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Purpura Fulminans

Report of a case successfully treated with heparin and hydrocortisone
Review of 50 cases from the literature

PETER F. HJORT, SAMUEL I. RAPAPORT
AND LEIF JØRGENSEN

VII Department (Medicine), Pediatric Department, and Department of Pathology, Ullevål Hospital, Oslo, Norway
and
Department of Medicine, University of Southern California School of Medicine, Los Angeles, California

Severe purpura fulminans (p.f.) developed in a three year old boy four days after an attack of diarrhea. Streptococci were found in his throat. He went into shock following massive bleeding into the skin. Haemostatic studies revealed moderate thrombocytopenia and profound clotting defects compatible with intravascular coagulation. Skin biopsies disclosed thrombosis of small blood vessels. He improved dramatically after treatment with heparin and hydrocortisone; his clotting factors quickly returned to normal. Following extensive skin grafting, he made a complete recovery.

Fifty selected cases of p.f. have been reviewed. P.f. appears to occur only in children, usually 1–4 weeks after a benign infection, such as scarlatina or varicella. The clinical findings have been described in detail. All patients appear to have one or more episodes of intravascular coagulation resulting in secondary haemostatic defects.

A concept of pathogenesis has been presented in terms of (1) preparation of the skin by mechanism as yet unknown, followed by (2) an episode of acute intravascular coagulation which deposits thrombi in small blood vessels of the prepared skin[*] ~~by mechanisms as yet unknown, followed by (2) an episode of acute intravascular coagulation which deposits thrombi in small blood vessels of the prepared skin~~ ~~have been discussed~~. Therapy should be based upon heparin to stop intravascular clotting and adrenal steroids to modify possible antigen-antibody reactions.

Purpura fulminans is a rare, unexpected, and sudden catastrophe characterized by rapid, massive bleeding into the skin. Usually, the patient either dies

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[*] Relations between p.f. and the Arthus and local Shwartzman reactions have been discussed.

within a few days or survives with the loss of large areas of necrotic tissue. Recovery without loss of tissue is rare. Serious clotting abnormalities have been demonstrated in several patients, but the pathogenesis of the disorder still defies explanation.

This is a report of a patient with purpura fulminans who exhibited marked clotting abnormalities compatible with intravascular coagulation. These abnormalities rapidly disappeared during treatment with large doses of heparin and hydrocortisone, and the patient made an unexpected recovery. Since most of the information about this disorder is found in single case reports, we have reviewed 50 cases in the literature in order to form a composite picture of this rare and difficult disease. On the basis of this analysis we have compared purpura fulminans with a group of related but different purpuras and have attempted to evaluate its possible pathogenic mechanisms.

CASE REPORT

R.S., a 3 year old boy, is the second of 3 children. His father had occasional attacks of urticaria; there was no other disease in the family.

The boy had been well all of his life except for mild scarlatina the previous summer. On January 10, 1962, the whole family, including the boy, was taken ill with diarrhea; the boy also vomited a few times. No blood was noted in stools or vomitus, and he was not ill enough to stay in bed. On January 12 he complained of a mild sore throat and of pain in his legs, but he played as usual. The rest of the family had recovered completely.

On January 14, the parents noticed a peculiar "rash" on the outer aspect of both of his thighs. He was afebrile and did not appear otherwise ill. By the next day the "rash" was larger and purple in color. He was drowsy, complained of pain in his legs, and refused to stand or walk.

When admitted to the Pediatric Department of Ullevål hospital on the afternoon of January 15, he appeared well developed and well nourished. His temperature was 37.2° C, and he did not look critically ill. A walnut-sized lymph node was felt under the left jaw, and several smaller nodes were felt in the neck and groin. The liver and spleen were not palpated. He was not icteric and had no petechiae. However, there were symmetrical, confluent areas of bleeding into the skin over the lateral surface of the thighs and the dorsal surface of the calves. The lesions on the thighs covered an area of the size of a hand; those on the calves were about the size of a silver dollar. In both areas, the skin was swollen, blue-black in the center and purple towards the periphery. The lesions were sharply demarcated from the normal skin by a red border measuring about 1 cm (see Figure 1).

The Hgb. was 11.6 g per cent; slight anisocytosis and polychromatophilia was noted, and about 1 nucleated red cell per 100 white blood cells was seen. The white blood cell count was 29,500 per μl with a differential count of 79 per cent segmented neutrophils, 4 per cent band forms, 13 per cent lymphocytes, and 4 per cent monocytes. The neutrophils exhibited heavy toxic granulation. A urinalysis was normal. Sedimentation rate was 2 mm per hour.

A throat culture on admission yielded a heavy growth of beta-hemolytic streptococci

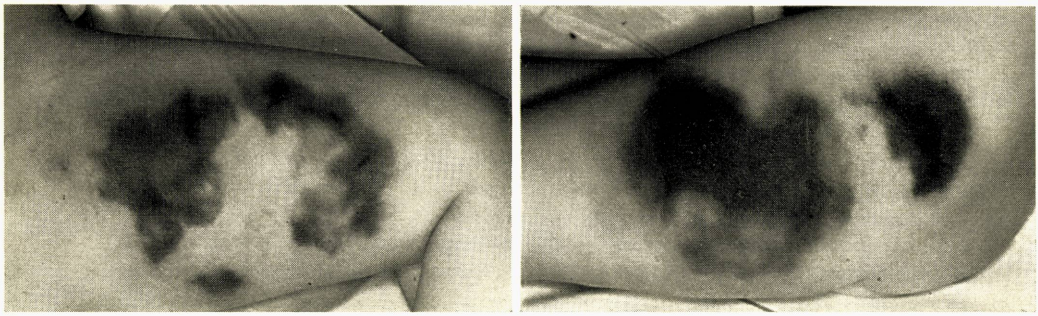

Figure 1. Appearance of the cutaneous haemorrhages in both thighs on Jan. 16, two days after the onset of bleeding.

