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Cutaneous Hemorrhages and Gangrenes Localized to the Lower Limbs in Patients with Collagen Diseases and in Diabetics

FOLKE LITHNER, GÖRAN HALLMANS and SVEN-OLA HIETALA

From the Departments of Medicine, Pathology and Radiology, University of Umeå, Umeå, Sweden

ABSTRACT

The appearance and development of cutaneous hemorrhages and gangrenes localized to the lower limbs in patients with certain systemic collagen diseases and in patients with purpura hyperglobulinemica Waldenström were compared to similar lesions in diabetics. There were characteristic differences, clinically as well as microscopically. The diabetic gangrene was clinically characterized by a surrounding zone of erythema. Such erythema was never seen in the patients with collagen diseases and gangrene. Especially in elderly diabetics, purpura was common and was localized to the erythematous areas of gangrenes as well as to non-erythematous areas. The cutaneous hemorrhages of the patients with collagen diseases were of varying size and were most often raised and palpable, in contrast to those in the diabetics. Large cutaneous hemorrhages in patients with collagen diseases often transformed into gangrenes. In diabetics, gangrene as well as purpura were generally precipitated by factors such as cardiac decompensation with edema of the legs. Such precipitating factors were not seen in the patients with collagen diseases.

In diabetics, the erythema adjacent to a cutaneous necrosis corresponded microscopically to dilated small blood vessels surrounded by only a small number of inflammatory cells. No thrombotic vessels were seen. In the patients with collagen diseases, thrombotic vessels were observed in the cutaneous areas adjacent to the necrosis. In and around the walls of the small blood vessels there was a pronounced deposition of inflammatory cells.

INTRODUCTION

Cutaneous hemorrhages and gangrenes, localized to the lower as well as to the upper limbs, have been reported in patients with collagen diseases such as systemic polyarteritis nodosa (PAN), Wegener's granulomatosis and systemic lupus erythematosus (SLE) (14, 15). Vasculitis with infarction is supposed to be the cause of these lesions (14). These reports on gangrene are based on singular cases and, to our knowledge, no systemic studies have been published.

Cutaneous hemorrhages and gangrenes, localized to the lower limbs in diabetics, have been studied by us for several years (7–12). In addition to distal gangrenes, non-distal gangrenes are common in elderly and middle-aged patients. A widespread area of cutaneous erythema—incipient gangrene—may or may not be transformed to necrotic or manifest gangrene. The manifest gangrene is surrounded by a zone of erythema. Precipitating factors for these lesions can usually be established, most often cardiac decompensation with edema of the legs or edema of the legs of other causes. These lesions were not connected to the diabetic metabolic derangement per se but to the presence of late diabetic lesions such as microangiopathy and polyneuropathy (7–12).

On the lower limbs of the diabetics mentioned above, there was often purpura concomitantly with incipient or manifest gangrene but also without the concomitant occurrence of gangrene. There was purpura within as well as outside the erythematous areas. Purpura without concomitant gangrene was precipitated by the same factors which precipitated the gangrenes. Gangrene and/or purpura occur in patients with open diabetes as well as in patients with not open diabetes.

Cutaneous hemorrhages and gangrenes localized to the lower limbs in patients with systemic collagen diseases have not previously been compared to similar lesions in diabetics. A comparison is therefore of interest, especially because there is a different pathogenesis for the lesions in the two groups of patients. In the present study the clinical as well as the microscopical appearances are compared.

Our material of patients with systemic collagen diseases is supplemented by a number of patients with purpura hyperglobulinemica Waldenström (17).

We have included colour illustrations in this re-

Table I. *Data on 16 patients with systemic collagen diseases or purpura hyperglobulinemica*

Diagnosis	No. of pats.	Women–men	Mean age (y.)	Cutaneous hemorrhages	Distal gangrene	Poly-neuropathy
Polyarteritis nodosa	5	2–3	50 (28–62)	5 (3)[a]	3	3[b]
Wegener's granulomatosis	3	0–3	36 (21–52)	3 (1)[a]	1	0
Systemic lupus erythematosus	5	5–0	46 (32–54)	5 (1)[a]	0	1[c]
Purpura hyperglobulinemica	3	3–0	56 (46–65)	3	0	1[c]
Total	16	10–7		16	4	5

[a] ( ) Numbers of patients who also had cutaneous hemorrhages with necrotic areas.
[b] Severe polyneuropathy in all 3 patients.
[c] Mild polyneuropathy.

port to demonstrate the difference in the clinical appearance of the lesions in the two groups of patients (Figs. 1–4).

