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Coagulation and Fibrinolytic Systems during the Course of Erysipelas and Necrotizing Fasciitis and the Effect of Heparin

HANS HAMMAR,[2] BERIT SVERDRUP,[1] ERIK BORGLUND[2] and MARGARETA BLOMBÄCK[1]

[1]*Department of Blood Coagulation Disorders and* [2]*Department of Dermatology, Karolinska Sjukhuset, Karolinska Institutet, Stockholm, Sweden*

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Necrotizing fasciitis (NF) is a grave infection of the skin leading to gangrene of the integument and often having a complicated and prolonged course. Studies on blood coagulation and fibrinolysis were done in 15 patients with NF and compared with 5 cases of erysipelas (E). In both conditions local fibrin deposition occurred initially in their course, but it was quantitatively more pronounced in NF than in E. Fibrinolysis decreased and stayed low at the site of NF up to 5 months (median) after discharge from hospital. Fibrinogen and activities of several plasma serine proteinases modifying coagulation were increased during the course of both diseases and even at the follow-up. Factor XII was decreased during the first week in E but a transient drop was present in NF only on days 3 and 4. The treatment of NF consists of high doses of appropriate antibiotics instituted early in its course. A beneficial effect of 300–500 IU heparin/kg/day was suggested from this open study. The hard induration preceding the appearance of skin gangrene was inhibited, if heparin was given early in the course of NF. We conclude that the enhanced fibrin deposition and vascular occlusions in the skin are the basis for most complications present in NF. *Key words: Streptococcal skin infection; Factors of coagulation and fibrinolysis; Treatment of Necrotizing fasciitis.* (Received April 11, 1985.)

H. Hammar, Department of Dermatology, Karolinska Sjukhuset, S-10401 Stockholm 60, Sweden.

During a 2½ years' period we identified several cases of necrotizing fasciitis (NF) as described by Meleney (1) among patients referred to our department with the diagnosis erysipelas (E). The clinical symptoms and signs of necrotizing fasciitis have been evaluated recently (2) and a diagnostic score table constructed in order to differentiate NF from E (Table I).

In both E and NF the infection with group A Streptococci is important, but no data are available to link specified streptococcal toxins to the distinct syndromes of E and NF (3, 4). In the course of NF it was found that 3/8 of the initial cases had a syndrome of disseminated intravascular coagulation (5). This prompted us to investigate the systems of coagulation and fibrinolysis in these conditions. The results indicated laboratory signs of hypercoagulability in patients both with NF and E but with quantitatively more alterations in the first group (2). The follow-up and course of disease in these patients are reported here. Special emphasis is laid on the parameters of coagulation and fibrinolysis. With respect to the signs of hypercoagulability found in these patients the effect of heparin in combination with antibiotics has been evaluated.

Table I. *Diagnostic scores given to features in history, symptoms and signs in patients with erysipelas (E) and necrotizing fasciitis (NF)*

	Points
History indicating no effect of oral antibiotics	3
Signs of cerebral confusion	5
Circulatory shock	5
Temperature >38.5°C	
During 2–3 days	1
During >3 days	2
State of affected area	
Tenderness by touch	1
Tenderness without touch	5
Oedema, soft	1
Oedema indurated	5
Erythema	1
Purpura	1
Papules	1
Vesicles	1
Pustules	1
Bullae	5
Cyanosis	5
Pallor	5
Ulceration, necrosis	5
Absence of lymphangitis	2
Maximum sum	53[a]

[a] The E patients had maximum 15 points; the NF patients 18 points or more.

MATERIAL AND METHODS

Patients

Five consecutive patients with E (4 males; 23–71 years old, median 53 years) and 15 with NF (7 males; 44–87 years old, median 58 years) admitted to the Department of Dermatology in the period 1974–1977 were studied. The diagnostic scores according to Table I ranged between 19–48 (median 30) points in NF and 4–11 (median 7) points in E. They supplied material for the laboratory analyses with exception for the first 3 NF cases. Alcoholism was noted in 8 NF and in 1 E patient. Venous insufficiency of the lower legs, and earlier deep venous thrombosis or leg ulcers were noted in 3 NF and in 1 E case; cardiac decompensation in 2 NF cases; senile pruritus and an earlier fracture of the same leg in 1 case each of NF; lichen simplex, palmoplantar pustulosis, bursitis and lymphedema simplex in 1 case each of E. The arm was the site of 4 NF and in 1 E patient and the leg was the site in all the other cases. Duration of symptoms before admission ranged 1–14 days, less than 4 days in 5 NF and 4 E cases. Ischemia assessed clinically either as blanched or cyanotic induration of the skin or as a new ulcer was present in 11/15 NF and in 1/5 E patients.