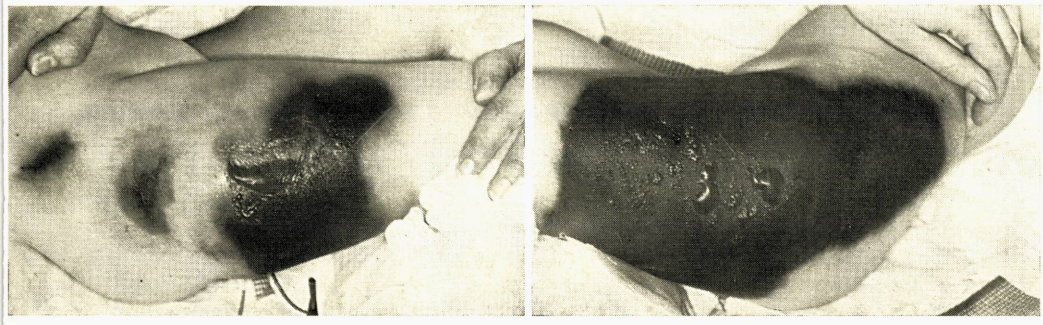

Figure 2. Appearance of the cutaneous haemorrhages on Jan. 19, after treatment with heparin and hydrocortisone for 12 hours.

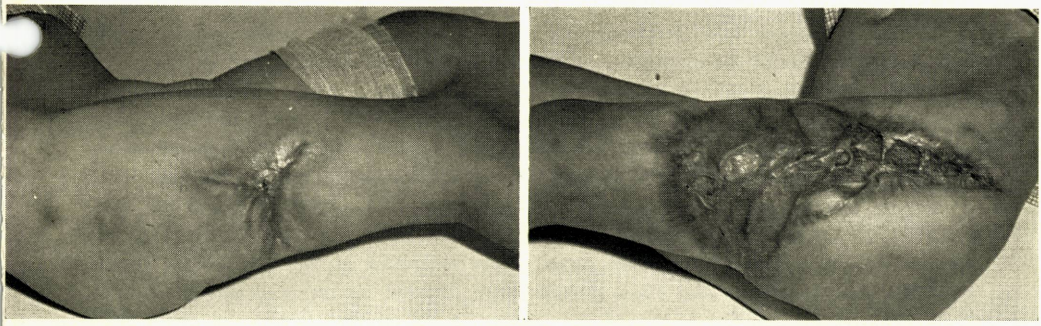

Figure 3. Appearance of the scars on Aug. 7, about seven months after the onset of bleeding.

and also Hemophilus influenzae. Two blood cultures were negative; a stool culture showed normal bacterial flora. The antistreptolysin 0 titer was 110 units. The serum protein concentration was 5.7 g per cent, and serum protein electrophoresis revealed: albumin 48 per cent, α_1-globulin 7 per cent, α_2-globulin 12 per cent, β-globulin 13 per cent, and γ-globulin 21 per cent.

The admitting clotting studies were: bleeding time (Duke method) 5½ minutes, clotting time (glass) 4 minutes, P-P value 100 per cent, platelet count 100,00 per μl.

Treatment was started with an oral sulfonamide preparation. For the following two days his general condition remained good, although his temperature rose to 38.2° C, and the haemorrhagic areas increased slightly. However, in the early morning of January 18, six days after the onset of pain in his legs and four days after the first evidence of bleeding, he was found in deep shock with enormous haemorrhages in the legs and buttocks, spreading to the lower part of the back and abdomen. The central areas in the thighs were black and blistered. The Hgb. had dropped to 8 g per cent. Blood transfusions were given. After 500 ml, the Hgb. was 6.7 g per cent, and the bleeding had progressed. After an additional 500 ml, the Hgb. increased to 11.5 g per cent and he slowly came out of shock. Thus, he appeared to have lost into his tissues an amount of blood equivalent to his entire blood volume.

That afternoon he was desperately ill. He vomited small amounts of fresh blood. No petechiae were noted, and the mucous membranes appeared normal. The white blood cell count had increased to 46,800 per μl with 68 per cent segmented neutrophils, 10 per cent band forms, 2 per cent metamyelocytes, 2 per cent eosinophils, 14 per cent lymphocytes, and 4 per cent monocytes. A bone marrow smear was very cellular with an M:E ratio of about 5:1. Increased numbers of myelocytes and metamyelocytes and a moderate eosinophilia were noted. Plasma cells were not increased. Megakaryocytes were seen in normal numbers. A urinalysis was normal.

The platelet count had dropped to 54,000 per μl. The bleeding time (Ivy method) was greater than 30 minutes. Coagulation studies revealed abnormalities compatible with intravascular coagulation (see Table I). Therefore, treatment with heparin was begun with an initial dose of 5,000 I.U. intravenously. This was followed by 1 g of fibrinogen, 200 mg of hydrocortisone, and 250 mg of chloramphenicol. He improved dramatically during the night. By the next morning, he was alert, the bleeding had not progressed (see Figure 2), and the clotting factors, with the exception of Factor VIII which was 38 per cent, had returned to normal. (Unfortunately, Factor VIII was not assayed on the first day).

Treatment with heparin, 5,000 I.U. four times daily, was continued for 12 days; anticoagulant therapy was then continued for an additional six weeks with oral phenylindanedione. Serial measurements of clotting factors and platelets during this period are summarized in Figure 4. Heparin in the blood samples was neutralized by Polybrene® according to the technique of Hasselbach & Hjort (1960) before the assays were carried out. It is important to note that evidence suggestive of continuing intravascular coagulation was still demonstrable during the first eight days of heparin therapy.

Steroid therapy with prednisone was continued for one month. The necrotic areas became infected and slowly demarcated. Thirty days after the onset of bleeding, the lesions were debrided, leaving very large ulcers extending to the fascia and, on the buttocks, through the fascia. These defects were covered by repeated skin grafts (Dr. C. F. Jenssen), and all finally healed (see Figure 3). At no time during the acute phase or later was there evidence of renal damage, abdominal cramps, joint pains, urticaria, or peripheral edema.

TABLE I

Tests for haemostatic functions on the afternoon of Jan. 18

	Normal ⇌	Patient
Duke bleeding time (min.)	> 30	1–5
Platelets per μl	54,000	138,000–421,000
Fibrinogen-titer	1/50	≧ 1/100
Fibrinogen (mg per cent)	113	150–400
Thrombin time (sec.)	18.2	17–20
Quick time (sec.)	20.1	13–16
Cephalin time (sec.)	63.4	57–64
Factor II & X (per cent)	68	80–120
Factor V (per cent)	35	80–120
Factor VII (per cent)	70	80–120
P & P test (per cent)	60	80–120
Fibrinolysis	No	

Note that blood for these tests was drawn after the transfusion of 1,000 ml of citrated blood. (See Borchgrevink *et al.* 1963 for references to methods. The fibrinogen-titer is the result of a rapid test for fibrinogen, see Hjort 1956).

