10% had hypocomplementaemia compared with 5% in the remainder.

Russell Jones and colleagues[9 10] have made some important contributions to this aspect of vasculitis, and their study of 24 patients with chronic urticaria showed a complete gradation between obvious vasculitis and ordinary chronic urticaria with regard to the severity of the histopathological features, appearances on direct immunofluorescence, immune complex determination, and serological changes. The detailed investigations by Callen and Kalbfleisch in nine patients with urticarial vasculitis showed the same merging with chronic urticaria.[11]

If, then, we accept that 5-10% of patients with ordinary chronic urticaria have leucocytoclastic vasculitis and that there is a continuum of overlapping changes, what are the possible mechanisms underlying ordinary chronic urticaria? It may well be that in many patients urticaria is due to immune complexes deposited in skin venules which then give rise to a varying degree of liberation of inflammatory mediators depending on many factors (including, rarely, complement abnormalities). These inflammatory mediators then give rise to reactions which can be modified by various drugs and chemicals. Thus, although the weals may be initiated by immune complexes, their development will be influenced by all the other factors known to effect the production of weals in urticaria.

The most effective treatment for urticarial vasculitis is with parenteral steroids, usually required in a full dose, and continued for months. Nevertheless, many patients with urticarial vasculitis eventually settle down spontaneously, and even in the face of a clear cut diagnosis steroid treatment is required in only a few patients who have not been helped sufficiently by conventional measures including adequate antihistamine treatment. A few of these patients respond to dapsone, particularly those with a picture similar to systemic lupus erythematosus.[12] In one report indomethacin was said to be effective in nine out of 10 patients with urticarial vasculitis[13]; this has not been the experience of other workers—and indomethacin may have an aspirin like exacerbating effect on urticaria.

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# *Regular Review*

# Venous ulceration

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Venous ulcers do not occur in any other animal, but they have probably afflicted man since he achieved an upright posture. Because they are an uncommon complication of simple varicose veins but a common sequel of deep vein thrombosis they may have been rare until the advent of "civilised" living. They must have been known to Hippocrates and the ancients, but the first to recognise the relation between venous thrombosis and ulceration is usually said to have been John Gay.[1] The connection was revived in 1917 by John Homans,[2] who also drew attention to the fact that legs with venous ulcers often had few visible varicose veins—thus banishing the commonly used but misleading term "varicose ulcer."

Once cause and effect—calf pump deficiency and ulceration—were established, little thought was given to the actual mechanisms. Yet even on close inspection it is difficult to see how an inefficient calf pump can cause necrosis of the skin on the lower medial aspect of the leg. The common explanations were venous stasis,[2] venous hypertension,[3] and tissue ischaemia secondary to microscopic arteriovenous fistulas,[4] but none of these theories fitted all the facts.

The extent to which the calf pump may be damaged by thrombosis became apparent as phlebography and measurements of intravascular pressure became easy and accurate during the 1940s and '50s. Phlebography showed that thrombosis often destroyed all the deep veins, leaving either narrow irregular valveless channels—if the veins recanalised—or tortuous dilated collaterals with incompetent valves if they did not. Measurements of pressure in the foot veins during exercise showed that this damage obstructed or reversed the

normal flow of blood from superficial to deep and then to proximal veins produced by exercise, leaving the superficial veins distended by a high pressure (90 mm Hg instead of 30 mm Hg) throughout exercise.[5] But how this loss of superficial venous hypotension during exercise caused ulceration was not apparent.

Most of the clinical studies of this period concentrated on patients with venous ulceration, but for every patient with an ulcer there are 20 or 30 with the characteristic changes in the skin and subcutaneous tissues that precede ulceration. In 1969 I thought that we might get more information by studying such patients, and there were two clues to indicate what lines to follow. The late Ian Whimster reminded me of an observation he had made in the 1950s of a pronounced increase in the number of capillary loops visible in a cross section of skin adjacent to a venous ulcer.[6] At the same time I had been impressed by the similarity of the clinical appearance of the tissues of the lower medial third of the leg in patients likely to develop venous ulcers to those of venous thrombosis and acute cellulitis, although neither were occurring, and the pioneering work of George Fearnley,[7] which had shown that there was a level of fibrinolytic activity in normal blood which might play a part in any disease which included the deposition of fibrin.

Two studies were, therefore, set in motion; firstly, to assess the level of fibrinolytic activity in the blood and vein walls of patients with venous disease and, secondly, to decide whether the changes in the skin capillaries seen in patients with venous disease were caused by the abnormal venous physiology and how these capillaries behaved. By chance both lines of research were fruitful. We found that patients with advanced skin changes secondary to venous disease had reduced amounts of fibrinolytic activator in the blood and the vein wall[8 9]; the leg veins of patients with preulcer changes were particularly deficient. Following the Fearnley approach I gave two patients with liposclerosis phenformin and ethyloestrenol. Their skin changes improved, and so a pilot study was begun of the effect of fibrinolytic enhancement with stanozolol on postphlebitic changes.[10] Later we found that the capillary abnormality was directly related to the severity of the damage to the calf pump,[11] as assessed from pressure studies of the foot veins during exercise, and that these capillaries were hyperpermeable, particularly to large molecules such as fibrinogen.[12] Histological studies showed a layer of fibrin around these capillaries which, we hypothesised, must act as a diffusion block to oxygen and so be the ultimate cause of tissue necrosis.[13] Since then, refined studies by Hopkins *et al*[14] with the Hammersmith Hospital positron emission tomography scanner have confirmed that there is an increased blood flow but a reduced utilisation of oxygen in preulcer tissues.