The preliminary diagnoses at admission were subsequently supported by the clinical course and by routine laboratory and microbiological data. All the NF patients were treated with a combination of 9 g benzylpenicillin and 6 g cloxacillin intravenously per day. The E patients received daily 3 g each of phenoxymethylpenicillin and cloxacillin orally. The oral treatment was subsequently given to the NF patients later on when their condition improved. Heparin was given as an initial dosage of 5 000 IU i.v. and followed by a continuous i.v. glucose infusion with 300–500 IU/kg b.w. and day until the non-pitting oedema had disappeared. Subcutaneous administration was given in 3 NF cases. Six NF patients were controlled after discharge from the hospital after 1.5 to 14 (median 5) months and 4 E cases after 2–4 (median 2.5) months. Informed consent was obtained before the patient was included in the study.

Case reports

Case 1. A 56-year-old male, who had since one day at his elbow a double hand-sized red and oedematous lesion, which was centrally indurated and responded favourably on intravenously administered penicillins and heparin. Heparin was discontinued on day 6, but had to be reinstituted on day 9 when redness, oedema and induration reappeared. These signs diminished within the next few days except for induration which subsided at a slower rate. No ulceration did appear and on day 19 heparin was discontinued but the penicillins were continued orally for several weeks thereafter.

Case 2. A 62-year-old female with a preceding trauma which led to swelling, tenderness and pain of the affected arm was admitted on day 4 with high fever and a minor ulcer near the elbow. She received high doses of penicillins and the next day a diagnosis of NF was made and i.v. heparin was supplemented. During the second week a period with cerebral confusion and electrolyte abnormalities occurred and she had a transient dyspnoic state, the reason of which was not explained. The heparin administration was discontinued on day 11, when she had recovered from the clinical emergencies. At this point in time, the oedema and redness of the skin lesions had diminished and the hard induration was limited to a minor area. She felt well and was afebril. On day 14, however, the indurated area had enlarged and ulcerated. Fever reappeared. On day 19 she was referred to the Department of Plastic Surgery for excision and secondary transplantation.

Laboratory methods

Diagnostic tests included microbiological cultures, streptococcal serology and histopatology of the lesions. A streptococcal serology was taken as positive, if one or more of the following titers were present and increased during the course: antideoxyribonuclease B≥400, antistreptolysin ●≥400 and/or antihyaluronidase ≥128.

In 8 cases, skin biopsies were obtained at the time of admission, after one week and at the follow-up and used for analysis of the histopathology and of the activity of the plasminogen activator (6). They were taken from the lesion, from adjacent skin and from the healthy leg and arm. The histopathological findings were graded: acute inflammation with vascular necrosis and thrombotization (3+), extensive vascular and perivascular inflammation with patchy endothelial necrosis but without thrombotization (2+) or dermal oedema with perivascular inflammation without vascular necrosis or thrombotization (1+).

Samples for analyses of coagulation and fibrinolysis were taken immediately after establishing the diagnosis of E or NF, on day 3 or 4, after one week and after discharge at an out-patient control. Methods used were the same as detailed previously (2, 7). Cl-esterase inhibitor was determined by rocket immunoelectrophoresis. A difference between patient and reference group was tested by *t*-test if necessary after correction for unequal variances (8).

RESULTS

Observations during the clinical course

The evolution of clinical symptoms and signs after admission supported the initial diagnosis of NF in 14/15 cases. In one remaining case NF was regarded as probable (diagnostic score 22 points). This patient developed multiple bullae and ulcers in the initially blanched hard non-pitting odematous area on her leg. Her course was otherwise uneventful. The 5 E cases had their predicted course.