He left the hospital in good health after four months. Two weeks later he had an uncomplicated attack of rubella. When examined two years later, he was completely well and not incapacitated by his scars.

Biopsies were taken from necrotic skin, subcutaneous tissue, and underlying muscle 30 days after the onset of bleeding. The muscle tissue showed only edema, atrophy, and occasional necrotic areas. Skin and subcutaneous tissue showed massive bleeding, necrosis, and a secondary inflammatory and reparative reaction with lymphocytes, plasma cells, macrophages, and fibroblasts, but only a few eosinophils. There were two striking findings, one positive and one negative. The positive finding was widespread thrombosis of the small vessels, especially capillaries and venules. The thrombi usually consisted of fibrin threads and clumps (Figures 5a and 5b); platelet aggregates were seen in only a few vessels (Figure 5c). Some of the thrombi displayed obvious signs of fibrinolysis: the fibrin strands were fragmented, the clumps gnawed and frayed (Figure 5b), as described by Jørgensen (1964). Organization with invasion of macrophages into some thrombi was noticed (Figure 5d). It was difficult to evaluate the age of the thrombi, but they probably dated back to the period of active bleeding. The negative finding was the absence of a primary vascular reaction. Although necrotic vessels were seen in areas of diffuse necrosis, thrombi were found in normal-appearing vessels in areas with little or no tissue necrosis. The most reasonable interpretation of these findings, therefore, is that fibrin and platelet aggregates had been deposited in small vessels without histological evidence of primary inflammation of the vessel wall, probably as a result of intravascular coagulation.

Summary: A three year old boy began to bleed into his skin four days after a mild attack of diarrhea. Beta hemolytic streptococci were grown from his throat. The bleeding

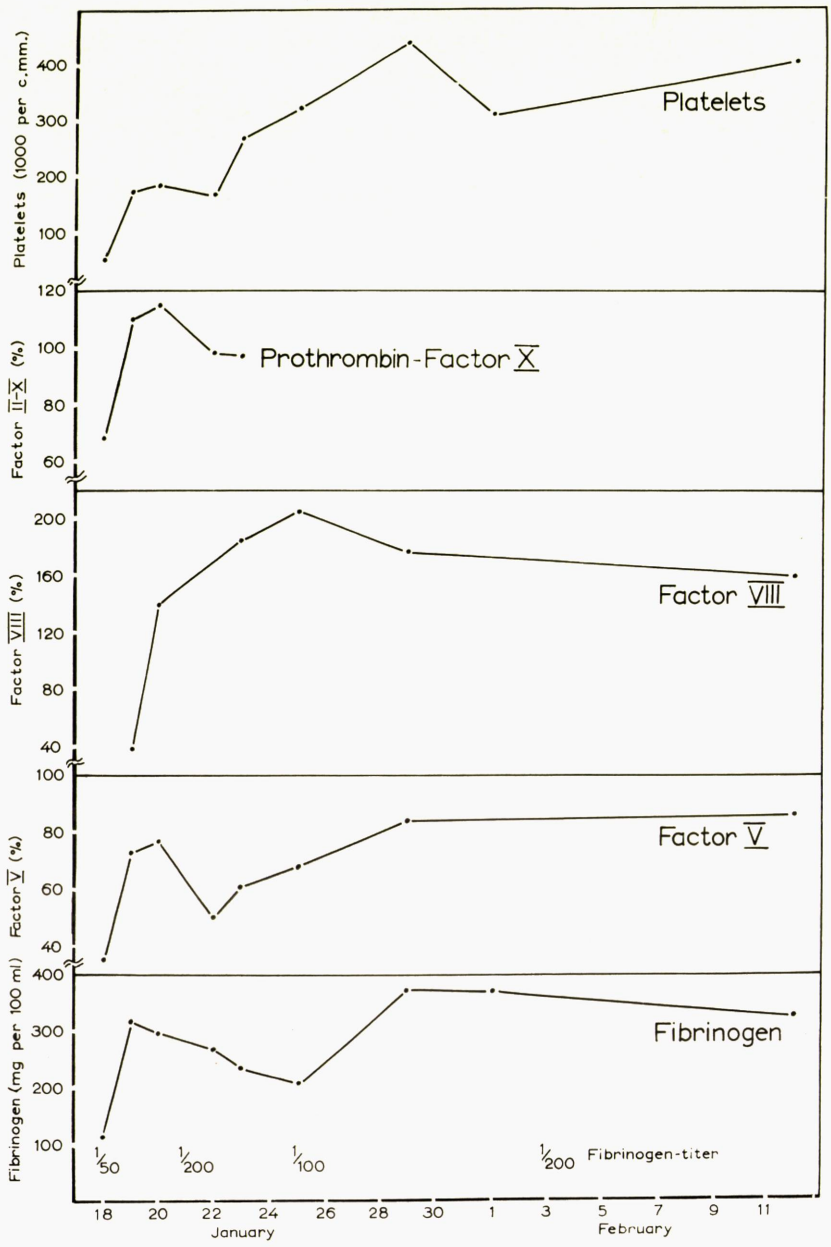

Figure 4. *Serial platelet counts and assays of some clotting factors.* Heparin was given from Jan. 18 to Jan. 29. During this period, heparin was neutralized in the blood samples by the method of Hasselbach & Hjort (1960) before the clotting factors were measured. Phenylindanedione was started on Jan. 26. (Factor VIII was kindly assayed by Dr. O. Egeberg).