PATIENTS WITH COLLAGEN DISEASES AND PATIENTS WITH PURPURA HYPERGLOBULINEMICA

These patients were clinically examined of one of us (F. L.) in the period 1969–76 (Table I) as were the diabetics. SLE was diagnosed upon the basis of the following criteria: abnormalities in at least two organ systems and the finding of a positive LE cell preparation (15). In patients with PAN and Wegener's granulomatosis, the diagnosis was based not only upon the clinical involvement of two or more organ systems but also upon biopsy (14). The biopsy was not conclusive in one patient: Male, 29 years old (B. S.) with distal gangrene of the right foot. Angiography of the affected foot revealed, however, that most of the digital arteries were occluded. He had purpura of the lower limbs and pronounced polyneuropathy in all four limbs, ulcerative colitis, azotemia, hematuria and increase of polyclonal gammaglobulins. He was diagnosed as PAN.

Purpura hyperglobulinemica (17) was diagnosed in three patients with relapsing purpura localized to the lower limbs and high values of polyclonal gammaglobulins (3.3–4.9 g/100 ml).

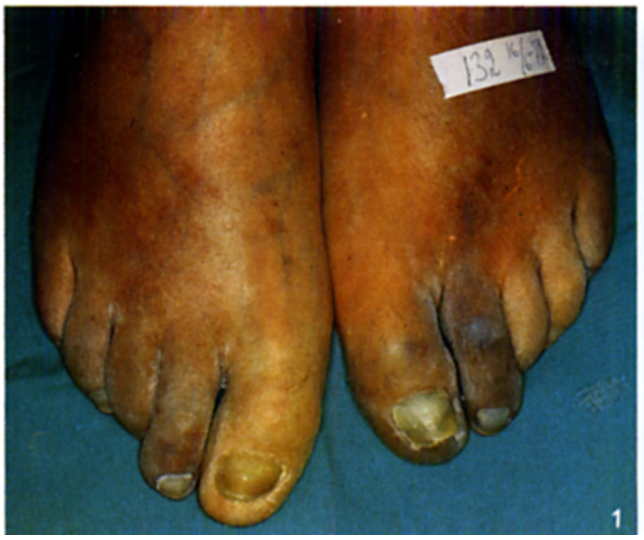
None of the patients with collagen diseases or purpura hyperglobulinemica had diabetes.

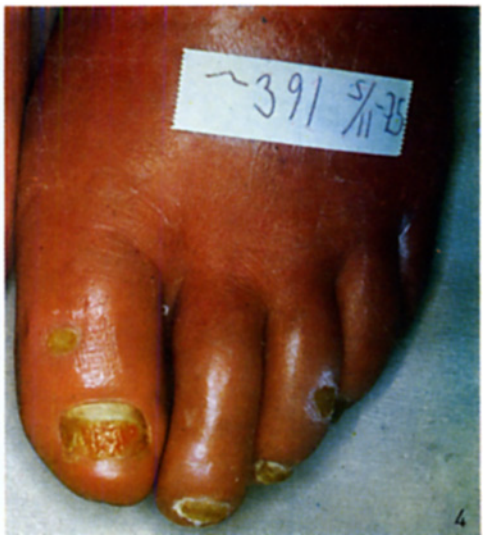
Cutaneous hemorrhages of varying size with or without gangrene

