SYSTEMIC sclerosis (SSc) is still an incurable disease, but not an untreatable one. Its present-day management should be based on: (i) subsetting the disease; (ii) staging the subset; (iii) earliest possible diagnosis of internal organ involvement; (iv) a proactive approach towards the recognition of an 'at risk' population and (v) knowledge of the current thinking about the pathogenesis of the disorder so that patients receive the most appropriate treatment.

The major pathological hallmarks of SSc are vascular change, perivascular and tissue accumulation of mononuclear leukocytes and an increased deposition of extracellular matrix in the skin and internal organs [1, 2]. This deposition would appear to be in response to a disruption of the normal steady-state of connective tissue turnover and regulated repair. These pathological processes are now known to be closely related and perhaps directly linked. The current most-favoured explanation implicates intimal vascular damage/activation resulting in increased vascular permeability and mononuclear leukocyte vascular adhesion with subsequent migration into the interstitium. Mediators are released, concomitant with, or subsequent to, these inflammatory events, and fibroblasts develop a fibrogenic phenotype; excess normal matrix is deposited and organ dysfunction eventually results.

Although the cellular infiltrate varies somewhat depending on stage of disease and the organs involved, the presence of IL-2 producing T-lymphocytes of the α/β subset expressing typical surface antigens, including CD3, CD4, CD45, HLA-DR and LFA-1, is consistently noted [3]. It is however not yet known whether the immune activation is triggered before or after the endothelial damage [4]. In addition, intense vasospasm (Raynaud's phenomenon) often occurs in the extremities and internal organs. This could lead to structural and functional change in the endothelium which might contribute to the development of the scleroderma lesion through the local effects of endothelial cell products such as nitric oxide, endothelium or cytokines [5]. A large number of cytokines, of different cellular origins, have been implicated as potential effectors of fibrosis within the context of scleroderma including TGFβ, PDGF, TNFα, IGFs, bFGF, IL-1, IL-4, IL-6, IL-8 and interferon-γ [6]. It is unlikely that any individual mediator can account for the complex pathology of SSc, but rather that they act in concert to establish the conditions that permit fibroblasts to develop the SSc phenotype [7]. The particular importance of any mediator may be dependent upon the stage of the disease, or indeed the disease subset, but key cytokines or growth factors may be future targets for therapeutic attack.

The ordering of therapy in SSc must marry these three elements; the vascular, the immune and the fibrotic to the subset and stage of the disease before the best combination of available drugs can be found for any individual patient. Once permanent vascular, dermal or integral organ changes appear, several physical and serological differences separate SSc patients into distinct groups, each with a distinct pattern of clinical presentation and a different disease course [8]. The extent of skin involvement and the associated pattern of internal organ damage forms the basis for one of the most used and current classifications of SSc (Table I). It is usually possible within the first year of observation to determine whether the pattern of skin sclerosis indicates diffuse disease (DSSc—involving skin of the upper arm, trunk and leg) or whether cutaneous involvement is restricted to the extremities and face indicating limited SSc (lcSSc). Limited disease is usually preceded by a lengthy period of Raynaud's and its vascular features are especially prominent. There are also rare cases of SSc in which the skin is never thickened but the internal organs are affected (scleroderma sine scleroderma).

Choice of treatment, and design of any therapeutic trial, should depend not only on the disease subset but also consider disease duration, otherwise the results
will be meaningless [9]. For example, patients with late stage dcSSc are usually not suitable for trials of immunosuppressive agents, as measurable improvement can hardly be expected when the disease has entered the phase of advanced fibrosis and vascular damage; equally, patients with lcSSc should not be included in trials of major antifibrotic agents, their problem being mainly a vascular one. Recognition of a 'pre-scleroderma' status before the disease is fully expressed is equally important in management of the scleroderma spectrum disorders. Between 5 and 10% of those who develop Raynaud's phenomenon (RP) will progress to a connective tissue disease, the most common of which is scleroderma [10]. Two markers of predictive value for the subsequent development of scleroderma are abnormal nailfold capillaries and antinuclear antibodies; it has been suggested that presence of both will detect over 90% of those destined to develop SSC [11, 12]. Identification of such patients will permit careful monitoring and the earliest possible therapeutic intervention.