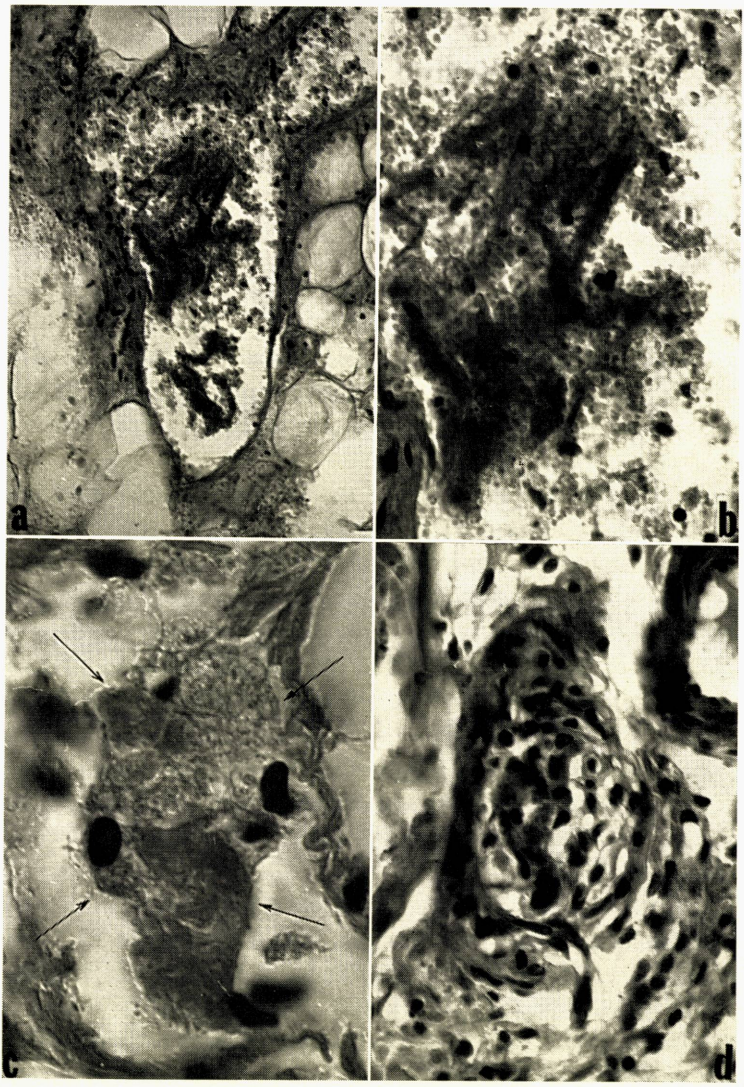

Figure 5. *Biopsies from the left thigh taken 30 days after the onset of bleeding (Lendrum's stain for fibrin).*

(a) Thin-walled vein with intact wall and no leukocytic infiltration. Clumps and threads of fibrin in the lumen. x 120.
(b) Detail of Figure 5a, showing fragmentation and frayed borders of fibrin clumps and threads. Red cells in fibrin mesh. x 300.
(c) Thrombosed venule from the area just outside of the necrosis. The thrombus consists of platelet aggregates (top) and fibrin clumps (bottom). x 800.
(d) Venule with organizing thrombus. Clumps of fibrin in the center, surrounded by macrophages and prolipherating endothelial cells. x 300.

progressed slowly at first, but after four days he went into shock secondary to sudden massive subcutaneous haemorrhages. Clotting tests at that time were compatible with intravascular coagulation. Treatment with heparin and hydrocortisone was followed by dramatic improvement: the bleeding stopped, the clotting tests became normal, and he recovered slowly but completely.

REVIEW OF THE LITERATURE

Henoch, in 1887, gave the name purpura fulminans (p.f.) to a "particular type" of purpura characterized by (1) bleeding into the skin which progressed with enormous rapidity, (2) the formation of bullae in the areas of haemorrhage, (3) the absence of bleeding from mucous membranes, (4) a rapid progression to death, and (5) negative autopsy findings except for evidence of anaemia.

Probably less than 200 cases similar to Henoch's patients have been published to date. After screening about 100 case reports, we have concluded that p.f. is a characteristic disease which should be *defined* as follows: (1) It is a disease of children. (2) It is preceded by a benign disorder, usually an infection. (3) After a variable but definite latent period, bleeding into the skin begins, spreads rapidly, and often progresses in waves. The bleeding results in severe anaemia. (4) If the child survives long enough, the more extensive lesions undergo necrosis. – With more information, two further criteria will probably be established. (5) Coagulation abnormalities compatible with intravascular clotting are demonstrable. (6) Histopathologic examination of the affected sites reveals widespread thrombosis of capillaries and venules.

Many cases called p.f. in the literature have been instances of some other type of fulminant purpura. For example, only a few of the 55 patients collected by Elliott (1909) appear to have had p.f. It is meaningless, therefore, to collect all cases called p.f. into a single group. For this review we have selected 50 cases (references 1–44) satisfying the first 4 of our criteria. Although admittedly open to the bias of selection, this procedure allows meaningful data to be collected about a disease which we, like Henoch, believe is a "particular type" of purpura.

We shall present this material in the following order: (1) a summary of the factual information contained in the 50 case reports; (2) a brief consideration of other forms of purpura related to p.f.; (3) a discussion of the pathogenesis of p.f.; and (4) recommendations for the therapy of p.f.

Summary of factual information

1. *Age.* The median age was 4 years and 11 months (range 0–14 years). The disease was present in one infant at birth, apparently starting *in utero* (20).

2. *Sex.* There were 25 boys and 25 girls.

3. *Familial incidence.* There are only two reports of more than one case in a family. Gibson & Hobson (1932) described p.f. after scarlet fever in a previously healthy brother and sister. van der Horst's (1962) patient died of p.f. eight days after birth; his brother had died of p.f. nine days after birth three years previously. Frequently, siblings have shared the "preparatory disease", but only one has developed p.f. In one such instance the patient had an identical twin (40).

4. *Previous health.* With three exceptions, the children were in good health prior to the "preparatory disease". One patient had empyema (35), one had congenital syphilis (25), and one had precocious physical and genital development (41).

5. *Season.* Twenty-two children were seen during the first quarter of the year, 14 during the second, two during the third, and eight during the fourth (no information in four cases). This reflects the increased incidence of infection in winter and spring.

6. *"Preparatory disease".* P.f. is nearly always preceded by another disease.

(a) *Scarlatina* is the commonest "preparatory disease"; it preceded p.f. in 23 of the 50 patients in this series. The scarlatina was mild in all cases, but at least nine patients either had a prolonged course or relapsed with angina and fever before the onset of p.f. Streptococci were found in the throat of seven patients during the course of the p.f. Two patients also had diptheria and had received serum therapy (21, 24).

P.f. is a rare complication of scarlatina: 1 in 23,000 cases (12), 3 in 67,000 cases (21), 3 in 10,547 cases (24), and none in nearly 40,000 cases (37). The exception is a report (14) of two siblings with p.f. amongst a total of seven patients with scarlet fever.

The interval between the onset of scarlatina and the onset of p.f. was 5–87 days for the group as a whole, but 14–28 days for 19 of the 23 patients. The median intervals was 19 days. Four patients had unusual "incubation periods" of 5 days (42), 50 days (3), 57 days (12), and 87 days (24). The duration of the interval was not related to the age of the child.