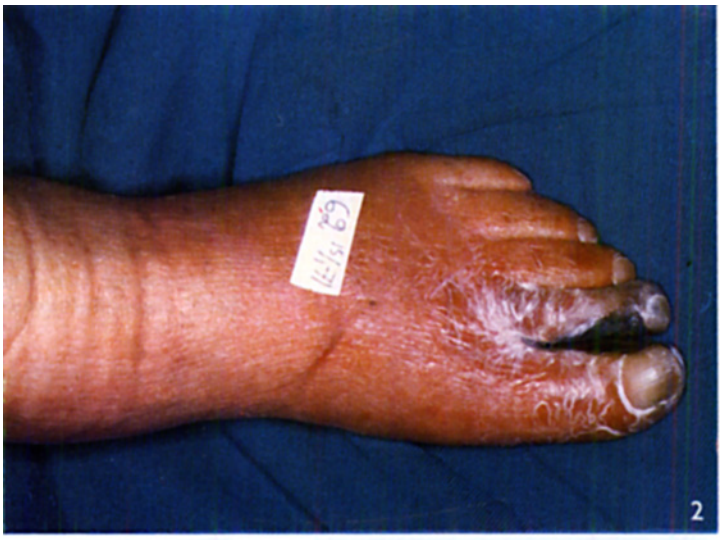
The cutaneous hemorrhages varied in size from 1 mm^2 up to 4×6 cm. The lesions were generally raised and palpable, especially in patients with PAN and Wegener's granulomatosis. In these latter patients the lesions were often transformed to bloodfilled bullae and often had necrotic areas. The largest lesions were irregular and sharply demarcated (Fig. 3) and were transformed to cutaneous areas of gangrene. There was usually pain localized to the gangrenous area. The skin surrounding the cutaneous hemorrhages always had a normal appearance. The three patients with purpura hyperglobulinemica had had relapsing, pronounced and partly confluent purpura on the legs for 7–14 years. The cutaneous hemorrhages in these patients were larger compared with those in diabetics and were sometimes palpable. In these patients, transformation of hemorrhages into areas of gangrene was never observed.

Distal gangrene. In 2 patients with PAN and distal gangrene, the development of the gangrene could be followed. It started with local coldness, cyanotic discoloration and pain (Figs. 2–3). Angiography of the affected foot was performed in one of these patients (B. S.). A pre-shaped polyethylene catheter (O.D./I.D.=2.2/1.2 mm) was passed down to the superficial femoral artery. The contrast material, Urografin 76%, was injected at the rate of 8 ml per second for 3 sec and serial radiographs were taken. Most of the digital arteries were occluded distally (Fig. 5). An aortofemoral angiography with moving table technique was also performed, it did not reveal any stenotic or occlusive processes of the larger arteries.

In all 4 patients with distal gangrene, the gangrene was localized to the toes. All had warm dorsal surfaces of the feet and palpable pedal pulses. There was usually pain localized to the gangrenous areas. One patient with PAN also had apical gangrenes on four fingers. In no patient with cutaneous hemorrhages or distal gangrenes could precipitating factors, such as cardiac decompensation, be demonstrated.







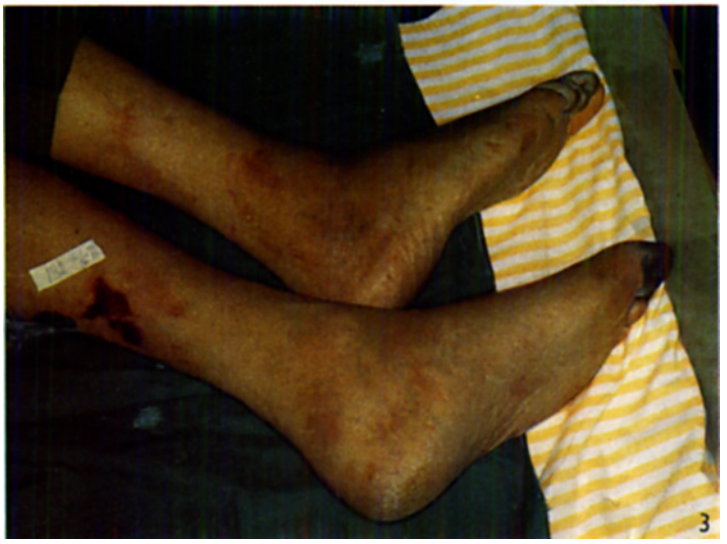


Fig. 1. The feet of a male (E. N.), 52 years old, with polyarteritis nodosa. Coldness and pain in the toes and cyanotic discoloration of several toes. Gangrenes in the toes I and II of the left and II of the right foot. No erythema. Good pedal pulses.

Fig. 2. The left foot of a male, 81 years old, with open diabetes. Myocardial infarction and cardiac decompensation with edema of the legs. Two days later erythema of the left foot. A week later necrosis of adjacent parts of digits I and II. No pain. Warm foot and good pedal pulses.

Fig. 3. The lower extremities of the same patient as in Fig. 1. Cutaneous hemorrhages of recent date above the right lateral malleolus. Somewhat older, painful hemorrhages on the posterior aspect of the left lower leg.

Fig. 4. The left foot of a male, 79 years old, with diabetic oral glucose tolerance curve. Erythema of the feet in connection with cardiac decompensation and edema of the legs. Small necrotic areas localized to digits I and II of the left foot. No pain. Warm feet. Good pedal pulses.

