Treatment of systemic sclerosis

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Similar to other members of the family of connective tissue diseases, systemic sclerosis (scleroderma) is a chronic, often disabling, and disfiguring disease which represents a major challenge for both patient and doctor. The patient often must contend with fatigue, cold intolerance, pain, deformity and loss of hand function, and change in facial appearance. These physical changes and limitations result in loss of self esteem and pessimism about the future. For these reasons a good relation with the managing doctor and a strong family support system are extremely important assets for the patient with scleroderma. The doctor faces the spectre of an unusual and highly variable disease with no widely recognised effective treatment and in which life threatening visceral disease may appear quickly and without apparent warning. Even for the rheumatologist, predicting the natural history of disease in an individual patient with scleroderma is difficult, and experience with certain complications is very limited. Thus in many circumstances consultation with an expert having both a special interest and extensive experience in the disease is useful.

Many vitamins, hormones, pharmaceutical drugs, and surgical procedures have been reported to be successful in the treatment of systemic sclerosis. Almost all of these treatments have been received with great enthusiasm but later abandoned after more rigorous and critical scientific evaluation. Too often success has been claimed solely on the basis of a diminution in subjective complaints—for example, a reduction in frequency of Raynaud's phenomenon, which may occur as a placebo effect with virtually any new treatment, or poorly documented 'softening' of the skin. The influence of psychological factors on these and many other symptoms is important. For these reasons this review focuses only on methods of treatment which have adequate rationale and more than a few patients studied. Although some agents may be promising, individual anecdotal reports about their effectiveness are too numerous to detail here.

Evaluation of the effectiveness of treatment has proved difficult for several reasons related to the disease itself.¹ Systemic sclerosis is variable in its severity and in its rate of progression. Therefore, the classification of patients into recognised clinical-laboratory subsets is important in the design of therapeutic trials. Conversely, interpretation of the results of studies in which this precaution was not taken is facilitated by this knowledge. For example, patients with late stage disease should

rarely be entered into clinical trials as improvement cannot be expected in those manifestations that are the result of far advanced tissue fibrosis with severe atrophy. Because spontaneous improvement in the diffuse disease variant often occurs after several years, untreated control patients are necessary for comparison to determine whether a therapeutic regimen being studied is superior. Finally, there are limitations in the availability and application of objective criteria for ascertaining improvement (or deterioration) in the condition, particularly with respect to visceral changes.

One recent review is both comprehensive, including virtually all publications, and critical, yet at the same time fair, in its interpretation of results.² This concise and informative article is highly recommended as a valuable reference on the current status of systemic treatment for systemic sclerosis.

Patient classification

The most important task of the managing doctor is to classify each patient into one of the recognised subsets of systemic sclerosis. This is possible at the time of the initial visit in two thirds of patients and during follow up in over 80% of cases. The two most common variants are those in which there is either diffuse (widespread) or limited (restricted) skin involvement.^{3 4} A great deal is known about the natural history of each of these subtypes; this information is useful, not only in educating the patient and family, but also in planning follow up visits and monitoring laboratory studies.

It is essential to identify diffuse disease as early as possible, and long before the appearance of diagnostic truncal skin thickening. This is the type and stage of scleroderma in which intervention has the greatest potential to modify the disease course. The earliest clues to evolving diffuse disease include sclerodermatous skin changes occurring before the patient's report of Raynaud's phenomenon, capillary 'dropout' on nailfold microscopy, rapid progression of skin thickening proximal to the digits, palpable tendon friction rubs, polyarthritides with hand joint contractures, and serum antibody to Scl-70.⁴ Subjects with this variant are at considerably higher risk for the early development of visceral involvement, especially renal crisis, myocardial failure, interstitial lung disease, and gastrointestinal complications.

In contrast, limited cutaneous disease is characterised by prolonged Raynaud's phenomenon before any skin thickening, non-progressive or only slowly advancing skin

changes, prominence of digital telangiectasias and subcutaneous calcinosis, and the presence of serum anticentromere antibody. Subjects with this subtype rarely if ever develop myocardial or renal disease, but are peculiarly susceptible to the late (after 10 years or more) development of 'primary' pulmonary arterial hypertension (not secondary to interstitial fibrosis), intestinal malabsorption, biliary cirrhosis, and Sjögren's syndrome with vasculitis.