(b) *Infection, probably streptococcic,* preceded p.f. in 13 patients: a sore throat or upper respiratory infection in eight (9, 15, 16, 17, 28, 29, 33, 34), otitis in one (2), diarrhea with a severe diaper rash in one (18), pneumonia

in one (19), infected eczema in one (25), and empyema in one (35). In only five of these patients were streptococci actually demonstrated (2, 18, 25, 29, 35). One patient had recently recovered from measles (17). The interval between the onset of infection and the onset of p.f. was 1–21 days with a median of 7 days. The very short intervals were in small children in whom the infection may have been overlooked initially.

(c) *Varicella* preceded p.f. in nine children (1, 9, 23, 32, 33, 37, 40, 41, 44). It was mild or moderate in all cases without evidence of secondary infection of the skin. The latent interval was 4–10 days, with a median of 7 days.

(d) *Miscellaneous causes* included measles (27), a second injection of diphtheria anti-serum (4), and vaccination against smallpox (22) in one case each.

(e) *No preparatory disorder* could be elucidated in two patients (16, 20).

7. *Trigger events.* An added local insult to the skin could *not* be implicated as a trigger mechanism in the great majority of cases. In three children (9, 33), trauma or subcutaneous injections may have been contributory factors, but the evidence is not convincing. One patient started to bleed while taking a hot bath (10).

8. The *clinical picture* is characterized by the combination of rapidly increasing bleeding into the skin and severe constitutional findings.

(a) *Sites of skin bleeding.* The lesions are fairly symmetrical and show a predilection for the face, buttocks, lower back, lateral surface of the thighs, dorsal surface of the calves, ankles, extensor surface of the elbows, and the back of the hands and feet. The bleeding does not follow segmental dermatomes; it frequently circles an extremity. The fingers and toes may be only moderately involved. No area is immune, but the chest, neck and scalp are rarely involved.

(b) *Type of skin bleeding.* The lesions always involve large areas. Typically, the uninvolved areas of skin appear normal, although scattered petechiae have been seen in some patients (5, 11, 12, 14, 34, 43). The affected areas are purplish-black, swollen, firm and sometimes hard, painful, and tender. They are surrounded by a narrow red border, which sharply demarcates the lesions from normal skin. Bullae are common. The arterial pulses are normal initially, but may disappear subsequently due to pressure or late thrombosis (1, 2, 17). If the patient survives long enough, the lesions develop a hard shell which is gradually sloughed, leaving deep punched-out ulcers.

(c) *Mucous membrane bleeding.* As emphasized by Henoch (1887), petechial bleeding in mucous membranes is rare. However, some patients do bleed from mucosal surfaces, either because of local lesions or because of a generalized bleeding tendency secondary to haemostatic defects (see below). In this series of patients, bleeding occurred from the conjunctiva in four,

from the nose in five, from the gums in five, in the vomitus in four, and in the stools in six patients. Twelve patients had gross haematuria.

(d) *Renal findings.* None of the 12 patients with gross haematuria had red cell casts, although four had proteinuria and granular casts. This suggests that the bleeding does not arise from glomerular lesions. An additional seven patients had proteinuria without haematuria. Two patients developed anuria and were shown at autopsy to have bilateral renal cortical necrosis (32, 33).

(e) *Constitutional manifestations* are usually severe. Fever may or may not be found. Shock is common. The patients are extremely pale and appear "washed out".

9. *Haematologic findings.*

(a) *Haemoglobin and red cells.* Haemoglobin levels fall rapidly as blood is lost into the tissues. Nucleated red cells may be found on blood smears. The Coombs test has been negative. Only one patient had evidence of haemolysis (24), and one patient had a red cell agglutinin (14).

(b) *White blood cells* were counted on admission in 41 of the 50 patients. Only two patients had counts below 10,000 per μl (4, 5). The median was 23,000 per μl; the range, 4,700–65,400 per μl. A marked shift to the left with heavy toxic granulation was seen in all instances except one (27). Eosinophils were low or absent, except in two patients who had a moderate eosinophilia (31, 42). The white blood cell count frequently continued to rise as the disease progressed.

(c) *The bone marrow* was examined in nine patients. The findings were non-specific: a cellular marrow with toxic changes in granulocytopoiesis, an increase in plasma cells and eosinophils, and adequate numbers of megakaryocytes. The increase in plasma cells was stressed by Gasser & Muralt (1950).

(d) *Serum protein* studies have been negative except in one patient with a cryoglobulin (17) and two patients with increased levels of gammaglobulins (13, 24).

10. *Bacteriology.* Blood cultures were sterile in 15 patients; streptococci were grown in two patients (18, 25) and streptococci plus staphylococci in an additional patient (29). The contents of the bullae were sterile in five patients and probably sterile in a sixth patient (28). Post mortem cultures grew streptococci in three patients (2, 35, 39) and staphylococci plus Candida in one patient (33). Thus, bacteriologic studies do not support the suggestion (18) that p.f. is secondary to a septicaemia.

11. *Haemostasis.* Widely different findings have been reported, and they can be understood only if one appreciates that these children undergo episodes of intravascular coagulation. Platelets and clotting factors are consumed in

this process, but the rate may vary at different periods in the individual patient and also between patients. At the same time, clotting factors enter the circulation from extravascular sources. Tests carried out at any one time may catch this dynamic process at a different stage, which explains why the reported findings differ and why these differences are not contradictory.

(a) The *platelets* were counted in 31 patients, 18 of whom had thrombocytopenia. In nine patients (6, 7, 9, 16, 20, 24, 29, 41) the count was between 10,000 and 50,000 per μl, and in four patients (2, 22, 32, 43) less than 10,000 platelets per μl were found. The counts were made at different times, frequently several days after the onset of the disease. Several patients with severe clotting factor defects (4, 10, 12, 23, 24, 28, 37) had a normal platelet count or only moderate thrombocytopenia, suggesting that intravascular coagulation need not produce marked thrombocytopenia.

(b) A *tourniquet test* was performed in 17 patients and was positive in only two patients with platelet counts of 54,000 and 164,000 per μl, respectively (1, 25). Three patients with platelet counts below 50,000 per μl (6, 7, 24) had negative tourniquet tests.

(c) The *bleeding time* was determined in 28 patients. It was markedly prolonged in eight (4, 6, 11, 12, 24, 37, 41), moderately prolonged in seven (5, 7, 9, 10, 17, 29, 43), and normal in 13 patients. Although the very long bleeding times were usually found in patients with thrombocytopenia, three patients had markedly prolonged bleeding times despite platelet counts of greater than 100,000 per mm^3. These patients had marked clotting factor defects.