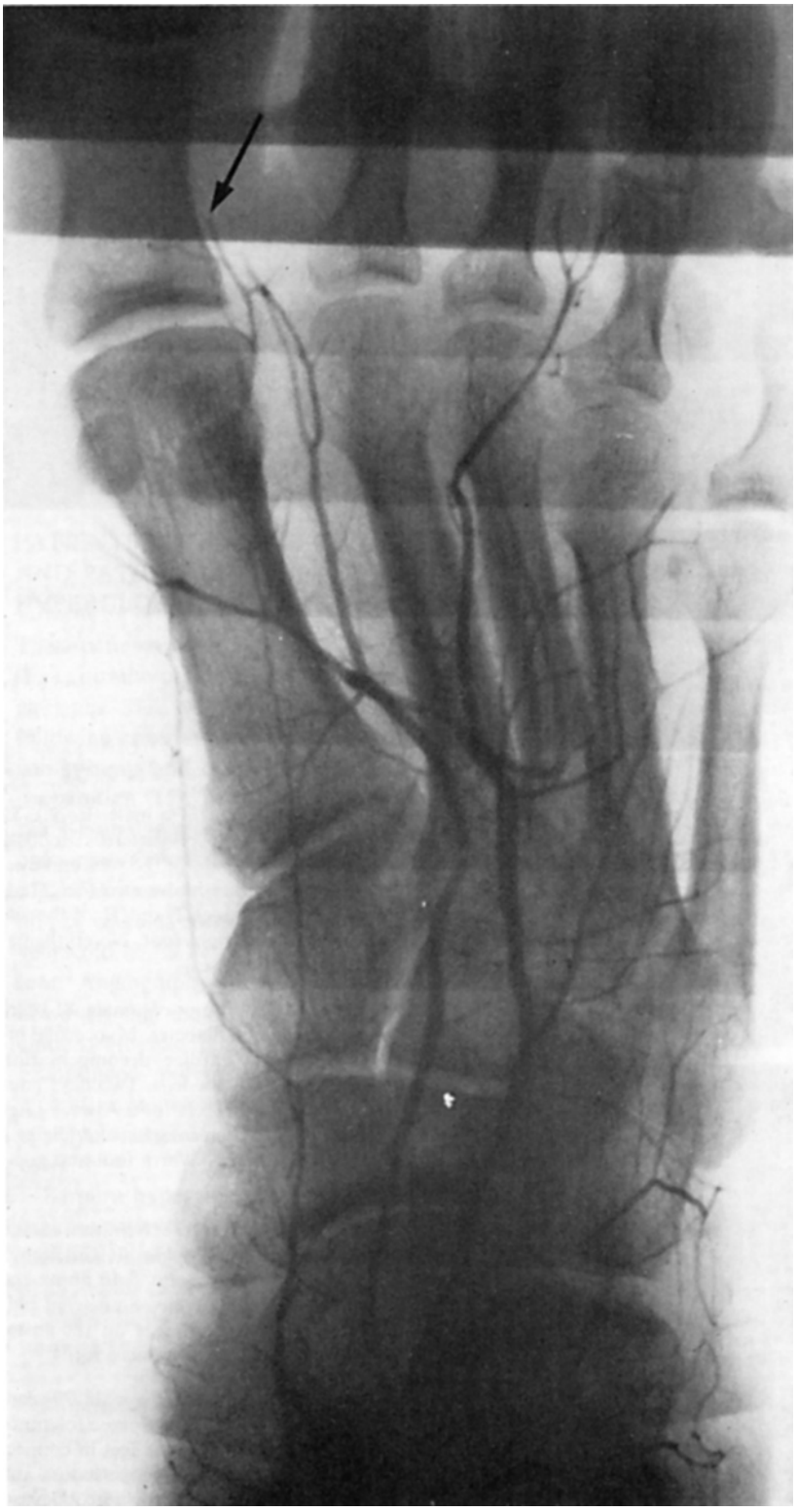


Fig. 5. The right foot of a male, 29 years old (B. S.) with polyarteritis nodosa and apical gangrenes of the toes I–IV. Arteriography, arterial phase. Most of the digital arteries are occluded distally. Such occlusions are clearly seen, especially of the arteries (arrow) of the first toe at the level of the metatarsophalangeal joint.