In 7/8 NF cases the histopathologic study of the lesions showed widespread thrombotization of dermal vessels together with a diffuse and intense inflammation (3+). In the remaining case of NF a severe dermal inflammation without thrombotization of the vessels was present (2+). In the 5 E cases the inflammatory reaction was graded as (1+).

The biopsy sites of lesions of NF and E were investigated for aerobic and anaerobic bacteria, all with a negative result except in one case, in whom group A Streptococci, E. coli and Acinetobacter calcoaceticus were retrieved. A streptococcal infection was supported from cultures taken from lesions and/or a serological reaction to streptococcal antigens in 13/15 NF cases. In 2 cases growth of Streptococci or a serological reaction towards these bacteria were not found. S. aureus was cultured in 10/15 NF cases. In 4/5 E patients cultures and/or serology for Streptococci were positive. In 2 of these cases S. aureus was also retrieved.

Table II. *Clinical outcome and effect of treatments in patients with necrotizing fasciitis*

		Resolution			Failure		
	Treatment present	No. of cases	Score[a] (mean)	Days in hospital (median)	No. of cases	Score[a] (mean)	Days in hospital (median)
Heparin ≥ 5 days (from days 0 or 1)	Yes	8	2.5	27	1	1	68
	No	2	2	14	4	0	71
Antibiotics started on day 1–4	Yes	7	2.6	24	4	0.3	68
	No	3	2	15	1	0	80

Test for effect of heparin given 5 or more days from admission: $Chi^2=5.0$; $p<0.05$.
Test for effect of early instituted antibiotics: $Chi^2=0.2$, $p<0.75$.

[a] Scores of resolution: Clinical improvement with disappearance of hard induration and decrease of oedema and redness within first week (3+), decrease in hard induration, oedema and redness leaving one or two minor areas affected (2+), decrease in inflammatory activity but leaving several areas affected (1+), inflammatory activity leading to gangrene unprovoked, course protracted (0).

The resolution of the clinical lesions and its relation to heparin treatment is illustrated by the case histories above and summarized in Table II. In totally 11 cases heparin was given in addition to antibiotics. Patients who were started on heparin at the day of admission or on the subsequent day and received heparin for at least 6 days thereafter were 9 in total. In 8/9 patients given heparin early in the course in addition to antibiotics, symptoms resolved satisfactory as indicated in Table II. An early resolution of the lesions might reverse, however, as a consequence of a too early discontinuation of the heparin treatment as presented in the two case histories. A syndrome of disseminated intravascular coagulation emerged on day 12 in one case. The marginal extension of the lesion abated in this case during heparin treatment.

Laboratory investigation

A summary is given in Fig. 1 and in Table III. Hypercoagulation was present during the first week of the diseases as evidenced by the very high levels of factor VIII and fibrinogen and the presence of circulating fibrin monomers (ethanol gelation test positive). Presence of activated thrombin was indicated by a decrease in NF of the main inhibitor of blood coagulation, antithrombin III, and the increase in both NF and E of fibrinopeptide A. Furthermore, a decrease in factor XII and prekallikrein was additional signs of factor consumption due to hypercoagulation.

The fibrinolytic system was altered (Table III). Activation was suggested from an increase in the fibrin degradation products, but consumption of plasminogen and the inhibitors $alpha_1$-antitrypsin and C1-esterase inhibitor was not evidenced as a decrease in their levels, which were unchanged or elevated. In the area of the lesion the decreased activity of the plasminogen activator indicated that fibrinolysis was low. A surprising finding was the discrepancy between the Reptilase and thrombin times, the former exhibiting a pronounced prolongation. Factor XII was decreased during the acute phase of E but only temporarily during days 3 and 4 in NF. All other components studied were changed more extensively in NF and stayed abnormal for a longer period in this condition compared to those in E.

The follow-up study after discharge was performed after about 5 months in NF and 2.5 months in E. At this time all subjects were clinically healthy.