(d) The *whole blood clotting time* was measured in 31 patients. Eight (4, 17, 23, 24, 33, 37, 43) had incoagulable blood; five (10, 12, 16, 28, 29) had a very long clotting time; four (2, 32, 36, 41) had a moderately prolonged clotting time; and the remaining 14 patients had a normal clotting time. The whole blood clotting time is a fairly insentisive test, which may be normal despite marked clotting defects.

(e) *Fibrinogen* was measured in only 12 patients. Four patients had afibrinogenaemia (4, 17, 29, 43), four had marked hypofibrinogenaemia (10, 20, 23, 28), and four had normal levels (9, 24, 33). Elevated *antithrombin III* titers have been reported in p.f. (17, 24, 33). McKay *et al.* (1962) believe that this could explain a failure to demonstrate fibrinogen, since only a small amount of thrombin is used in fibrinogen assays. However, they admit that an increased level of antithrombin III does not result in incoagulable blood. Moreover, Brühl (1931) could not precipitate fibrinogen from his patient's plasma at 56° C. There can be no doubt, therefore, that several patients have had extremely low levels of fibrinogen during

the active phase of the disease. Increased levels have been found at later stages.

(f) The *prothrombin time* was measured in 19 patients. It was greatly prolonged in nine (10, 12, 17, 24, 28, 29, 37, 43), moderately prolonged in six (5, 9, 32, 33, 42), and slightly prolonged in four patients (6, 16, 20). Fibrinogenopenia undoubtedly contributed to the long prothrombin time in some patients.

(g) *Specific assays of clotting factors* were performed in only a few patients. Prothrombin was low in three (17, 29, 33) and normal in two patients studied by an insensitive method (24). Very low levels of *Factor V* were found in four patients (24, 29, 37) and normal levels in two patients (33, 42). *Factor VII* was low in one patient (37) and normal in three (17, 29, 40). *Factor VIII* was markedly reduced in two patients (29, 37) and normal in one (33). *Factor IX* was normal in two patients (29, 33). In general, these findings are compatible with intravascular coagulation. Factor V appears to be the most sensitive indicator of this process. An adequate method must be used, and samples must be drawn during an active phase of the disease.

(h) A *circulating anticoagulant* has not been found in p.f. (33)

(i) *Fibrinolysis* was increased in three patients (16, 24) and normal in five (17, 20, 28, 29, 33).

12. *Duration of the active phase.* During the active phase new lesions may appear and old lesions progress. It is essential to appreciate the duration of this phase in order to understand the mechanism of p.f. and to plan effective therapy. Tabel II reveals that the active phase frequently lasts for several days. This evaluation is crude but supported by laboratory data. Thus, Beinhauer (1929) found no platelets in his patient until day 8, Dyggve (1947) found a

TABLE II

Duration of the "active phase" in 50 patients with purpura fulminans selected from the literature

Duration of "active phase"	No. of patients	
	Died	Survived
< 24 hours	4	4
1–3 days	15	7
4–6 days	3	6
7–10 days	2	4
> 10 days		2
Unknown	2	1
Total	26	24

fibrinogen level of 57 mg per cent on day 5, Marthaler *et al.* (1957) found 10 per cent Factor V activity on day 3, and Frödin (1946–47) observed a sudden drop of haemoglobin in his patient on day 3. In some patients the disease advanced relentlessly, but in others it started slowly and progressed in a wavelike pattern over several days (7, 17, 28, 37). Some patients also had premonitory symptoms, especially pain in the legs, for a few hours or even for several days before bleeding was observed (4, 12, 23, 24, 44).

13. *Outcome.* Twenty-six of these 50 patients died: 17 within 3 days, five after 4–6 days, and four after 8 days or longer. Of the 24 survivors, 10 required major amputations and nine lost less extensive but significant amounts of tissue. Only five patients survived without loss of tissue. These survival figures are more accurate than Elliott's (1909) mortality rate of 93 per cent, which is frequently cited, for his series included many patients with septicaemia, especially meningococcaemia. Modern treatment with steroids, transfusions, and antibiotics has not significantly improved the prognosis. Seven of 17 patients seen in the period 1931–50 died as compared with eight of 21 patients seen in the period 1951–63.

14. *Pathology.* There are 22 autopsy and 12 biopsy reports in this series of 50 cases. As expected, the main finding in the *skin* is haemorrhage; several investigators, including Henoch (1884), believed it to be the only finding. Massive bleeding and necrosis make detailed histopathologic studies difficult. Nevertheless, careful observations have revealed two additional findings. The first is an inflammatory reaction, often with perivascular cuffing with leukocytes, occasionally including eosinophils (9, 17, 33). Fibrinoid necrosis of the vessel wall has also been observed (5, 12, 33, 42). The second is thrombosis of small vessels, especially capillaries and venules (2, 5, 9, 17, 28, 30, 33, 42). These findings are characteristic of the Arthus and the local Shwartzman reactions (86) and suggest that the pathogenesis of p.f. is related to these reactions (see later). One could argue that these findings are secondary to bleeding and necrosis. However, the age of the thrombi and the evidence of intravascular coagulation in the blood suggest that the thrombi are primary. The timing of the inflammatory reaction can only be elucidated by serial biopsies and must be left open at present. Larger vessels are not involved initially but may be occluded by thrombi after several days (1, 8, 17, 33).

Renal lesions were noted in five of the 22 autopsies. Glomerular capillary thrombosis was found in one patient (29) and extensive bilateral cortical necrosis in two other patients (32, 33). These lesions are of particular interest because they may be produced by intravascular clotting in the generalized Shwartzman reaction (McKay & Shapiro 1959). Two additional patients were said to have changes compatible with glomerulonephritis (11, 30).

Haemorrhages in internal organs were found in many patients: in the

bladder and ureter (5, 11, 20, 29, 30, 32); in the ovaries and broad ligaments (5, 11, 32); in the large intestine (20, 29, 30); in the brain (24, 29, 32); in the pleura, peritoneum or pericardium (5, 29, 32, 38); and, less commonly, in the stomach (29), testes and myocardium (33). One patient, who also had streptococcal septicaemia (35), had bilateral adrenal haemorrhage. Two patients bled into the abdominal cavity (5, 12). These haemorrhages may be secondary to small vessel thrombosis (20, 30), to the haemostatic defect which follows intravascular coagulation, or to both processes. Three patients had *thrombosis of major veins* (5, 20, 33).