We think that the fibrin stays deposited in the tissues because the increased load presented to the interstitial tissues through the hyperpermeable capillaries exceeds the normal clearing capacity, which itself is diminished because of the reduced fibrinolytic activity in the tissue fluid. The interstitial deposition of fibrin causes fibrosis, and so I called the changes seen in the skin before an ulcer develops lipodermatosclerosis, usually shortened to liposclerosis.[15] These hypotheses[16] gained support when we found in the pilot study[10] that a drug which enhanced fibrinolysis accelerated the resolution of the changes in the skin and subcutaneous tissues, an observation that was later confirmed by a controlled crossover study.[17]

These studies may be relevant to other diseases. Physiologists have paid little attention to the factors that control the movement of interstitial fluid and keep the interstitial spaces clear. Perivascular deposition of protein is a common finding in many diseases, especially autoimmune and inflammatory conditions. Further studies of this backwater of the circulation may throw light on some of the connective tissue/collagen diseases.

The "postphlebitic leg" results from the combined effects of a disordered muscle venous pump and disordered interstitial fluid clearance. In most cases the latter is probably caused by the former, but if the disordered fluid clearance predates the thrombosis, the stage is set for a severe postphlebitic syndrome. The possibility that a disordered fibrinolytic system may precede the damage to the calf pump is supported by the observation that a reduced blood fibrinolytic activity is both a precursor and a predictor of deep vein thrombosis.[18] The whole process may be a vicious circle, poor fibrinolysis → deep vein thrombosis → disordered calf pump → hyperpermeable capillaries → excess interstitial fluid fibrin not removed because of poor fibrinolysis and exhaustion of fibrinolytic activator stores → further thrombosis. The spin off from this circle is tissue death from poor oxygenation—the venous ulcer.

## Clinical diagnosis

Lipodermatosclerosis is a sign of severe calf pump dysfunction and a warning of the possibility of ulceration. In its early stage it presents as redness or pigmentation of the skin or both. The skin and subcutaneous tissues then become thickened and often hot to touch. The heat and the redness often mislead the clinician to diagnose cellulitis or superficial thrombophlebitis, but the condition is chronic, painful, and tender, slowly enlarges, is not associated with any systemic signs of infection, and is rarely localised to the course of a subcutaneous vein. Thus it should not be wrongly diagnosed if the leg is carefully examined.

If liposclerosis is treated vigorously it can be reversed and ulceration prevented. Treatment consists in investigating the calf pump with a view to surgical restoration of pump function if possible, the use of high grade below knee elastic stockings of 40 mm Hg compression, and if these measures fail the use of drugs which enhance fibrinolysis such as stanozolol 5 mg twice daily. This regimen takes three to six months to work, and patients must not interrupt treatment.[17] It is a treatment for liposclerosis, not for ulceration.

Once an ulcer develops the situation changes completely. There is a skin defect and a bed of granulation tissue. The granulation tissue is usually healthy but growing from an area of subcutaneous fibrosis. The regrowth of the skin depends on many factors, not just the calf pump dysfunction. We do not know if the fibrinolytic deficiency prevents healing. The capillaries forming the ulcer granulation tissue may never become surrounded by fibrin, but when there is a profuse fibrinous exudate healing is usually delayed. If the exudation and venous congestion are abolished by putting the patient to bed, the ulcer will dry and heal. This change has been shown to be associated with better perfusion and a return to normal capillary permeability in the granulation tissue.[19]

How, then, should we treat venous ulcers? The causal abnormality—the calf pump dysfunction—must be corrected if possible. When the venous abnormality affects only the superficial and communicating veins, the standard forms of surgery, such as ligation of the saphenous and communicating veins, work well and restore calf pump function to near

normal levels. Healing of the ulcer may need to be hastened by skin grafting, but the skin should then remain healed and healthy provided no further venous dysfunction develops and provided the veins are supported and the calf pump assisted by the regular and perpetual use of good quality elastic stockings.

Sadly, only a few patients with ulceration have pure superficial vein disease. Most have damaged deep veins, usually a mixture of venous obstruction and valvular incompetence. In these patients surgery to the superficial veins invariably fails to achieve permanent healing of the ulcers.[20] At the moment we do not have accurate methods of diagnosing the precise abnormalities of the deep veins or any proved methods for correcting them. Most of the recent attempts to correct deep vein obstruction or valvular incompetence by surgical methods have been disappointing, and none has been tested in the long term.[21] Consequently we have to begin by reducing the raised superficial venous pressure with the simplest of remedies—an elastic stocking, or when an ulcer is present an impregnated bandage. When these methods fail bed rest and sometimes skin grafting may be necessary. Once the ulcer has healed a patient should be able to keep it healed with careful skin care, the diligent use of elastic support, and intermittent courses of stanozolol.

Regrettably many patients with ulcers are old, fat, and arthritic and cannot pull on elastic stockings. All we can offer these unfortunate souls is regular visits to an ulcer clinic for dressings and bandaging—an extremely expensive form of treatment when we add up doctors' and nurses' time, transport to and from hospital, and dressings. This desperate remedy can be avoided by doing our utmost to prevent deep vein thrombosis and treating any calf pump abnormality and any defect of fibrinolysis when the first tell tale signs of liposclerosis appear. Once an ulcer appears the skin has been irretrievably damaged, and the chance of restoring the leg and the skin to normal has been lost.

With postphlebitic ulcers the case is not one of "prevention being better than a cure"; we must prevent because we have no cure.

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