Table III. *Summary of changes in factors of coagulation and fibrinolysis*

	Erysipelas					Necrotizing fasciitis				
	A	B	C	D	Deviation	A	B	C	D	Deviation
Screening test for hypercoagulation										
Thrombocytes	–	–	–	–	–	–	–	–	–	–
Normotest	–	–	–	–	–	–	–	–	–	–
Thrombotest	–	–	–	–	–	–	–	–	–	–
Thrombin activation										
Factor V	ND[a]	ND	ND	ND	ND	–	–	–	–	–
Factor VIII	ND	ND	ND	ND	ND	0.001*	0.001*	0.01*	–	↑
Factor XII	0.01	0.01	0.001	–	↓	–	0.01	–	–	↓
Prekallikrein	ND	ND	ND	ND	ND	0.02	0.02	–	–	↓
Fibrin formation										
Fibrinogen	0.001*	0.001*	0.001*	–	↑	0.001*	0.001*	0.001*	0.01*	↑
Fibrinopeptide A	0.05*	–	–	–	↑	0.05*	0.05*	–	–	↑
Ethanol gelation	0.001	0.001	–	–	↑	0.001	0.001	0.001	–	↑
Fibrin degradation										
Thrombin time	0.001	–*	–*	–	↑	–	0.02*	0.05*	–	↑
Reptilase time (fragments X, Y)	0.01*	0.01*	0.01*	–*	↑	0.01*	0.01*	0.01*	0.01*	↑
FDP (fragments D, E)	–	–	–	–	–	0.01	0.001	–	–	↑
Plasminogen	ND	ND	ND	ND	ND	–	–	0.01	0.05	↑
Plasminogen activator in skin lesion	0.001	ND	0.001	0.01	↓	0.001	ND	0.001	0.05[b]	↓
Inhibitors										
Antithrombin III	–	–	–	–	–	0.01	0.01	–	–	↓
α_2-Antiplasmin	–	–	–	–	–	–	–	–	0.05	↑
α_1-Antitrypsin	0.001	0.001	0.001	0.01	↑	0.001	0.001	0.001	0.01	↑
α_2-Macroglobulin	–	–	–	–	–	0.05	0.05	0.05	–	↓
C1 esterase inh.	ND	ND	ND	ND	ND	0.001	0.01	0.001	0.05	↑
Antikallikrein	ND	ND	ND	ND	ND	–	–	–	–	–

* Variance different from that of the reference.
[a] Not done. [b] One value.

Restoration of laboratory findings towards normality was almost complete in the E patients. In NF fibrinogen was still increased, plasminogen was raised above the normal level and several of the inhibitors still showed high activities. The fibrinolytic system was found abnormal at the follow-up both in NF and E since the activity of the plasminogen activator was still decreased in the earlier damaged skin.

DISCUSSION

There is no definite clue to the reason, why a flegmonous infection leads to NF. A predisposing factor may be alcoholism or old age. Both are well represented in the patient