This approach should also be extended to the earliest possible detection of internal organ involvement, which again might allow for its containment. Pulmonary involvement (fibrosis or vascular disease) is now the major cause of death in SSc [13]. The judicious use of high-resolution computerized tomography (HRCT) and technetium-99m diethylene triamine pentacetate (DPTA) scanning is beginning to provide much earlier diagnosis and indication of progression of lung disease [14]. The correlation between CT patterns (reticular or amorphous parenchymal opacification) and histological findings at biopsy, predominantly fibrosis or inflammatory, respectively [15], will almost certainly reduce the need for histological staging prior to therapy. Using these tools for diagnosis and serial monitoring, the place of steroids and cyclophosphamide and other therapies for lung disease can be accurately evaluated [16]. Pulmonary hypertension is a particularly difficult problem, and drugs to influence its ultimate outcome are lacking. However, detection at an early stage, particularly in the limited subset who are often otherwise quite well, with yearly estimation of peak pulmonary systolic blood pressure by Doppler-echocardiography plus serial pulmonary function testing with DLCO, allows the earliest non-invasive detection of pulmonary hypertension and so therapies such as long-term anticoagulation and repeated or continuous infusions of iloprost can be used. Both these agents have been found to be useful in patients with primary pulmonary hypertension [17, 18].

No single drug or combination of drugs has proved satisfactory in the treatment of SSc in suitably controlled prospective trials [19, 20]. This is entirely understandable when one considers that the concepts of the aetiopathogenesis of SSc are still evolving. SSc may represent more than one disease; lcSSc could represent a separate vascular entity or at least a far flung element from diffuse disease. The events that give rise to these conditions are several, they may occur simultaneously or sequentially and the ultimate therapy for SSc and its subsets may well be varied. In diffuse disease it may transpire that initial treatment is directed towards the immune system with later anti-fibrotic and vascular therapy. In contrast, optimum therapies in lcSSc may be primarily vascular throughout the disease, perhaps with using of agents to modulate endothelial cell properties when such drugs become available.

Presently many drugs are being used in SSc, thankfully some are now under formal testing in several countries of the world and multicentre multinational trials are almost certainly needed if we are to successfully evaluate new potential therapies for this uncommon condition. Some treatments (see Table II), particularly vascular ones, are tried and tested and in daily use. As yet there are no 'targeted' therapies for SSc and a rather 'blanderbuss' approach with non-specific immunosuppression, antifibrotic and vascular agents has been adopted. However, careful consideration of subsets and natural history together with the stage and internal organ involvement in the individual patient can optimize the use of drugs currently available (Table III). For the future there should be hope; the level of interest and active research into the condition is increasing and increased knowledge should

### TABLE I
**Classification: systemic sclerosis subsets**

1. "Pre-scleroderma"
   - Raynaud's plus nailfold capillary changes disease specific circulating antinuclear antibodies (topoisomerase-I, anti-centromere [nucleolar], digital), ischaemic changes.

2. **Diffuse cutaneous SSc (dcSSc)**
   - Onset of skin changes (puffy or hidebound) within 1 yr of onset of Raynaud's.
   - Truncal and acral skin involvement.
   - Presence of tendon friction rubs.
   - Early and significant incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial involvement.
   - Nailfold capillary dilatation and capillary drop out.
   - Antitopoisomerase-I (ScL-70) antibodies (30% of patients).

3. **Limited cutaneous SSc (lcSSc)**
   - Raynaud's for several years (occasionally decades).
   - Skin involvement limited to hands, face, feet and forearms (acral).
   - A significant (10-15 yr) late incidence of pulmonary hypertension, with or without interstitial lung disease, skin calcifications, telangiectasia and gastrointestinal involvement.
   - A high incidence of ACA (70-80%).
   - Dilated nailfold capillary loops, usually without capillary drop out.

4. **Scleroderma sine scleroderma**
   - Raynaud's ±.
   - No skin involvement.
   - Presentation with pulmonary fibrosis, scleroderma renal crisis, cardiac disease, gastrointestinal disease.
   - Antinuclear antibodies may be present (ScL 70, ACA, nucleolar).

