Raynaud’s phenomenon: its relevance to scleroderma

Jill J F Belch

It is now over 125 years since Maurice Raynaud first described his clinical syndrome. By definition, it is episodic digital ischaemia provoked by cold and emotion. It is classically manifest by pallor of the affected part followed by cyanosis and rubor. The pallor reflects vasospasm, the cyanosis results from removal of oxygen from the static venous blood, and rubor is caused by reactive hyperaemia following return of flow. Raynaud’s phenomenon has an overall prevalence of about 10%, though it may affect as many as 20–30% of younger women. Although it can be a benign condition (primary Raynaud’s disease), it may be associated with an underlying disorder (Raynaud’s syndrome). It is particularly associated with the connective tissue diseases (table 1). Raynaud’s syndrome occurs in between 90 and 98% of patients with systemic sclerosis, and more importantly proves to be the first symptom in 70% of patients with this disease and may precede its development by up to 20 years.

In this review it is proposed to evaluate the relevance of Raynaud’s phenomenon to systemic sclerosis in two ways. Firstly, by reporting the evidence supporting Raynaud’s phenomenon as a precursor of systemic sclerosis and, secondly, by discussing its importance as a complicating symptom in fully established systemic sclerosis.

Raynaud’s phenomenon as a precursor of systemic sclerosis

Based on various studies, the prevalence of systemic sclerosis ranges from 0.1 to 13.8 per 100,000 population. This is far lower than the prevalence of Raynaud’s phenomenon, and thus only a proportion of patients presenting with Raynaud’s phenomenon will progress to systemic sclerosis. One of the earliest studies of disease progression was carried out by Gifford and Hines, in a study of 629 female patients over 28 years of age they found progression to a connective tissue disease in 24%. Another earlier study suggested a figure of 50%. Both these studies, however, were published before 1970 and since then there has been an increasing awareness that Raynaud’s syndrome may be much more common than previously thought. At the present time the frequency with which secondary conditions are recognised varies widely in reported studies and may depend in part on doctors’ referral patterns, duration of Raynaud’s phenomenon at the time seen, and the thoroughness with which a search for an associated disorder is undertaken. Moreover, the development of more sophisticated laboratory tests has produced a shrinking in the group with Raynaud’s disease and an expansion in the numbers of patients with Raynaud’s phenomenon and one or more features of systemic sclerosis. These patients are sometimes referred to as suspected secondary Raynaud’s syndrome.

It should be noted, however, that the above applies to patients referred to hospital because of their Raynaud’s phenomenon and should not be applied to patients with Raynaud’s phenomenon in the general population. This is clearly shown by the low incidence or absence of connective tissue disease in a group of patients with Raynaud’s phenomenon in the general population followed up by questionnaire. Both from a clinical and prognostic point of view, however, it is important to be able to detect, if possible, those patients with Raynaud’s phenomenon who will develop a connective tissue disease. Furthermore, the study of the pathophysiology of systemic sclerosis might be enhanced by identifying patients at risk or those presenting early in the disease. This early detection of a connective tissue disease in patients with Raynaud’s phenomenon can be difficult, but, recently, more clearly defined abnormalities have been detected which have a strong link with disease progression (table 2). These are: (a) certain clinical features; (b) abnormal nailfold vessels; (c) some immunological tests; and (d) test of blood coagulation and rheology. Each will be dealt with in turn.

### Table 1: Conditions associated with Raynaud’s phenomenon

<table>
<thead>
<tr>
<th>Immuneological disorders</th>
<th>Other immune disease</th>
<th>Systemic sclerosis</th>
<th>Systemic lupus erythematosus</th>
<th>Mixed connective tissue disease</th>
<th>Dermatomyositis</th>
<th>Rheumatoid arthritis</th>
<th>Cryoglobulinaemia</th>
<th>Sjogren’s syndrome</th>
<th>Occupational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid autoimmune disease</td>
<td>Thoracic outlet syndrome (e.g., cervical rib)</td>
<td>Atherosclerosis (especially Beurger’s disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Others</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignancy</td>
</tr>
</tbody>
</table>