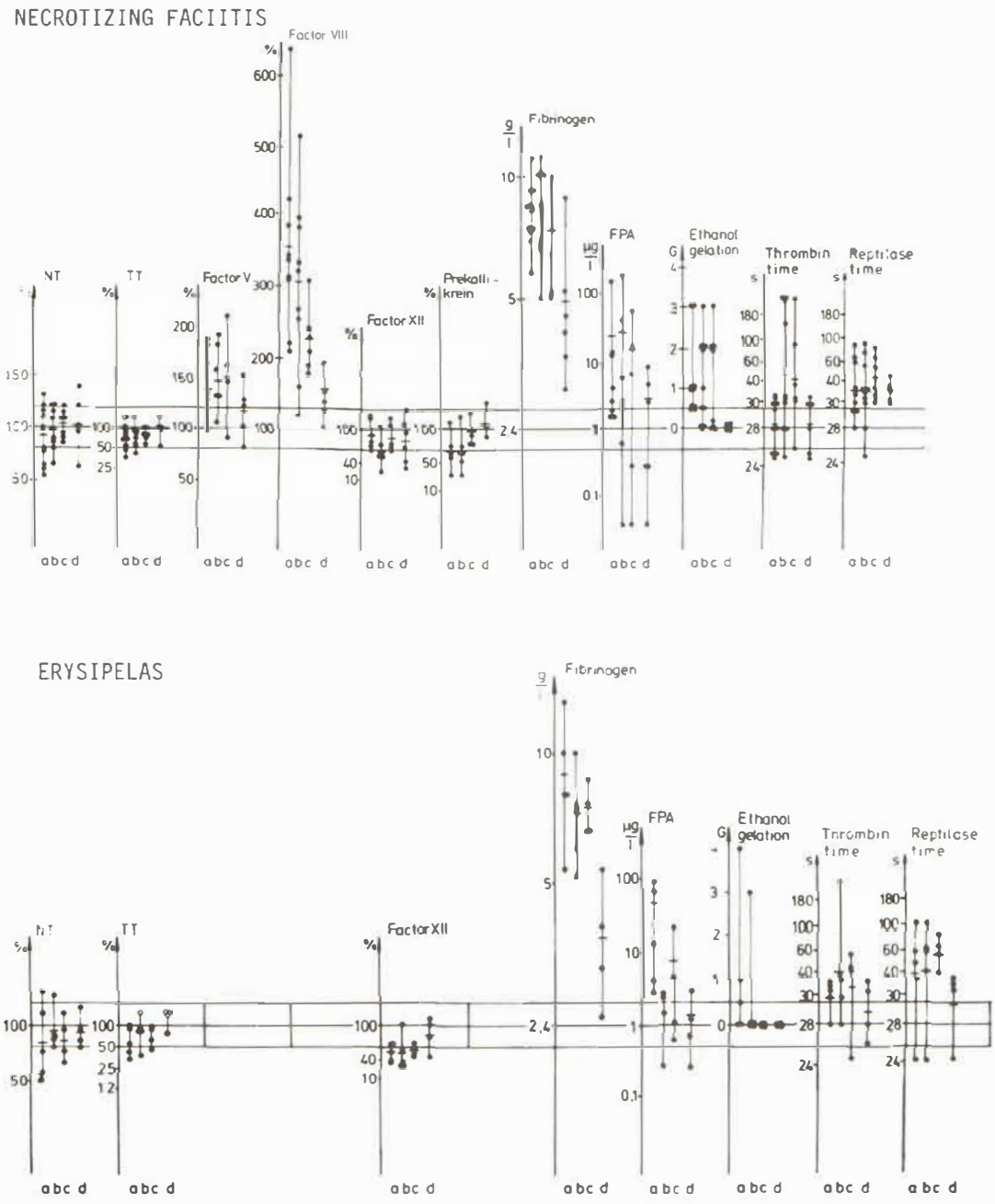

Fig. 1. Coagulation and fibrinolysis in erysipelas and necrotizing fasciitis. All values are referred to the same scale with the standard deviation as base. The mean ± SD are shown as parallel lines. Logarithmic transforms were done for fibrinogen, fibrinopeptide A (FPA), fibrin degradation products (FDP) and plasminogen activator using the ratio $\ln\{X_p/\bar{x}_c\} \div \ln\{(\bar{x}_c + SD_c)/\bar{x}\}$. For thrombin and Reptilase time the ratio $((X_p - X_c)/X_c) \div SD_c/\bar{x}_c$ was used where X are individual values, the subscript p for patient and c for control and $\bar{x}$ and SD the mean and its standard deviation. The third root of the ratio was taken to encompass variation. The time of sampling is indicated (*a*) at admission, (*b*) on 3rd–4th day, (*c*) on 7th day and (*d*) at follow-up. The attached numbers (1–3) for plasminogen activator indicate sampling (1) in the lesion, (2) about 1 cm outside the lesion and (3) in a healthy area on contralateral extremity. The values are given in arbitrary enzyme units (e.u.). Ethanol gelation is given by the grades G++++ through zero.