Small foci of necrosis, hyperplasia of reticulum cells, and plasma cells were seen in the spleen and lymph nodes (24, 29, 33).

Differentiation from other types of purpura

The literature contains case reports in which fulminant purpuras of other types have been confused with p.f. This has occurred particularly in the following disorders.

1. *Meningococcaemia* can induce a fulminant purpura which frequently is referred to as p.f. For example, Guelliot (1884) is often credited with the first description of p.f., although his three patients almost certainly died of meningococcaemia.

Clinically, the two forms of purpura are quite different. Purpura develops early in meningococcaemia, with no latent interval. The skin lesions vary from petechiae to large blotches; they contain meningococci (66, 68), and they rarely result in necrosis (54, 92). The mucous membranes are often involved. This picture contrasts sharply with the large, firm, purplish-black, well demarcated, sterile lesions in p.f. Shock may occur in both disorders, but meningococcic shock is out of proportion to bleeding and responds poorly to blood transfusions. However, despite their different etiology and clinical manifestations, meningococcic purpura and p.f. may be related pathogenetically, for intravascular coagulation (75, 77) and thrombosis of small vessels (66) also occur in meningococcaemia.

2. *Henoch-Schönlein purpura* and p.f. share the following features: both occur in children; both are more common during the first part of the year; both are frequently preceded by a benign infection; the latent interval may be the same for both disorders; the lesions are found in the same general distribution; bacteria cannot be demonstrated in the lesions, and, finally, their histopathology is similar (60, 91). However, there are also major differences. Henoch-Schönlein purpura usually starts with urticarial lesions (60), and the typical recurring crops of small purpuric spots bear little resemblance to the lesions in p.f. Furthermore, the gut, the kidneys, and

the joints are more commonly involved in Henoch-Schönlein purpura, which also has a characteristic tendency to recur.

Occasionally, patients with severe Henoch-Schönlein purpura have extensive areas of purpura with necrosis. Such cases have been called p.f. (51, 55, 61, 74) or given the name *purpura necrotica* (53, 59, 83). It has been suggested that p.f. is simply an extreme form of Henoch-Schönlein purpura (60, 61). However, patients with severe Henoch-Schönlein purpura do not have thrombocytopenia, probably do not have clotting defects (detailed clotting studies in this disorder have not been published), and usually recover. For these reasons, it seems important to us to distinguish between severe Henoch-Schönlein purpura and p.f.

3. *Post-infectious purpura* may follow scarlet fever (46, 50, 57, 70, 73), chicken pox (52), and measles (56). This purpura is usually generalized with petechiae, ecchymoses, and mucous membrane involvement, and it runs a benign course. Cases following scarlet fever have sometimes been classified under the name "purpura haemorrhagica". Review of these reports today suggests that an occasional case represents post-infectious thrombocytopenic purpura, whereas the majority represents examples of severe Henoch-Schönlein purpura.

4. *Lesions in adults resembling p.f.*

(a) Severe purpura has been seen during *pregnancy* or following delivery. In some patients, it has been similar to p.f. in both its clinical and histological manifestations (58, 82, 88).

(b) Skin lesions frequently develop during *ulcerative colitis*. A patient has been described (62) with large, confluent purpuric areas closely resembling p.f.; histologic studies revealed perivascular inflammation and thrombosis of capillaries and venules. The authors concluded that the haemorrhagic necrosis represented a variant of pyoderma gangrenosum, probably arising from a local Shwartzman reaction.

It is apparent that lesions similar to p.f. may occur in different clinical situations. Many of these lesions are associated with small vessel thrombosis and, thus, may share with p.f. a common final pathogenetic mechanism. Nevertheless, p.f., as we have delineated it, is a striking and separate clinical syndrome.

Pathogenesis

1. *Pathogenetic factors*

Clinical observations suggest that p.f. results from a two-step reaction involving a mechanism which *prepares* the skin and a mechanism which then *triggers* the process. The coagulation abnormalities in the blood offer convincing evidence of intravascular coagulation and strongly suggest that

thrombosis of the capillaries and venules in the affected skin is the cause rather than the result of bleeding. We conclude, therefore, that intravascular coagulation plays a primary role both in the triggering and in the rapid progression of the lesions. Bleeding may be aggravated by the haemostatic defects which result from intravascular coagulation. However, such a failure of haemostasis plays only a secondary role, for, despite massive purpura, the patient improves rather than worsens with heparin therapy.

Further comments on pathogenesis remain largely speculative at present. Two essential questions cannot be answered: (1) how is the skin prepared, and (2) what triggers the intravascular coagulation? Since p.f. usually follows infections which involve the skin, e.g., scarlatina or varicella, it is reasonable to assume that the preceding illness somehow prepares the skin. This is supported by the lack of a local precipitating cause, such as trauma or local infection, in nearly all patients.

Several mechanisms may trigger coagulation. (1) Activation of Hageman factor triggers intrinsic coagulation *in vitro*, but no evidence implicates this mechanism in the pathogenesis of p.f. (2) Tissue thromboplastin could be released from the necrotic lesions and perpetuate intravascular coagulation, but it is hard to see how this could start the process. Furthermore, p.f. has stopped spontaneously in several patients in spite of massive necrosis. (3) Bacteriological endotoxin triggers intravascular coagulation both in animals (78) and in patients (79). Although our own patient had a mild diarrhea, there is usually no evidence of gastrointestinal disease which could lead to absorption of endotoxin from the intestine. However, streptococci may release products with effects similar to endotoxin from gram-negative bacteria (81, 87), and minute amounts of endotoxin may induce sufficient intravascular coagulation to result in fibrin-like thrombi in capillary beds altered by antigen-antibody reactions (47). (4) Antigen-antibody reactions may also trigger coagulation, both *in vitro* (80) and *in vivo* (76). The latent interval between the "preparing illness" and the p.f. fits with a process requiring circulating antibody. Moreover, p.f. complicating scarlatina sometimes follows a relapse of the streptococcal infection, suggesting that a fresh supply of antigen might have triggered intravascular coagulation.

The two later possibilities are both attractive, but neither is as yet supported by solid evidence.