### Table 2: Features associated with progression of Raynaud’s disease to Raynaud’s syndrome

<table>
<thead>
<tr>
<th>a Clinical symptoms and signs</th>
<th>c Detection of antibodies</th>
<th>d Blood coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any features of connective tissue disease</td>
<td>Antinuclear factor</td>
<td>Raised factor VIII von Willebrand</td>
</tr>
<tr>
<td>Asymmetry of vasospastic attacks</td>
<td>Antiendothelium</td>
<td></td>
</tr>
<tr>
<td>Digital ulceration</td>
<td>Anticardiolipin</td>
<td></td>
</tr>
<tr>
<td>Schleroderma 70</td>
<td>Type IV collagen</td>
<td></td>
</tr>
<tr>
<td>Very young children</td>
<td>Laminin</td>
<td></td>
</tr>
<tr>
<td>Return of chilblains in older age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older age at onset of Raynaud’s phenomenon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very young children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal nailfold vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raised factor VIII von Willebrand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor antigen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raised β thromboglobulin</td>
<td></td>
</tr>
</tbody>
</table>
Clinical features associated with connective tissue disease development

The American Rheumatism Association (ARA) criteria for systemic sclerosis have a high specificity but low sensitivity for the disease. Thus patients who quite clearly have a scleroderma spectrum disorder presenting with isolated features such as sclerodactyly, or pitting scars and digital ulceration do not fulfill the ARA criteria. It is reasonable to suspect on clinical grounds that the disease in such patients will evolve with time into fully established systemic sclerosis, and indeed this impression is supported by prospective clinical studies. Thus isolated features of connective tissue disease occurring in association with Raynaud’s phenomenon should alert clinical suspicion.

The age of onset of Raynaud’s phenomenon may also be important. As stated, Raynaud’s phenomenon is common in young women and most of these patients probably have primary Raynaud’s disease. When Raynaud’s phenomenon develops in older subjects the likelihood of an underlying connective tissue disease is increased. Kallenberg reports a study of 90 patients, in whom the median age of onset of vasospastic symptoms in Raynaud’s disease was 14 years, and 36 years in patients with a definite connective tissue disease. Eighty per cent of patients presenting with onset of Raynaud’s phenomenon at the age of 60 years or above will have an associated condition, but the incidence of connective tissue disease remains the same as in the general population. The higher number of secondary cases reflects a larger proportion of patients with atherosclerosis (29% vs 5% in the total Raynaud’s population) and to a lesser extent, hyperviscosity syndromes secondary to a malignancy. Conversely, Raynaud’s phenomenon occurring in very young children, though rare, is usually due to an underlying connective tissue disease.

Other suspicious but, as yet, unvalidated symptoms which perhaps should alert the clinician are those such as the presence of digital ulceration. Digital ulceration does not occur in Raynaud’s disease. The reoccurrence of chilblains in an adult may also raise suspicions, as should the occurrence of severe attacks persisting throughout the summer. Furthermore, asymmetrical colour change with few digits affected suggests Raynaud’s syndrome rather than Raynaud’s disease. It is also of interest that those patients who do develop systemic sclerosis are much more likely to develop limited cutaneous systemic sclerosis (CREST syndrome) than Raynaud’s phenomenon. If the history of the preceding Raynaud’s phenomenon is over many years or decades. Those presenting with systemic sclerosis within one year of onset of Raynaud’s phenomenon tend to have diffuse systemic sclerosis (progressive systemic sclerosis). The above clinical symptoms, however, can only act as a guide to the clinician as age and symptomatology vary widely at presentation. A more reliable guide is the finding of abnormal nailfold vessels on capillary microscopy.