A third group of patients has coexistent features of systemic sclerosis and polymyositis. At least three serum autoantibody markers have been identified (anti-Jol, anti-PM-Scl, and anti-U1RNP), and the clinical syndromes associated with them have certain distinctive features.

Disease modifying treatment

No drug (or combination of drugs) has been proved to be of value in systemic sclerosis in adequately controlled prospective trials or is generally accepted as being useful. Perhaps this is understandable because most of the current concepts of its pathogenesis have been developed only within the last decade. The main cellular and extracellular participants in this disorder and possible sites for therapeutic intervention are the vascular endothelium, mononuclear cells, fibroblasts, and collagen.⁵ Rational treatment would be designed to (a) prevent endothelial cell cytotoxicity by mononuclear cells; (b) alter communication between mononuclear cell subsets; (c) prevent mononuclear cell stimulation of fibroblasts; (d) prevent mast cell degranulation; (e) block fibroblast production of procollagen; and (f) increase solubilisation of preformed collagen. The cells and cell products to which such intervention may be directed, and the types of treatment available today for the connective tissue diseases in general have been reviewed.⁶ Patients with diffuse disease in whom skin thickening is advancing are prime candidates for disease modifying treatment. In contrast, treatment is optional in subjects who present for initial evaluation after having passed the peak of skin thickening, and in those seen after spontaneous regression of skin changes no systemic treatment is indicated.

There has been recent interest in the development of laboratory tests linked to these pathogenetic events which may reflect disease activity. For example, preliminary studies suggest that damage to endothelial cells is reflected by plasma levels of factor VIII-von Willebrand factor antigen⁷; activation of lymphocytes is associated with increased serum levels of soluble interleukin 2 receptors⁸; and procollagen production by fibroblasts is followed by increased serum procollagen III peptide breakdown products.⁹

Anti-inflammatory agents

Anti-inflammatory drugs and corticosteroids have been disappointing in systemic sclerosis, perhaps because the inflammatory phase of the

disease gives way rapidly to a fibrotic stage, in which such agents would not be expected to be of benefit. Because of their potential toxicity corticosteroids should be restricted to patients with inflammatory myopathy or symptomatic serositis. On occasion, refractory arthritis and the 'oedematous' phase of skin involvement respond favourably to relatively small doses of corticosteroids, such as prednisone 5–10 mg/day. Myositis, however, may require higher doses. After the first two years of diffuse disease corticosteroids are seldom indicated and usually can be discontinued uneventfully. High dose corticosteroid treatment may precipitate acute renal failure, especially of the normotensive type with prominent microangiopathic haemolytic anaemia.¹⁰

Immunosuppressive methods

As noted above, there is mounting evidence that humoral and cell mediated immune abnormalities play an important part in the pathogenesis of systemic sclerosis. Consequently, various forms of immunosuppression have been proposed. Several potential beneficial effects can be suggested, including altered interactions between immunocompetent cells and inhibition of overactive fibroblasts by soluble mediators.¹¹

Azathioprine (150 mg/day, mean 24 months) was considered beneficial in an uncontrolled trial, although only eight of 21 patients had skin softening and ulcer healing and three discontinued the drug because of fever.¹² Chlorambucil results have been mixed.^{13 14} A recent three year, double blind, controlled trial of chlorambucil versus placebo in 65 patients with systemic sclerosis was negative.¹⁵ At the doses used (increasing to 0.1 mg/kg daily after one year and remaining the same thereafter) there was evidence of immunosuppression as the group treated with chlorambucil developed significant reduction of the mean absolute lymphocyte count compared with the untreated group. As in rheumatoid arthritis,¹⁶ late developing malignancy may be a limiting feature of the use of such alkylating agents.

Apheresis has been advocated,¹⁷ but its effects are not uniformly beneficial¹⁸ and are difficult to evaluate because of confounding immunosuppressive and corticosteroid treatment and lack of controls. Lymphoplasma-pheresis seems to have a better rationale than plasmapheresis, and a preliminary report was encouraging.¹⁹ In the latter investigation six patients treated with lymphoplasma-pheresis and five with plasmapheresis were randomly allocated to receive pheresis for three months and were compared with five untreated controls. The lymphoplasma-pheresis group had a significant improvement in disease 'score' compared with the other two groups. Both pheresis groups had better doctor and patient global assessment scores, but these results might have been influenced by the single blind design and because the doctor was aware of the treatment groups. Difficulty with vascular access, local haematomas and infections, and high costs are limiting features of this procedure.

