contractures, and resultant disability.[1,2] A median interval of 4·9 months was calculated from the onset of symptoms of polymyositis to diagnosis, with 22% of diagnoses taking longer than one year.[4] The corresponding figure was 25% in another study,[8] with a mean interval of 13 months from first manifestation of the disease to diagnosis.

Diagnosis is based on clinical findings and serum creatine phosphokinase activity, supported by either electromyography or muscle biopsy. Only a few patients have all the criteria.[2] Muscle strength may be normal in some cases[6] but, conversely, objective testing may disclose weakness when the patient had not complained of it.[2] Cutaneous signs may be subtle, transient, or absent. Serum enzyme activity is the most reliable diagnostic test, creatine phosphokinase activity being raised in virtually all cases of acute and subacute myositis.[1] There is no correlation between enzyme activity and grade of disability or weakness at presentation,[2] so that apparent haematuria may be the first obvious manifestation of rhabdomyolysis. It was this sign that brought our first patient to his doctor and led to the third patient's prompt referral, diagnosis, and treatment. Though doctors may be expected to respond by testing the urine with a reagent strip and collecting a midstream urine specimen for culture, the potential relevance of "stix haematuria" against a background of a flu-like illness, non-specific generalised aches, or weakness may not be appreciated immediately. It should be remembered that both haemoglobin and myoglobin cause a positive reaction. Conceivably some patients might be treated inappropriately with antibiotics or be investigated from an erroneous approach, causing undue delay. We can only guess at how many patients pass through the phase of "haematuria" into the oblivion of chronicity.

In conclusion, we suspect that apparent haematuria as a reported symptom and on strip testing may be more common than realised and therefore an important sign of polymyositis. It seems reasonable to assume that it is most apparent when rhabdomyolysis is most active, though the muscle damage may be subclinical. We suggest, however, that this may be the optimum time to begin treatment.

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For Debate . . .

Causes of venous ulceration: a new hypothesis

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Abstract

Previous hypotheses about the causes of venous ulceration are inconsistent with recently published data. In patients with chronic venous insufficiency the number of functioning capillary loops visible in the skin on microscopy fell after the legs had been dependent for 30 minutes. Another study had shown that leucocytes became trapped in the circulation in dependent legs. A new hypothesis linking these two findings proposes that the trapped while cells occlude the capillaries and result in ischaemia of the skin of the leg.

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Introduction

Venous ulceration is a major unsolved problem: over half a million patients currently receive treatment for it in the United Kingdom.[1,2] Treatment is unsatisfactory, only bed rest and compression being effective. The association between venous ulcers and underlying damage to the deep veins is well established.[3] The damage results in a persistently raised pressure in both the deep and superficial veins of the leg.[4] The mechanism by which venous ulceration is caused is less clear. Several hypotheses have been advanced, the most recent being the pericapillary fibrin cuff hypothesis.[5] The cuff is seen in the skin of patients with chronic venous insufficiency, and Browse and Burnand propose that it prevents diffusion of gases and results in tissue hypoxia, which causes ulceration. No one has shown, however, that the fibrin cuff presents a true barrier to diffusion.

Using capillary fluorescence microscopy, Bollinger *et al* found that in patients with chronic venous insufficiency there were areas of skin with no apparent flow of blood.[6] The flow was restored when the patients wore compression stockings. Bollinger *et al* suggested that some of the capillaries were not functioning because of thrombosis.

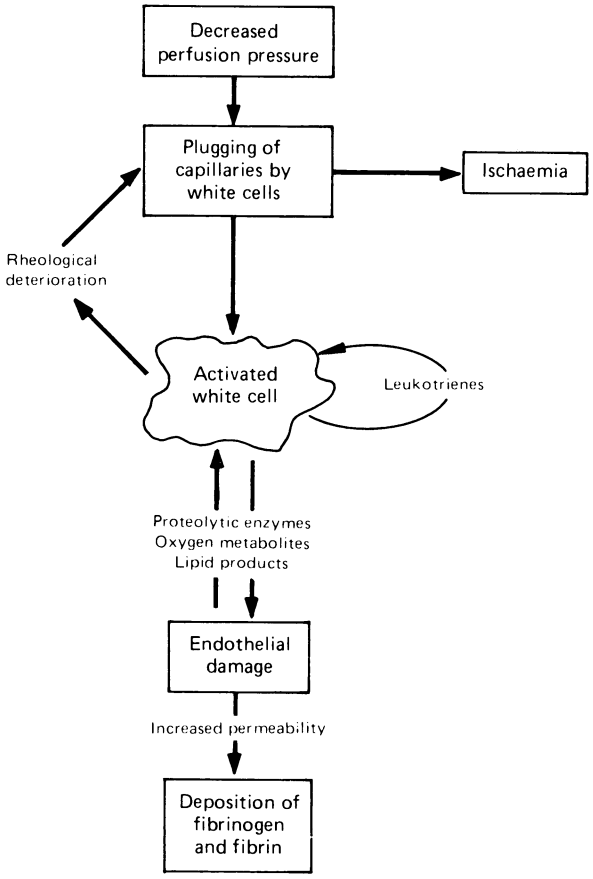
In rats white cells become trapped in the capillaries in response to slowing of the circulation, which causes increased peripheral vascular resistance owing to capillary occlusion.[7] White cells trapped in this way release proteolytic enzymes and superoxide radicals that cause endothelial damage.[8] We have shown that white