Nailfold capillary microscopy

A more reliable indication of systemic sclerosis is the microvascular involvement by the disease, which results in characteristic patterns of capillary abnormalities in the skin of the fingers, especially at the nail fold, that can be seen by in vivo microscopy. Direct observations of capillaries in human skin date back to 1912, but the best known early description of nailfold capillary abnormalities in systemic sclerosis was published by Brown and O’Leary in 1926. Recent refinements have permitted photographic recordings of the row of horizontal capillary loops at the nail fold just proximal to the cuticle, but less sophisticated apparatus allows a clinician to examine the nailfold vessels as part of his or her routine clinical procedure. Nailfold capillary abnormalities have been seen in many diseases, but their most characteristic pattern is found in the scleroderma spectrum disorders; systemic sclerosis, mixed connective tissue disease, overlap syndromes, and dermatomyositis. They are also seen in patients with Raynaud’s phenomenon at risk of developing systemic sclerosis. Fitzgerald et al in a prospective study showed that an abnormal nailfold capillary pattern was strongly associated with the subsequent development of systemic sclerosis both limited and diffuse. This is true both for children presenting with Raynaud’s phenomenon and for adults. The main characteristics of vessel abnormalities are: (a) enlargement of all three parts of the capillary loop: arterial, apical, and venular and (b) the loss of capillaries either diffusely or in localised areas (figure). Those with limited systemic sclerosis (CREST) tend to develop only enlargement of vessels, whereas in those patients with diffuse systemic sclerosis (progressive systemic sclerosis) both patterns are seen.

Immunological factors

Improvements in the techniques of antinuclear antibody determination have substantially increased the usefulness of this approach in...
systemic sclerosis. In particular, the change in nuclear substrate to that of rapidly dividing human cells has produced an increase in the proportion of patients with systemic sclerosis with detectable serum antinuclear antibodies from 33% to better than 95%. Recent attention has focused particularly on the anticientromere antibody and the scleroderma 70 antibody (Scl 70). Anticentromere antibody is found in patients with limited systemic sclerosis (CREST). In contrast, Scl 70 is found in patients with diffuse systemic sclerosis. Work by Cruz et al and by Goldman has shown anticientromere antibody and Scl 70 in the blood of some patients with Raynaud’s disease alone. Both groups suggested that such patients may be the ones who progress to systemic sclerosis. Kallenberg et al investigated this possibility further by following up 85 patients with Raynaud’s phenomenon for six years. In those presenting with Raynaud’s disease alone anticientromere antibody had a predictive value for the development of limited systemic sclerosis (sensitivity 60%, specificity 98%) and Scl 70 for diffuse systemic sclerosis (sensitivity 38%, specificity 100%). Interestingly, Steen et al looked at anticientromere antibodies as a predictor of severity within the group with systemic sclerosis and found that antinuclear antibody positivity did not relate to survival or to the development of pulmonary hypertension. Thus it seems that the presence of antinuclear antibodies, particularly anticientromere antibody and Scl 70, in patients with apparent Raynaud’s disease may indicate later progression to systemic sclerosis. Once the clinical syndrome is established, however, the antinuclear antibodies lose their prognostic value.

Of interest, is recent work by Gabrielli et al who investigated antibodies against type IV collagen and laminin. Most patients with systemic sclerosis were found to have one or other of the antibodies in their blood. Additionally, about 25% of serum samples from patients with clinical Raynaud’s disease were also positive. Of these, 80% later developed additional serological or clinical manifestations of systemic sclerosis. As the incidence of antinuclear antibodies and abnormal nailfold vessels is not stated in the group who progressed, however, it is not possible to assess the importance of the above findings.

Blood coagulation and rheology
Blood flow in the microcirculation depends directly on the properties of the cellular elements of both blood and plasma. Hard erythrocytes, activated platelets, and leucocytes have all been reported in Raynaud’s phenomenon, as have increased plasma viscosity and decreased fibrinolysis. Most of these abnormalities are best seen in patients with established systemic sclerosis. This is also true of the endothelial cell injury that may contribute to the Raynaud’s syndrome in systemic sclerosis. The exceptions to this are plasma β thromboglobulin concentrations and factor VIII von Willebrand factor antigen (vWFAg).

Platelet activation either primary or as a result of endothelial damage may contribute to structural changes in the blood vessel by the release of factors such as serotonin and platelet derived growth factor. β Thromboglobulin is a further protein released by activated platelets and this can be measured in plasma by a sensitive radioimmunoassay. Raised concentrations of β thromboglobulin have been detected in systemic sclerosis and also in some studies of Raynaud’s disease, though not in others. In the later study concentrations of β thromboglobulin were raised in patients with Raynaud’s phenomenon and in patients with systemic sclerosis, suggesting that raised concentrations might help predict those who will develop fully established systemic sclerosis.