Cyclosporin A has been used in a limited

number of patients,²⁰ and higher doses have been followed by instances of hypertension and renal insufficiency, both of which could be attributed to either the drug or scleroderma. Lower doses of cyclosporin may be an important compromise, but inadequate numbers of patients have been studied thus far. An extension of a previous study²¹ includes 16 patients, almost all of whom had diffuse disease. They received 2.5–5.0 mg/kg daily and have been followed up for an average of 16.8 months. The mean skin thickness score decreased over 40% and a weighted organ score improved from 7.4 to 5.7 after one year, but the diffusing capacity was unchanged. Four patients developed renal disease, three considered to be due to scleroderma and one to cyclosporin.

Recombinant interferon gamma, which is capable of inhibiting collagen synthesis by fibroblasts in vitro,²² has been evaluated in a pilot study. It was given in a dose of 100 µg/day intramuscularly for six months, and the authors reported significant improvement in skin thickness, several musculoskeletal measurements, dysphagia, and creatinine clearance without serious toxicity.²³

Intravenous 5-fluorouracil was used in an open trial in 12 patients treated for a mean of over eight months.²⁴ After initial 'induction' with a total of 8 mg every other day and, later, daily doses of 8–12.5 mg/kg, a weekly maintenance dose of 10–20 mg was given. The results of this uncontrolled study were encouraging.

Renewed interest in the use of methotrexate in rheumatoid arthritis and polymyositis has raised the possibility that this drug might be effective in other connective tissue diseases. Improvement in two patients with systemic sclerosis treated with methotrexate has been reported,²⁵ and three of the four patients we have treated for 0.8–2.5 years have had reduced skin thickening (Medsger T A, unpublished data).

These preliminary observations would appear to justify a larger pilot study.

Two reports of patients with cutaneous sclerosis (probably diffuse fasciitis) and aplastic anaemia have been published, in which the skin improved after treatment with antithymocyte globulin.^{26, 27} In contrast, a small controlled study of total lymphoid irradiation was negative, with only transient skin improvement and progression of oesophageal and interstitial lung disease.²⁸

To date, there is no general agreement on the effectiveness of immunosuppressive therapy in systemic sclerosis. More information on the abnormal mononuclear cell subsets involved is needed before specific treatment can be designed to regulate them. Nevertheless, the use of immunosuppressive measures is justified in patients with rapidly progressive, life threatening or disabling disease, provided there is informed consent and close surveillance for adverse effects.

Colchicine

Colchicine can inhibit the accumulation of

collagen by blocking the conversion of procollagen to collagen, probably through interference with microtubule mediated transport,²⁹ or perhaps by stimulation of collagenase production.³⁰ Although toxicity is not a serious limiting factor, only one short term, double blind study³¹ and its subsequent long term open follow up have suggested improvement.³² Nineteen patients (15 with diffuse disease) were treated for 19–57 months with a mean of 10 mg colchicine per week. Seventeen of these patients improved in at least three categories of end points, most of which were subjective in their reporting or measurement. Without a control group these data cannot be interpreted and may represent only the natural history of late stage diffuse disease. Several other short term trials of 12–18 months were negative,^{33, 34} and in some patients progression of skin, musculoskeletal, and pulmonary involvement was reported.³³ The lack of long term controlled studies makes definitive conclusions impossible, but the data available to date do not support a role for colchicine in treating the systemic aspects of scleroderma.