2. *Relation to the Arthus and the local Shwartzman reactions*

Two "prepared" reactions result in haemorrhagic necrosis of the skin in experimental animals. One, the Arthus reaction, is a specific antigen-antibody reaction in which the same antigen is used for preparation and provocation. Initial injections of the antigen sensitize the animal by producing pre-

cipitating antibody. A subsequent injection of antigen into the skin is followed by a local antigen-antibody reaction within the walls of small blood vessels, resulting in an acute necrotizing vasculitis of capillaries and venules with platelet and leukocyte thrombi.

Can p.f. be a human equivalent of the Arthus reaction? As already mentioned, the long "incubation period" and the association of p.f. in some patients with a relapse of streptococcal infection suggest that an antigen-antibody reaction is involved. Moreover, one need not have a local deposit of antigen in the skin for an Arthus reaction to develop; circulating antigen-antibody complexes can localize at the site of a cutaneous anaphylactic reaction and provoke the Arthus reaction (85). Perhaps the same localization could follow other types of damage to skin vessels, e.g., by streptococcal toxin? Intravascular coagulation may well be triggered by the underlying antigen-antibody reaction, but it is not essential for the Arthus reaction, since heparin reduces but does not completely prevent it (69).

The second "prepared" reaction producing haemorrhagic necrosis of skin is the local Shwartzman reaction. This is an unspecific reaction in the sense that antigenically different materials can be used for preparation and provocation. Any agent capable of causing the local accumulation of granulocytes (or their granules) prepares the skin for the local Shwartzman reaction (89). Once the skin is prepared, a variety of materials – endotoxin, kaolin, starch – can be given intravenously to provoke the reaction. All of the provoking agents are capable of triggering coagulation. This fact, plus the ability of heparin to prevent the reaction completely (63), indicate that intravascular clotting is essential for the local Shwartzman reaction.

The arguments in favour of considering p.f. a human equivalent of the local Shwartzman reaction are: the severe intravascular coagulation, the occasional discovery of visceral lesions – particularly bilateral renal cortical necrosis – suggestive of the generalized Shwartzman reaction, and the therapeutic effectiveness of heparin. It should be re-emphasized that Gram-negative bacterial endotoxin need not be involved in a Shwartzman reaction. It may be produced by streptococcal filtrates (81, 84, 87), by virus (72) and by antigen-antibody reactions (84).

This brief review indicates that an Arthus reaction or a local Shwartzman reaction could be involved in p.f. These two reactions are not mutually exclusive. Experimental lesions have been produced which combine elements of both reactions (48, 86). P.f. could well represent a human equivalent of such a combined reaction.

3. *Individual host factors*

The extreme rarity of p.f. must mean that the disorder requires a combina-

tion of several pathogenetic factors and an extreme host sensitivity. Rabbits vary greatly in their sensitivity to the Shwartzman reaction. Many factors influence the reaction: leukocytes, platelets, coagulation, fibrinolysis, steroids, catecholamines, blood flow, and the activity of the reticuloendothelial system. It is possible that each of these factors plays a role in determining whether or not an individual patient develops p.f.

Therapy

In despair, nearly every known form of therapy has been tried, from splenectomy to injections of snake venom. We believe therapy should be based upon the following considerations:

1. *Intravascular clotting must be stopped.* This appears to us the single most important point in preventing the progress of the disease. Therefore, we recommend that heparin be given immediately by the intravenous route in large doses of about 150 I.U. per kg every six hours.

Our patient's course clearly demonstrates the efficacy of heparin therapy. Heparin was also of remarkable benefit in two patients reported in the literature (15, 28). Heparin has been given late in the illness in two additional cases (33, 40).

The recommendation to use *large doses* initially is based upon the evidence of massive intravascular coagulation in these patients plus the observation that large doses are required to block the local Shwartzman reaction in animals (63). The data of Figure 4 suggest that the active phase of the disease may persist for at least eight days. Therefore, heparin should be continued for this interval, possibly in reduced dosage to be determined by careful clinical observation. Renewed disease activity may follow premature discontinuation of heparin therapy (15). It may also be a worthwhile precaution to continue anticoagulant therapy with an oral anticoagulant for several weeks after stopping heparin.

2. *Shock must be combatted.* Shock in p.f. is due to hypovolaemia secondary to loss of whole blood into the tissues. It should therefore be treated vigorously with adequate amounts of blood, preferably *fresh blood* because of the associated haemostatic defects. Since rapid extension of p.f. has been observed during and after transfusion (5, 36, 40), we believe that heparin should be given before transfusions are started. Exchange transfusion, which has been advocated (13) is probably not necessary if heparin is used.

Vasopressors have been used to treat shock in p.f. However, since vasopressors may produce intense vasoconstriction in the skin and since the shock of p.f. responds to volume replacement, they should probably not be used.

3. *Secondary haemostatic defects must be corrected.* Thrombocytopenia, fibrinogenopenia, and reduced levels of Factors V, VIII and prothrombin result from intravascular coagulation. These haemostatic defects require correction because they may aggravate bleeding into the skin and may cause bleeding from other sites. Marked fibrinogenopenia may dictate replacement with fibrinogen preparations. Very fresh whole blood will provide platelets and all clotting factor activities. We emphasize that haemostatic factors should not be replaced before heparin has been given. Otherwise one runs the risk of inducing a new wave of intravascular clotting.

4. *Antigen-antibody reactions must be stopped.* The reasons for suspecting that antigen-antibody reactions may play a role in p.f. have been discussed above. They form the basis for the following recommendations:

(a) If p.f. follows scarlatina or other illnesses suggestive of streptococcal infection, large doses of *penicillin* should be given in an attempt to remove fresh sources of antigen. Other antibiotics may be indicated later to treat secondary infection of necrotic tissue.

(b) Many patients with p.f., and also with severe Henoch-Schönlein purpura (45) have been treated with *adrenal steroids.* One gets the impression from reviewing these reports that steroid therapy has been of value. The use of adrenal steroids might be questioned because they are known to enhance the Shwartzman reaction (90); however, heparin protects animals against a cortisone-induced generalized Shwartzman reaction (63). Since steroids are known to control other disorders secondary to antigen-antibody reactions, we believe that patients with p.f. should receive steroids in addition to heparin.

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Authors' addresses:

Peter F. Hjort, M.D.
Medical Department A, Rikshospitalet
Oslo, Norway

Samuel I. Rapaport, M.D.
Department of Medicine
University of Southern California
School of Medicine
Los Angeles, California

Leif Jørgensen, M.D.
Department of Pathology, Ullevål Hospital
Oslo, Norway