cells accumulate in the dependent legs of normal subjects and that this phenomenon is much more pronounced in patients with chronic venous insufficiency (see accompanying paper, p 1693). After patients had been sitting for 30 minutes nearly 30% of the white cells entering their legs were trapped there. In the light of this preliminary work and further work described below we propose an alternative hypothesis that better fits the available evidence.

Method and results

The skin of the legs of 10 patients with chronic venous insufficiency was examined by direct microscopy. Two patients had active venous ulcers and the rest lipodermatosclerosis. Doppler ultrasonography and photoplethysmography were used to confirm the presence of deep venous insufficiency. In all patients the area examined was non-ulcerated skin within 5 cm of the medial malleolus. In those patients with active ulcers the area of the ulcer was avoided. All examinations were performed with the patients lying supine to eliminate changes produced by other physiological responses invoked by changes in posture.[9] Microscopy was carried out in a chamber in which the environment was controlled at a constant temperature of 22°C and a relative humidity of 30%. Patients were examined at 2 pm and had been advised not to wear their usual support stockings on the day of the examination. Patients lay supine and were examined after 30 minutes; they then sat with their legs dependent for a further 30 minutes and were re-examined lying supine. The mean number of capillary loops visible per mm^2 was determined over the same area of 40 mm^2 at each examination.

After lying supine for 30 minutes patients had a median of 5·6 capillary loops/mm^2 (range 2·8-12·3); after sitting with their legs dependent for 30 minutes they had a median of 5·0 capillary loops per mm^2 (range 2·2-9·8). Both these values were significant ($p<0·05$, Wilcoxon log rank test). Fewer capillary loops were visible in nine of the 10 patients after 30 minutes of sitting.



Proposed mechanism by which trapping of white cells in peripheral circulation results in formation of venous ulcers.

Discussion

Our previous work (see accompanying paper, p 1699) showed that loss of white cells, expressed as the percentage change in the ratio of white to red cells in blood from the long saphenous vein, was significant in patients with chronic venous insufficiency and small in patients with normal deep veins (28% *v* 5%, $p<0·01$). This study showed that fewer capillary loops were visible after 30 minutes' dependency in patients with chronic venous insufficiency. Measurements were made in the 5-10 minutes after the patient had returned to the supine position, which in our previous study was shown to result in a prompt efflux of white cells within 2-3 minutes of reducing the pressure. Capillary loops are visible only when they contain red cells. When circulation through them stops they empty of red cells and thus become invisible on direct microscopy. As all readings were taken with the patients lying supine physiological changes resulting from dependency are unlikely to have accounted for our findings.

An explanation of these two sets of data (figure) is that the capillary occlusion observed by Bollinger *et al*[6] and implied in our data is caused by white cells sticking in the capillaries of the skin. Raised pressure in the venous system during standing or walking reduces the capillary perfusion pressure. The capillary flow rate is reduced, and this alone is sufficient to cause trapping of white cells. The trapped cells release toxic oxygen metabolites and proteolytic enzymes that result in damage to the capillaries, making them more permeable to large molecules and more likely to trap additional white cells. The increased permeability to large molecules results in loss of fibrinogen and other plasma proteins and leads to the formation of the fibrin cuff.[5] The trapped white cells prevent further circulation in the affected capillaries and result in areas of ischaemia around these capillary loops.

The trapping of white cells is at least partially reversible, but the time for which cells remain trapped cannot be estimated accurately from these preliminary data. The phenomenon certainly persists for the five to 10 minutes required to count the capillary loops. Such persisting occlusion will result in certain areas of the capillary bed remaining unperfused for a substantial time. This does not conflict with the data of Hopkins *et al*, who suggested that blood flow is increased in the subcutaneous tissues of arms and legs with chronic venous insufficiency.[10] Blood flow will be diverted from occluded capillary loops to those remaining open without necessarily occurring any change in overall flow. This mechanism will result in heterogeneous perfusion of the skin, and not all parts will receive an adequate supply of blood. The areas in which the capillary loops are occluded will receive their blood supply by diffusion from the functioning capillaries. This process is far from efficient—for example, a doubling of the diffusion distance will result in a fourfold reduction in the supply of gases. The defect in perfusion will affect all nutritive substances and metabolites, not just gases as proposed by Browse and Burnand.[4] Our theory takes into account published data as well as our own observations and provides a more satisfactory explanation of the cause of venous ulcers than any previous theory.

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