D-Penicillamine

D-Penicillamine is a compound capable of interfering with the intermolecular cross linking of collagen³⁵ and also possesses immuno-suppressive activity. Reports on systemic sclerosis from England,³⁶ Denmark,³⁷ and the Soviet Union³⁸ have been optimistic. In a large retrospective analysis of patients with diffuse scleroderma, with disease duration of less than three years, 73 treated patients showed significantly reduced skin thickness and joint contractures after 18–30 months compared with 45 untreated patients with comparable initial disease duration and severity.³⁹ Patients treated with D-penicillamine also had better survival, owing in part to a considerably lower incidence of subsequent renal disease. In another report all of 18 patients with diffuse disease had improvement of skin thickening while receiving D-penicillamine, with a mean maximum percentage of skin surface affected declining from 65% to 15% after 4.6 years.⁴⁰

The initial D-penicillamine dose of 250 mg/day (on an empty stomach to enhance absorption) is increased every two to three months to a maximum of 750 to 1500 mg/day. In these studies most patients with early diffuse disease had progression of skin changes during the first six to 12 months of treatment. Thereafter, the pace of skin thickening diminished and improvement began. The first areas to clear were the last to have been affected—that is, central areas, including the trunk, upper arms, and thighs. Regression was often dramatic, with only sclerodactyly remaining after three to five years of treatment. Late recurrences after discontinuation of the drug have been seen,⁴⁰ and thus continuation of a low maintenance dose (250 mg/day) is recommended in patients who have improved.

The use of D-penicillamine may be accompanied by a disturbing plethora of potential side

effects, including haematological abnormalities and a variety of autoimmune problems, such as pemphigus, nephrotic syndrome, a lupus-like or polymyositis-like illness, Goodpasture's syndrome, and myasthenia gravis. Up to a quarter of patients are forced to discontinue the drug permanently, especially during the first three to six months.⁴¹ Careful monitoring of white blood cell and platelet counts and of urine protein are required.

Other drugs

N-acetylcysteine may reduce disulphide bonds, thus having an action similar to D-penicillamine on collagen, but a one year randomised, prospective double blind study of this agent versus placebo in 22 patients showed few differences.⁴² Cyclofenil, a weak oestrogenic compound, inhibits sulphate incorporation into proteoglycan. It has been studied in two placebo controlled trials of six months' duration with mild but unimpressive improvement in the groups treated with cyclofenil.^{43 44} An open trial of cyclofenil versus D-penicillamine up to two years in duration showed no differences.⁴⁵ Hepatotoxicity is a limiting factor.

Dimethyl sulphoxide, a commercial solvent, is a vasodilator, an analgesic drug, and can alter collagen metabolism. Although a number of uncontrolled studies and anecdotal reports have indicated its efficacy, three adequately controlled trials concluded that dimethyl sulphoxide is not useful for treatment of skin thickening, digital tip ulcers, or visceral disease.⁴⁶⁻⁴⁸

p-Aminobenzoic acid has been considered as a possible therapeutic agent for systemic sclerosis. A large retrospective analysis compared 223 patients treated for seven to 26 months with *p*-aminobenzoic acid and 96 patients treated with other drugs.⁴⁹ Most patients treated with *p*-aminobenzoic acid showed 'moderate to marked' skin improvement during follow up, but the time of first observation was biased in favour of *p*-aminobenzoic acid. On the basis of these results, and in the absence of long term controlled studies, this drug has not been proved to be effective.

Vascular protection

Circulating platelet aggregates and plasma β thromboglobulin concentrations are reduced after treatment with dipyridamole and aspirin,⁵⁰ but a randomised double blind trial of these agents versus placebo for one to two years showed no significant improvement in the treatment group.⁵¹ Factor XIII may play a part in facilitating collagen clearance by macrophages as it complexes with fibronectin and collagen. Two preliminary short term (three week) intravenous infusion studies of factor XIII have been performed with encouraging results for subjective improvement and functional capacity.^{52 53} Rigorously controlled long term studies should be done.

The selective serotonin antagonist ketanserin, although reported to be effective in the treatment of Raynaud's phenomenon due to

systemic sclerosis,⁵⁴ did not alter skin or visceral disease compared with that of untreated patients after a one year trial (unreported). α -Methyldopa with propranolol was likewise ineffective in altering disease during a two year study.⁵⁵ Because of the dramatic antihypertensive effect of captopril in many patients with 'renal crisis'⁵⁶ the angiotensin converting enzyme inhibitors have been considered as a possible primary treatment for the vascular component of systemic sclerosis. One strategy, as yet untested, would be to treat all patients with early diffuse disease with one of these drugs.