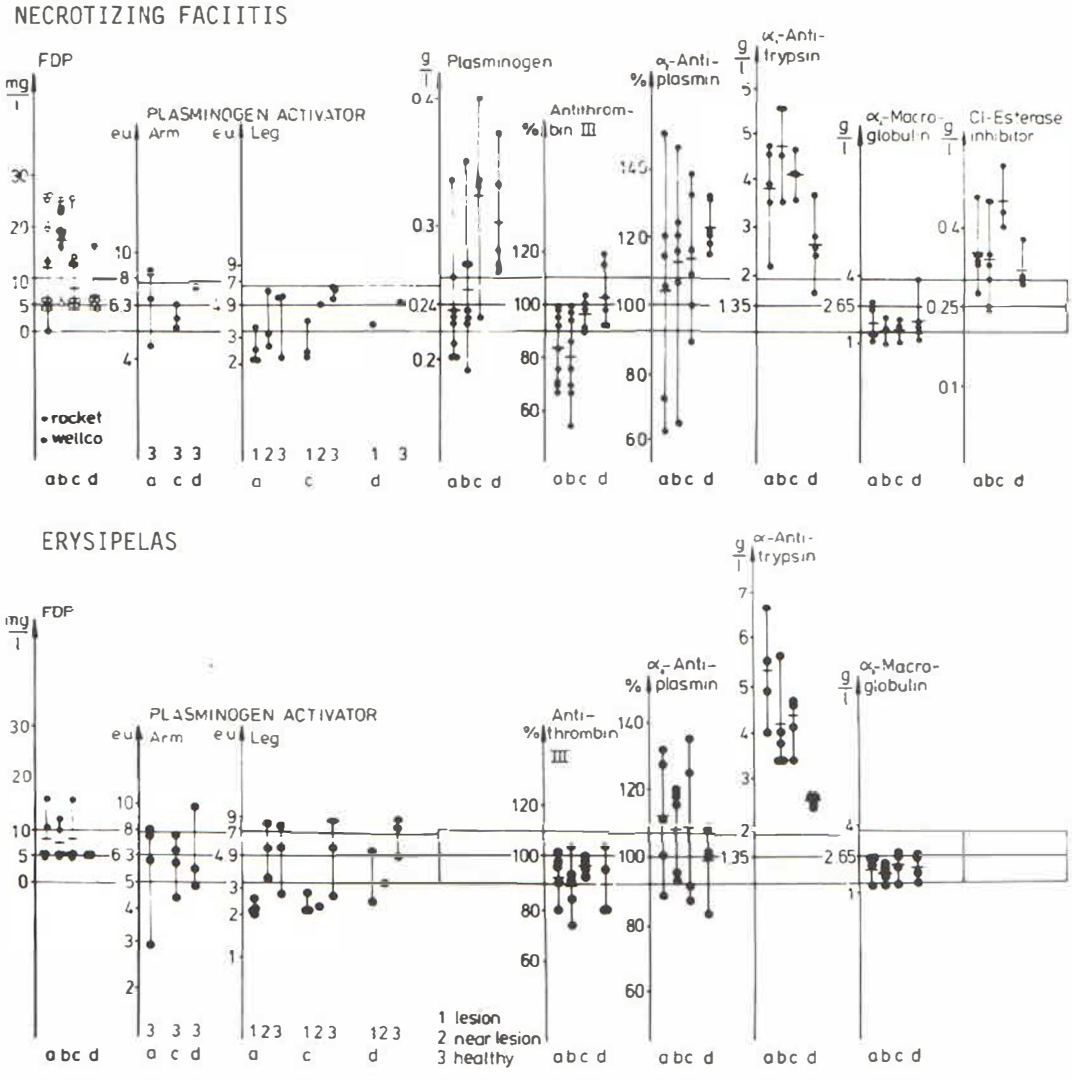

Fig. 1. (Continued)

A significant change in the mean level in disease from its reference is indicated by the corresponding p-value; (arrow up) indicates an increased mean level compared with the reference and (arrow down) a decreased level. A (−) indicates that the level does not differ in the comparison. Significances were obtained from t-tests according to Dunnett (14) or from Chi^2-test (ethanol gelation). A = time at admission, B = day 3–4, C = day 7, D = time at follow-up.

material of NF. However, these groups of patients are represented among E patients as well (4). An important sign in the NF infection is the hypercoagulability syndrome evidenced as widespread microthromboses in the skin (5). Signs of hypercoagulability are present in E but to a less severe degree than in NF and there is evidence for a disturbed homeostasis of coagulation and fibrinolysis especially in NF (Table III).

