the time of onset of shock, acuteness and severity of infection, defense mechanisms of the body, extent of liver injury, and final outcome of the septic process as modified by therapy. Initial response of fibrinogen to septic shock has been either a decrease from a previously normal level or "no response" reflected by initial normal values. Since onset and duration of shock are not well defined in relation to sepsis, it is conceivable that by the time the first blood samples are obtained, the patient is already in the second phase of fibrinogen response—marked elevation. The degree of elevation is not different in surviving or nonsurviving patients. However, the transitional behavior of fibrinogen from the second to the third phase depends on the effectiveness of therapy. In surviving patients, a sustained elevation remains elevated as long as disease is present and active. During recovery, fibrinogen concentration decreases progressively and slowly to normal within 2 to 8 weeks. In acute fatal cases, response of fibrinogen in the third phase is quite different. There is an abrupt fall to normal or subnormal within 12 hours after maximal response to septic shock. This decrease resembles experimental responses observed in dogs and rabbits by Hardaway[4] and Gans.[3]

This general response of fibrinogen is altered by the severity of infection and defense mechanisms, especially in older patients. In these patients, the fibrinogen levels decrease significantly in some and remain unaltered in others. It is difficult to relate this response to original fibrinogen levels, since these values are not available. However, such a response is a poor prognostic sign since it is seen exclusively in fatal cases.

Summary

Coagulation changes in 23 patients in septic shock were studied. A cyclic behavior of alternating hypercoagulability and hypocoagulability could be demonstrated. This cycling decreased in amplitude and frequency in surviving patients but increased in fatal cases. The mechanisms leading to such changes are discussed. The behavior of fibrinogen was studied in 42 patients with septic shock. The pattern was affected by individual variations, age, severity of sepsis, bacterial defense mechanisms, and survival or death. In general, the response was triphasic. In the first phase the level was either normal or slightly elevated. In the second phase there was a marked and sustained elevation, and in third phase a gradual return to normal in surviving patients. In fatal cases there was an abrupt fall to normal or hypofibrinogenemic levels.

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