Low molecular weight dextran is thought to decrease red blood cell aggregation and thus reduce blood viscosity. A controlled study of dextran infusion resulted only in a strong subjective (placebo) effect on the peripheral circulation.⁵⁷ The potent vasodilator prostaglandins and prostacyclin have been examined in both uncontrolled and controlled studies. Intravenous infusions of both prostaglandin E₂⁵⁸ and carboprostacyclin⁵⁹ appear promising in reducing the frequency and severity of Raynaud's phenomenon and in promoting the healing of ischaemic digital tip ulcers; their beneficial effects may be prolonged. Plethysmographic evidence for improvement is less convincing. The potent vasoactive substances released when mast cells degranulate are believed to be important in fibrosing conditions.⁶⁰ Mast cells have been found in increased numbers and in a degranulated state in sclerodermatous skin.⁶¹ To this end a mast cell stabilising drug, ketotifen, is being studied in a formal clinical trial.

Supporting measures

Although the natural history of systemic sclerosis may be extremely difficult to alter, there are many individual organ system complications which can be treated successfully and can improve the patient's quality of life.

Peripheral vascular system

In systemic sclerosis Raynaud's phenomenon results from endothelial cell damage, subintimal thickening, and reduced luminal size with a normal vasoconstrictive response to cold exposure and emotional stress, rather than from exaggerated vasospasm. Most patients are able to minimise the frequency and severity of Raynaud's episodes by avoiding the cold and abstaining from tobacco. Dressing warmly with layers of clothing on the trunk, using mittens or electric gloves, and covering the head (a major source of heat loss) are important. Biofeedback techniques may be helpful in some patients.⁶²

Vasodilating drugs are beneficial only to the extent that severe luminal narrowing of blood vessels is absent. Thus these agents are more effective in Raynaud's disease than in Raynaud's phenomenon secondary to connective tissue disorders. As noted above, several promising new pharmacological agents have proved helpful in some patients in double blind studies, including the calcium channel blocker nife-

dipine, which relaxes vascular smooth muscle⁶³; a selective α_1 adrenergic receptor antagonist, prazosin⁶⁴; a serotonin antagonist which selectively blocks 5-hydroxytryptamine receptors, ketanserin⁵⁴; topical nitroglycerine⁶⁵; prostaglandin E_2 ⁶⁶; and prostaglandin I_2 (prosta-cyclin).⁶⁷ Inhibitors of platelet aggregation may be added in the hope of preventing the formation or propagation of thromboses, or both.

When non-healing digital tip ischaemic ulcers are present, or there is threatened gangrene, a more aggressive approach is required. Patients are often admitted to hospital and given adequate analgesics to control pain. Despite a negative controlled study of intra-arterial reserpine⁶⁸ we use the available substitute, phentolamine, 1.0 mg into the brachial or femoral artery once every four to six weeks in this more pressing circumstance. Intermittent cervical sympathetic blocks with local anaesthetic, as often as every other day for one to two weeks, may be a helpful adjunct. Digital sympathectomy is sometimes recommended, but there are insufficient reports to evaluate this technique. Surgical thoracic sympathectomy is not often recommended in systemic sclerosis as it is typically followed by partial, usually transient, improvement in Raynaud's phenomenon.⁶⁹ When large vessels are affected—for example, the radial and ulnar arteries, as suggested by palpation and confirmed by Doppler tests, arteriography should be performed because successful microvascular surgical reconstruction has been reported.⁷⁰ After large digital tip infarctions or gangrene have occurred, tissue demarcation achieved by autoamputation is preferred. However, if pain is severe or bacterial superinfection develops, surgical intervention is indicated.⁷¹

Skin

Maintaining adequate skin lubrication is difficult because thickened collagen 'chokes out' normal sweat and eccrine glands. Patients are urged to bathe less than daily, to avoid direct contact with household detergents, and to use lubricating creams (especially those containing lanolin). Intense pruritus may lead to excessive scratching with excoriation. This symptom tends to occur early in the course of diffuse disease, especially over the forearms, and disappears after months or several years.

Ischaemic digital tip ulcers are protected (a small plastic 'cage' for the fingertip) and immobilised. Secondary infection is signalled by abrupt erythema, swelling, and increased pain, and is almost always due to staphylococcus. Owing to the expected reduced vascularity, intravenous rather than oral administration of antibiotics is preferred.