Factor VIII vWFAg is made and released by vascular endothelium, and various noxious physical and chemical stimuli will increase its production. It seems to be a marker for vascular damage and through its action on platelets and in the coagulation cascade has a prothrombotic effect. Kahaleh et al reported raised concentrations of factor VIII vWFAg in systemic sclerosis, and later work showed raised concentrations in both Raynaud’s and Raynaud’s syndrome which is known to suggest transformation from Raynaud’s disease to Raynaud’s syndrome. These data on both β thromboglobulin and factor VIII vWFAg need to be confirmed in large prospective studies.

Extent of vasospasm
It has been suggested that the severity of the vasospasm may be useful as a guide to those who later develop systemic sclerosis. It would seem possible, therefore, that the extent of vasospasm might also be a useful marker. Raynaud’s phenomenon is recognised clinically by the characteristic vasospasm induced colour changes in the fingers and toes. Similar findings are also observed in the ear lobes, tip of the nose, and other extremities. Cold induced vasospasm has also been detected in the brain (migraine headaches), heart, lung, and oesophagus of patients with Raynaud’s phenomenon. What is of interest, however, is that this vasospasm is not limited to those patients with systemic sclerosis, and patients with Raynaud’s disease can also have migraine, lung and oesophageal vasospasm. At the present time, therefore, it seems unlikely that the presence of systemic vasospasm will be helpful in separating Raynaud’s disease from early Raynaud’s syndrome.

Connective tissue diseases such as systemic sclerosis often have an insidious onset with Raynaud’s phenomenon being the first symptom in most cases, preceding the disease by many years. Raynaud’s phenomenon is common, however, particularly in young women, but will progress to systemic sclerosis in only a minority. For prognostic and possibly therapeutic reasons it is important to know which patients have Raynaud’s disease which will develop, or is already evolving, into systemic sclerosis. The above clinical and laboratory factors may be useful in determining which patients with
Raynaud’s disease will progress to Raynaud’s syndrome. Indeed, it has been suggested that nailfold capillary microscopy and serum antinuclear antibody determinations can detect more than 90% of patients destined to have systemic sclerosis. Abnormal nailfold vessels and the presence of antinuclear antibodies in the blood, combined with other clinical guides, such as age of onset and vasospasm severity, should provide helpful guidelines for the diagnosis of Raynaud’s syndrome associated with systemic sclerosis.

Raynaud’s syndrome in systemic sclerosis

There are two important aspects in the study of Raynaud’s syndrome as part of the manifestations of systemic sclerosis: (a) the possible role of the vasospasm/abnormal vasculature in the actual pathogenesis of systemic sclerosis and (b) the management of the troublesome symptoms produced by a combination of the Raynaud’s syndrome, blood abnormalities, and skin thickening.

Vascular factors and the pathogenesis of systemic sclerosis

Although the pathophysiology of systemic sclerosis is not fully clarified, microvascular changes and the process of fibrosis are both thought to be involved. As Raynaud’s phenomenon can result from simple injury to the vasculature, as is seen in cold, vibration, and traumatic injury, it is possible that the Raynaud’s phenomenon seen early in systemic sclerosis is a manifestation of early vascular damage. A serum factor cytotoxic for endothelial cells has been described in systemic sclerosis and is dealt with later in this issue. As this cytotoxic factor has also been detected in the serum of patients with Raynaud’s disease there is a possibility that vasospasm itself combined with vascular damage and viscous blood may allow progression of the disease. The diffuse nature of the vasospasm and microvascular destruction in systemic sclerosis leads to a state of underperfusion and chronic ischaemia of various organs. Data show that human fibroblasts exhibit prolonged growth and extended life span at decreased oxygen concentrations. An increase in skin thickness secondary to hypoxia may underlie the scleroderma process in systemic sclerosis. Such a hypothesis can, however, only be examined when effective enough treatments for vasospasm are used over the longer term. If prevention of disease progression occurs with such treatments it would be a useful pointer to the pathogenesis of systemic sclerosis.