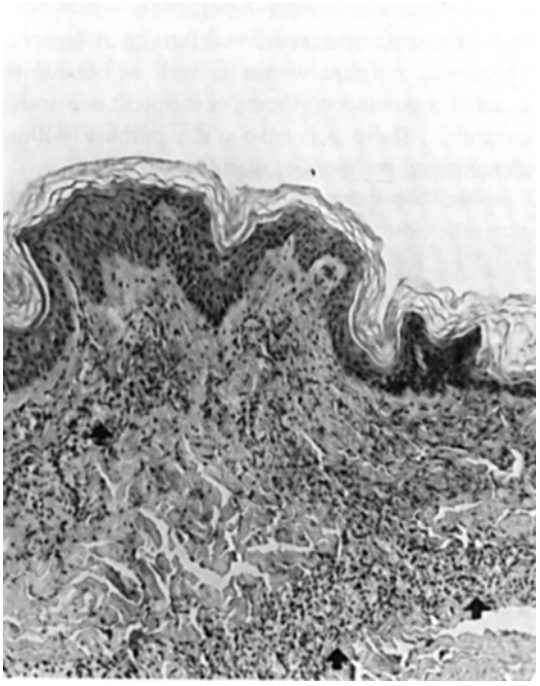


Fig. 6. Skin from lower leg. Male (M. K.), 21 years old, with Wegener's granulomatosis. In and around the walls of the small dermal vessels there is deposition of inflammatory cells (*arrows*). For further information, see text. Hematoxylin-eosin, ×105.

DIABETICS

The patients and the findings are reported elsewhere (7–12).

MICROSCOPICAL OBSERVATIONS IN PATIENTS WITH COLLAGEN DISEASES AND IN DIABETICS

The pieces of skin examined were autopsy material from the diabetics and biopsy material from the patients with the collagen diseases. The skin pieces were stained with hematoxylin-eosin, Van Gieson's method, periodic acid-Schiff (PAS), toluidine blue and Ladewig's method.

Patients with collagen diseases. The microscopical appearance of the skin adjacent to hemorrhages were examined in one patient with PAN, one with Wegener's granulomatosis (Fig. 6) and one with SLE. Within and adjacent to the necrotic areas there were thrombotic vessels in all patients and close to the necrosis dilated subepidermal vessels and intensive inflammatory reactions in and around the vessel walls were found.

Diabetics. Skin adjacent to necrotic areas were examined in 3 patients. Microscopically, a necrosis surrounded by a small number of inflammatory cells and dilated vessels was seen in the upper part of dermis (Fig. 7). Some distance from the necrosis,

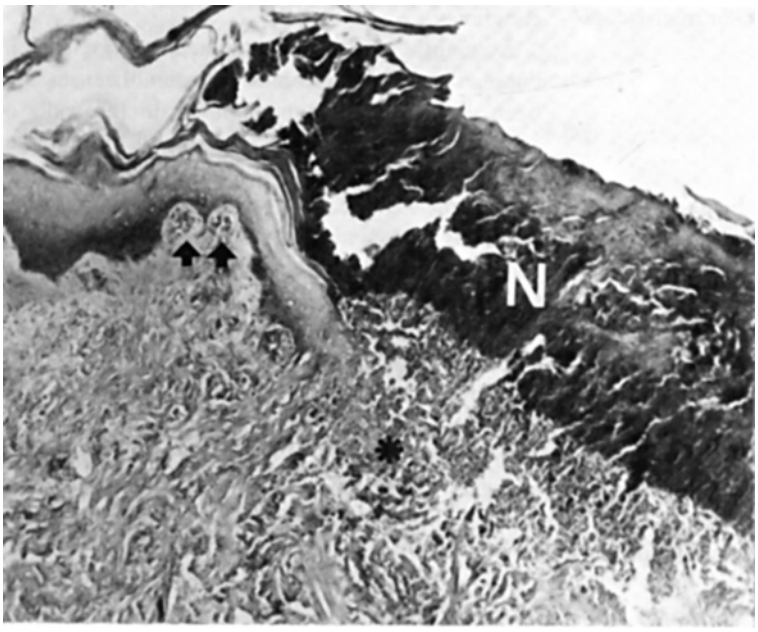


Fig. 7. Skin from lower leg. Male, 67 years old, with open diabetes. Necrosis of the upper part of dermis (*N*). Beneath the necrosis collections of inflammatory cells (*). Subepidermally dilated vessels (*arrows*) which are surrounded by only a small number of inflammatory cells. There are no thrombotic vessels. In the dermis surrounding the necrotic area are signs of edema. Hematoxylin-eosin, ×60.