Ulcerations over the proximal interphalangeal joints, elbows, and malleoli are most commonly attributable to both local trauma and ischaemia. Skin over these bony prominences is often thin and atrophic rather than thick. Radiographs are indicated to detect underlying septic arthritis or osteomyelitis, which require a surgical approach. Small ulcers may be managed with half strength hydrogen peroxide soaks two to three times

daily, followed by gentle local debridement. Topical care for larger lesions includes the protective cover of an occlusive dressing, such as Duoderm.

Calcinosis

Accumulation of calcium deposits in the form of hydroxyapatite is greatest in sites of excessive use or trauma (olecranon, patella) and those affected by Raynaud's phenomenon (fingers, especially palmar surfaces). Calcinosis is particularly common in subjects with limited cutaneous disease and serum anticentromere antibody, but those with longstanding diffuse disease may also develop extensive calcinosis.⁷² Simple surgical excision can sometimes be performed, provided the overlying skin is intact and is not infiltrated with calcium, which may interfere with wound healing.⁷¹ Unfortunately, recurrence is common. When skin breakdown and draining fistulous tracts from deeper levels have developed, primary wound closure is not possible. Three deaths in our series were attributed to septicaemia from infected deep calcinosis.

On occasion there is an intense, sterile, inflammatory reaction surrounding these hydroxyapatite deposits, along with constitutional symptoms such as low grade fever. This process may be dramatically improved by a course of oral colchicine 0.5 mg once or twice daily for seven to 10 days.⁷³ Unfortunately, no diminution of calcific mass follows this treatment.

No satisfactory medical approaches to calcinosis have yet been developed. Chelation and probenecid treatment have failed. Low dose warfarin anticoagulant (Coumadin 1.0 to 2.0 mg/day) has been advocated in the hope of interfering with the γ carboxylation of glutamic acid, an amino acid common to the coagulation and calcification pathways.^{74 75} However, there is no convincing evidence of the effectiveness of this regimen.

Joints and tendons

Early in disease polyarthralgias, polyarthritis, and tenosynovitis (including carpal tunnel syndrome) are treated with non-steroidal anti-inflammatory drugs or, occasionally, low doses of corticosteroids (prednisone 5.0–7.5 mg/day). Local steroid injections and carpal tunnel release procedures are occasionally beneficial. Rarely, inflammatory arthritis dominates the course, requiring the addition of a remittive agent as in rheumatoid disease. In a few unusual cases with diffuse scleroderma, extensive par-articular bony lysis occurs, leaving telescoped digits and psoriatic arthritis-like 'mutilans' deformities.

Joint symptoms often disappear after two to three years, but some patients, especially those with diffuse disease, are left with significant flexion contractures of the digits. Appropriate early treatment consists of physical therapy with emphasis on active extension and range of motion exercises to preserve all finger joint motions. Dynamic splinting is not effective in retarding the progression of deformities.⁷⁶

Later, should there be severe contractures leading to more than 90 degrees of proximal interphalangeal joint flexion, fusion of these joints in 45 degrees of flexion with shortening is often recommended.⁷¹ The result is a straighter, more cosmetically appealing finger position and reduced disability from traumatic ulcerations, but hand function may not improve. Proximal interphalangeal joint replacement arthroplasties have also been performed with improvement in both hand function and appearance.⁷⁷ These surgical approaches are usually elective rather than urgent, but if septic arthritis with osteomyelitis develops there is little choice but to use intravenous antibiotics, to excise infected and devitalised tissue promptly, and to fuse the joint.

Muscle

Most patients with systemic sclerosis have a bland myopathy with increased perimysial and epimysial connective tissue deposition but without evidence of inflammation. Muscle shortening and contracture may result, but are usually mild. A daily physical therapy programme emphasising full range of motion of all large joints should be prescribed.

Some patients with scleroderma have an overlap with polymyositis, in which the typical signs of muscle inflammation are present. These subjects should be treated with corticosteroids, using prednisone (up to but not exceeding 20 mg/day) alone or in combination with methotrexate, azathioprine, or another immunosuppressive agent.