Treatment of Raynaud’s syndrome

In Raynaud’s syndrome associated with systemic sclerosis the symptomatology can be severe, with skin nutritional changes, digital ulcers, and even gangrene. Although the vasospasm contributes to these symptoms, other factors combine to produce what is for many patients the worst feature of their disease—continual digital ischaemia. It has long been recognised that structural changes can be seen in the small vessels throughout the body in systemic sclerosis. Eighty per cent of digital arteries studied showed luminal narrowing of 75% or more. Furthermore, whether the hard red cells, activated platelets, and abnormalities of fibrinolysis are a cause or consequence of the damaged endothelium, they contribute further to decreased blood flow in the microcirculation. The combination of vasospasm, narrowed vessels, and blood abnormalities produces a significant clinical problem which requires urgent management.

MILD DISEASE

Although most patients with systemic sclerosis have severe disease, some patients with mild Raynaud’s disease can benefit from simple measures. Many patients are apprehensive about their disease, reassurance is often required, and information about the self help group, the Raynaud’s Association, is often gratefully received. If the use of tobacco is stopped, this can produce immediate benefit, as can a change in occupation. Withdrawal of drugs known to be associated with Raynaud’s phenomenon can also be useful. Although the contraceptive pill has been linked anecdotally with the development of Raynaud’s disease, this has never been clearly proved in epidemiological studies. It is current practice to stop the contraceptive pill only if there is a clear link with the time of onset of the disease.

Protection from cold is very important. To achieve this without subscribing to a hermit like existence is difficult, but there are practical solutions to the problem. Electrically heated socks and gloves are, for some, the ideal solution—a rechargeable battery worn round the waist provides up to three hours of warmth. The wires are concealed beneath the clothing providing a normal appearance. Budget restraints in some health board areas mean that these batteries can be difficult to obtain, but they are very popular with patients, though occasionally irritation of ulcers by the added heat has been noted. Chemical hand warmers obtainable from local sports shops provide a satisfactory alternative source of heat. ‘Comfort shoes’ obtainable from surgical appliance departments can help the feet of patients with

Table 3 Blood and vessel wall factors which contribute to poor flow in the microcirculation of patients with systemic sclerosis

<table>
<thead>
<tr>
<th>Platelet</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased aggregation</td>
<td>Increased fibrinogen</td>
</tr>
<tr>
<td>Increased β thromboglobulin</td>
<td>Increased viscosity</td>
</tr>
<tr>
<td>Increased serotonin</td>
<td>Increased lipid peroxides</td>
</tr>
<tr>
<td>? Circulating aggregates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cell</td>
<td>Vessel wall</td>
</tr>
<tr>
<td>Decreased red cell deformability</td>
<td>Increased factor VIII von Willebrand factor antigen</td>
</tr>
<tr>
<td>Increased superoxide dismutase</td>
<td>Decreased fibrinolysis</td>
</tr>
<tr>
<td></td>
<td>Decreased prostacyclin production (later stages)</td>
</tr>
<tr>
<td></td>
<td>Endothelial cytotoxic factor</td>
</tr>
</tbody>
</table>

*Raynaud’s and Scleroderma Association Trust, 112 Crewe Road, Alsager, Cheshire ST7 2JA.*
Raynaud’s phenomenon: its relevance to scleroderma

Raynaud’s phenomenon—The padded soles relieve the pressure on the toes, which can result in vasospasm, and also keep the feet warm.

SEVERE DISEASE
Drug treatment of Raynaud’s phenomenon remains symptomatic, directed towards the spasm itself or to blood constituents which contribute to decreased blood flow.

Vasodilators The use of vasodilators in Raynaud’s syndrome remains controversial as most studies have been uncontrolled. Some encouraging results have been obtained with these compounds in patients with mild disease. Patients with systemic sclerosis tend to have more severe symptoms, and work with vasodilators in these patients has been disappointing, however, with side effects being the limiting factor.

Nifedipine This calcium channel blocker is currently the recommended treatment for Raynaud’s phenomenon, at a starting dose of 10 mg three times a day, which should be increased gradually to 20 mg three times a day. Its mechanism of action in Raynaud’s phenomenon is predominantly vasodilatory, but it is also an antiplatelet agent and may have other potential antithrombotic effects. The major problem with nifedipine is that to obtain a significant therapeutic effect, intolerable vasodilatory side effects may be induced. In addition, it has been suggested that in systemic sclerosis such profound vasodilatation can have a steal effect, producing decreased digital blood flow.