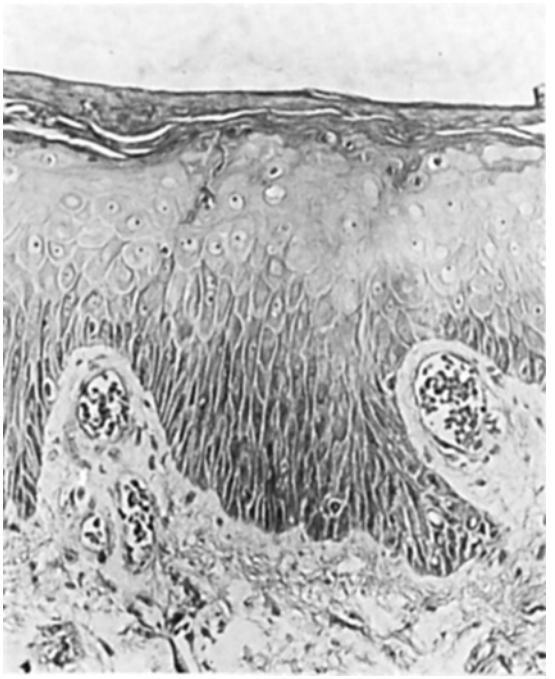


Fig. 8. The same piece of skin as in Fig. 7. View of subepidermally located, dilated vessels. The vessels are not adjacent to the necrosis. The connective tissue of the dermis is split up by edema formation. Hematoxylin-eosin, ×175.

dilated vessels without any inflammatory cells were observed subepidermally (Fig. 8). No thrombotic vessels were seen. There was a similar microscopical picture in all the 3 patients.

DISCUSSION

The appearance of the cutaneous hemorrhages of the patients with certain collagen diseases, described in the present study, is in agreement with earlier findings (14, 15). The fact that there is no erythema around the cutaneous hemorrhages with and without necrosis has never been described, however. The hemorrhages in these patients differ strikingly from similar lesions in diabetics. In patients with the collagen diseases mentioned above, the cutaneous hemorrhages were of varying size and generally palpable. Large cutaneous hemorrhages were often transformed into areas of gangrene.

In diabetics, the cutaneous hemorrhages consisted of numerous small petechiae which were never palpable or transformed into necrotic areas. There was purpura within as well as outside the areas of cutaneous erythema of incipient or manifest gangrene. There was also often purpura without concomitant incipient or manifest gangrene.

In the two cases of collagen disease and distal gangrene where the development of the gangrene could be followed, the lesions started with local coldness, cyanotic discoloration and pain—signs of insufficient blood supply. No cutaneous edema or erythema were seen. In diabetics the gangrene started with erythema and often also with edema. Signs of arterial insufficiency were rare. The diabetic gangrene was surrounded by erythema.

The patients with collagen diseases and gangrene oftan had pain localized to the gangrenous areas as was also the case in patients with severe polyneuropathy, which was common in our patients with PAN. In diabetics with gangrene localized to the lower limbs, there was no pain except in connection with arterial insufficiency. This lack of pain in most diabetics with gangrene is assumed to be due to peripheral polyneuropathy (3). The reason why the gangrenes of patients with PAN are painful, despite severe polyneuropathy, is reported to be due to a patchy involvement of the nerves—mononeuritis multiplex (1, 13, 14).

In our patients with collagen diseases and lesions of the lower limbs, we did not find any precipitating factors such as were typical for the diabetics with gangrenes.

As mentioned in the Introduction, vasculitis in connection with systemic collagen diseases has been described. Immunoglobulins in the walls of small blood vessels have been found in these patients (2, 4, 6, 16) and have been suggested to be of pathogenic significance in the lesions of vasculitis (16). Vasculitis with infarction is believed to be the cause of the cutaneous hemorrhage and gangrene (14). In the present study we also demonstrated vasculitis and thrombotic small blood vessels of the affected cutaneous areas with necrosis. Occluded arteries to gangrenous areas were demonstrated angiographically in one of our patients.

In the microscopical study of the small blood vessels of the areas adjacent to the cutaneous necrosis in the diabetics we observed dilated vessels without occlusive lesions.

Immunoglobulins in the walls of the small blood vessels in diabetics have also been described (5, 18)

but the pathogenic significance of these immunoglobulins is not clear and remains to be elucidated.

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Address for reprints:

Folke Lithner, M.D.
Department of Medicine
University of Umeå
S-901 85 Umeå
Sweden