Until more is known about the aetiopathogenesis, the above provides a useful working classification. There is the possibility that with the increasing number of autoantibodies now being described in SSC we will be able to define smaller clinical subsets and this may influence our ability to offer more accurate prognosis.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Examples</th>
<th>Comments</th>
<th>Efficacy in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uncontrolled/Controlled</td>
</tr>
<tr>
<td>1. Vasodilator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Oral</td>
<td>Calcium channel blockers:</td>
<td>Nifedipine retard, diltiazem</td>
<td>Response is idiosyncratic</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors:</td>
<td>Captopril, enalapril</td>
<td>In DcSSc may be renoprotective</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>Fish oil, vitamin E, epogam</td>
<td>Innoceous agents with some symptomatic benefits</td>
<td>Yes</td>
</tr>
<tr>
<td>(b) Intravenous</td>
<td>Prostanoids</td>
<td>Prostacyclin, PGE</td>
<td>Benefit persists up to 4 months, can be given prophylactically for winter-time protection from digital ulceration</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Immunomodulatory</td>
<td>Non-selective immunosuppressives:</td>
<td>Cyclophosphamide, Chlorambucil, azathioprine</td>
<td>Particularly in lung fibrosis</td>
<td>Yes</td>
</tr>
<tr>
<td>(a) Non-selective immunosuppressives:</td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>(b) Selective immunosuppressives:</td>
<td>Cyclosporin-A</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Antithymocyte globulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasmapheresis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Photopheresis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human gammaglobulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Antifibrotic</td>
<td>d-Penicillamine</td>
<td></td>
<td>Inhibits collagen fibril cross-linking</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Interferon</td>
<td>α or γ</td>
<td>Reduces fibroblast collagen production</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Colchicine</td>
<td></td>
<td>Inhibits fibroblast collagen release</td>
<td>No/yes</td>
</tr>
<tr>
<td>4. Anti-inflammatory</td>
<td>Corticosteroids</td>
<td>Prednisolone</td>
<td>Beneficial for myositis, arthralgia, lung disease</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>Methylprednisolone</td>
<td>For arthralgia, tendinitis, pericarditis</td>
<td>Yes = proven benefit</td>
</tr>
</tbody>
</table>

= proven benefit
No = proven no benefit
? = inconclusive/conflicting results
### TABLE III
Therapy for visceral manifestations in systemic sclerosis

<table>
<thead>
<tr>
<th>Organ</th>
<th>Site</th>
<th>Manifestations</th>
<th>Treatment available</th>
<th>Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Interstitial</td>
<td>Inflammation, fibrosis</td>
<td>Corticosteroids</td>
<td>Prednisolone</td>
<td>Alternate day regimen preferred</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Pulmonary hypertension</td>
<td>Immunosuppression, Oral anticoagulation, Pulsed i.v. prostacyclin</td>
<td>Cyclophosphamide, Warfarin, Iloprost</td>
<td>Useful in primary pulmonary hypertension, role in SSc unproven</td>
</tr>
<tr>
<td>Bowel</td>
<td>Oesophageal</td>
<td>Reflux oesophagitis, spasm, stricture</td>
<td>Proton pump inhibitors, H2-blockers, Antispasmodics</td>
<td>Omeprazole, Ranitidine, Cisapride</td>
<td>40-60 mg daily may be required</td>
</tr>
<tr>
<td>Midgut</td>
<td></td>
<td>Colic, diarrhoea</td>
<td>ACE inhibitors, Rotational antibiotics, Somatostatin analogues</td>
<td>Captopril, Enalapril, Ace inhibitors infusion</td>
<td>For breath test positive bacterial overgrowth, beneficial for diarrhoea, Surgery best avoided</td>
</tr>
<tr>
<td>Anorectal</td>
<td>Incontinence</td>
<td>Renal SSc crisis management</td>
<td>NSAIDs corticosteroids, Anti-arrhythmics, Corticosteroids</td>
<td>Naproxen, prednisolone, Prednisolone</td>
<td>Management directed by clinical severity, in collaboration with cardiologist</td>
</tr>
<tr>
<td>Heart</td>
<td>Pericardial</td>
<td>Pericarditis, effusion</td>
<td>NSAIDs corticosteroids</td>
<td>Naproxen, prednisolone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>Palpitations</td>
<td>Anti-arrhythmics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial</td>
<td>Heart failure</td>
<td>Corticosteroids</td>
<td>Prednisolone</td>
<td></td>
</tr>
</tbody>
</table>
translated quite quickly into rational therapy delivered at the earliest possible stage.

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REFERENCES