The course of the disease in NF patients who were early treated with high doses of appropriate antibiotics did not differ from that in patients, who came under medical

attention at a later occasion (Table II). The addition of heparin to the treatment program seemed beneficial on outcome, as shown in Table II. A withdrawal of heparin, if done too early, might promote the reappearance of the hard pale non-pitting oedema. This may lead to skin necrosis later on, as was seen in the case reports and in one patient earlier reported (5). Our results also indicate that heparin is not necessary in every case, especially if the appointed score total is low, as seen in 2 of the cases. Surgical revision of necrotic skin (9) as done in some of our earlier cases became unnecessary as a consequence of heparin treatment in more recent patients. A controlled study on the effect of heparin was initiated but was abandoned, since new NF cases subsided.

Fibrin formation decreased in patients given heparin as evidenced by a normalization in levels of fibrinopeptide A. Degradation of fibrin(ogen) increased as shown by the occurrence of fragments D and E after the 4th day. These laboratory findings displayed heparin effects that are important in order to alter the course of the disorder.

Infection is often followed by increased coagulation (10, 11, 12). At the same time as coagulation is activated, several additional systems as the kallikrein and the fibrinolytic systems are activated as well. In the acute stages this may lead to consumption of coagulation components such as factors V and VIII, fibrinogen and antithrombin III. The fibrinolytic system is modified by consumption of plasminogen and alpha$_2$-antiplasmin (11).

In our patients factor VIII and fibrinogen were increased substantially and antithrombin III decreased (Table III). Fibrinolysis was low as shown by the decreased plasminogen activation in lesioned skin. The normal levels of plasminogen and alpha$_2$-antiplasmin indicated a low consumption of these factors. The discrepancy, that was observed between hypercoagulation and fibrinolysis, differs from the syndrome of disseminated intravascular coagulation, in which both pathways are generally activated (10). In several of the disorders where hypercoagulation is present, this may not necessarily have to manifest itself as an acute syndrome. Contrary, a chronic type of hypercoagulation syndrome is also described (11) which fits well to the presented data.

The presence of increased amounts of degradation products of fibrin (fragments X and Y) is indirectly measured as a prolongation of the Reptilase time. This occurred throughout the course in NF and during the acute phase of E. A disturbed liver function secondary to alcoholism or infection is a known reason for this change (13). However, this was not probable since liver enzymes and coagulation factors, synthesized by the liver, did not show low levels. An abnormal fibrinogen released from the liver may be a factor inhibiting Reptilase. This was not the case since a radioimmunoassay of the material for abnormal fibrinogens was negative (B. Kudryk, personal communication). Therefore, we surmise that the prolonged Reptilase time indicated increased fibrin degradation.

The changes in the levels of C1-esterase inhibitor and antikallikrein were different although their activities are generally considered to follow each other. The former was measured to give protein concentration and the latter functional activity. The problem of this difference could be resolved assuming a lack in functional capacity of the C1-esterase inhibitor.

The acute phase reactants, fibrinogen, alpha$_1$-antitrypsin, and factor VIII were increased. These are increased in other situations besides infection as in high age, malignancy and diabetes (12). However, the relationship among these factors may vary due to the underlying condition. In conclusion, the data presented in our patients imply an imbalance in the formation and consumption of fibrin.

At the time of the follow-up fibrinogen averaged 5 g/l in NF and 3.8 g/l in E. Concomitantly, high levels of alpha$_2$-antiplasmin and alpha$_1$-antitrypsin suggested that the elicited reaction especially by NF was still going on. The inhibitors mentioned can be considered

as inhibitors of fibrinolysis. It was also shown that the patients had a decreased activation of plasminogen at the site of the prior skin infection. The combination of low fibrinolysis months after clinical recovery together with enhanced availability of fibrinogen may set the stage for a relapse of the disease as observed in 3 of our cases. Anticoagulant therapy during the months after recovery of NF or severe E may therefore be a point of consideration.

An observation from the study of E was the low levels of factor XII throughout the first week of its course contrasted with a transient drop on days 3 and 4 in NF. Activated factor XII controls several pathways. It initiates coagulation, activates complement and kinins as well as promotes fibrinolysis. Possibly, the consumption of factor XII in E is a benevolent sign indicating that the inflammatory response and the concomitant tissue destruction turn to a less severe course. At present, it is not known, if factor XII masters the scheme in such a way that a harmful process becomes limited in its extent upon its activation and consumption.

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