Much of the recent research, therefore, has concentrated on attenuation of the side effects. Friedman et al recommended a maximum dose of 10 mg three times a day in elderly patients with concomitant administration of aspirin for headache relief. As most side effects are related to the degree of acute vasodilatation, however, an approach designed to minimise such effects should be investigated. A slow release preparation is already used by most clinicians, and Challenor et al demonstrated significant benefit in patients given both 10 and 20 mg slow release nifedipine preparations (nifedipine retard) twice a day. The dose can be increased to 20 mg of the retard preparation three times a day.

Prostaglandin infusion The vasodilator antiplatelet prostaglandins, prostaglandin E1 and prostaacyclin, may also be useful in the management of Raynaud’s phenomenon. These drugs have to be given by intravenous infusion (prostaglandin E1 by central line) and therefore require at least hospital attendance if not admission. Side effects of both prostaglandin E1 and prostaacyclin are related to vasodilatation, but these disappear at the end of the infusion. It is interesting that the vasodilator antiplatelet effects are short lived, but the duration of response can be up to six weeks. This may be explained by the beneficial effects of the prostaglandins on fibrinolysis and white and red blood cells. Unfortunately, these treatments do not cure the patient and repetition of the regimen is required. This means that in practice prostaglandin treatment is usually reserved for patients with intractable digital ulceration. More recently, stable prostacynol analogues have become available and a recent study confirmed the benefit of iloprost (Schering chemicals) as a treatment for Raynaud’s syndrome complicated by systemic sclerosis. The side effects seen were vasodilatory but occurred only during the three day infusion. The good tolerance of this drug prompted Rademaker et al to compare intravenous iloprost with oral nifedipine in Raynaud’s syndrome secondary to systemic sclerosis. Both drugs were found to be effective but the side effects seen with nifedipine were considered to be more troublesome. Alternative approaches continue to be investigated, such as orally and transdermally absorbed stable prostaglandin analogues, and this may allow more prolonged treatment. The long term effects of prostaglandins on bone and tumour growth must, however, first be established.

As prostaglandins are endogenous local hormones, an attractive concept is to stimulate production of the body’s own vasodilator prostaglandins by giving the appropriate precursor essential fatty acid. Evening primrose oil contains the precursor of prostaglandin E1. Study results of evening primrose oil have been somewhat disappointing, however, and although some subjective improvement has been reported, no objective improvement of blood flow has been shown. Further controlled work is required. Fish oil contains eicosapentaenoic acid, the precursor of the three series prostaglandins. Fish oil has been shown to have antiplatelet and viscosity lowering effects. The study of fish oil by DiGiacomo et al, however, showed that although patients with Raynaud’s disease apparently benefited from such treatment, patients with Raynaud’s syndrome failed to respond.

Ketanserin Ketanserin (Janssen Pharmaceuticals), a serotonin antagonist with slight , adrenergic antagonist effects, has been shown possibly to be useful in the treatment of Raynaud’s phenomenon in a recent large multicentre study. Jay et al showed that ketanserin significantly improved the subjective symptoms of patients with both primary and secondary Raynaud’s phenomenon. Unfortunately, owing to the multicentre nature of the study, objective tests of blood flow could not be measured.

Viscosity fibrinolysis and red cell deformability At the present time drugs such as low molecular weight dextran or ancord, a defibrinating agent, have not been conclusively proved to be of use in Raynaud’s syndrome. Moreover, they both require parenteral admission and careful patient monitoring. Stanozolol, an anabolic steroid which increases fibrinolysis, has been used in patients with Raynaud’s phenomenon, and early work suggests some benefit when given in a dose of 5 mg twice a day. Side effects are those usually associated with anabolic steroids, including virilisation of women and increased activity of liver enzymes. This treatment is therefore reserved for severely affected men and postmenopausal women who have normal liver function. Results of a large study carried out in
Raynaud's phenomenon: its relevance to scleroderma