Gastrointestinal tract

MOUTH

Maintaining oral hygiene may be difficult because of limited access, hand deformities, loose teeth related to loss of lamina dura, and accelerated dental caries due to associated Sjögren's syndrome. Regular visits to a dentist for prophylaxis, a long-handle tooth brush, and mouth stretching exercises are recommended.⁷⁸ For edentulous subjects with microstomia a flexible prosthesis has been designed to augment the exercise programme.⁷⁹ Rarely, surgical resection of perioral fibrotic tissues is indicated. Another recognised cause of limited oral aperture amenable to surgical repair is bony erosion of the mandibular condyle at the temporomandibular joint.⁸⁰ Patients should learn to chew food thoroughly and to avoid those foods that are likely to cause substernal dysphagia—for example, meat and bread.

OESOPHAGUS

Two available prokinetic drugs may improve oesophageal motor function—metoclopramide 5–10 mg 15 minutes before meals and at bedtime⁸¹ and cisapride.⁸² Both are effective but only if oesophageal smooth muscle is not severely atrophic or replaced by fibrous tissue. Nifedipine causes both vascular and intestinal tract smooth muscle relaxation, and while improving Raynaud's phenomenon, it may

simultaneously worsen pre-existing oesophageal hypomotility and symptoms of reflux oesophagitis.⁸³ In this circumstance diltiazem may be a safer vasodilator.⁸⁴

Symptoms of reflux oesophagitis should be eliminated to minimise acid damage of the distal oesophageal mucosa, a cause of bleeding, and to prevent oesophageal stricture and Barrett's changes, the latter predisposing to oesophageal carcinoma. Appropriate antireflux measures include maintaining an upright position during and after eating, avoiding large meals and food before bedtime, raising the head of the bed on blocks, taking antacids 45 to 60 minutes after meals and at bedtime, and using histamine 2 (H₂) receptor blocking drugs and mucosal cytoprotective agents—for example, sucralfate slurry 1.0 g before meals and at bedtime. If symptoms cannot be adequately controlled, direct visualisation by upper endoscopy is performed to detect distal oesophageal ulceration, candidiasis, or other unexpected or unrelated disease. Stricture, should it occur, generally requires periodic dilatation. Although these outpatient procedures are usually well tolerated, they should not be considered routine, as oesophageal perforation or excessive bleeding may result. Successful excision of strictures and elimination of gastro-oesophageal reflux by a variety of surgical procedures have been reported,^{85–86} but there is a high rate of recurrence. Partial oesophagectomy with short segment colon interposition may eliminate stricture, but the colon itself is often affected by scleroderma.

SMALL INTESTINE

Primary small bowel involvement with marked atrophy and fibrous replacement of the intestinal musculature leads to gross abdominal distension, diarrhoea, weight loss, and a malabsorption syndrome. When such changes are evident from plain radiographs or clinical information, barium studies should be avoided because they may cause life threatening impactions, and calcium channel blockers should be used with great caution as they may worsen small bowel motility. Metoclopramide is of theoretical but little practical benefit.⁸⁷

Temporary improvement in steatorrhoea can be achieved after the administration of antibiotics, which reduce proximal small intestinal overgrowth of micro-organisms interfering with the absorption of fats and fat soluble vitamins. Empirically, broad spectrum agents, such as ampicillin, tetracycline, co-trimoxazole, and metronidazole, are given, usually in two to three week courses, and then rotated, including a time with no antibiotics. A more accurate choice of antibacterial agents requires quantitative aerobic and anaerobic cultures of duodenal contents obtained by upper endoscopy. Replacement of calcium and fat soluble vitamins, iron, vitamin B-12, and use of medium chain triglycerides and protein supplementation also may be necessary. Ultimately, complete or partial parenteral hyperalimentation will be required.⁸⁸ With careful attention to sterile technique, venous access may be main-

tained for two or more years,⁸⁹ but the risk of septicaemia is high and premature death is the rule.

Abdominal bloating and episodes of pseudo-obstruction from adynamic ileus are frequent. Radiographs may suggest a focal, segmental problem, and it is often tempting (but dangerous) to consider an exploratory laparotomy. Manipulation of the sclerodermatous bowel often results in prolonged ileus, and thus conservative intraluminal decompression is preferable. Partial bowel resection is rarely indicated as the disease is almost always generalised and recurrence is the rule. Pneumatosis cystoides intestinalis results from dissection of luminal gas into the bowel wall. This condition is typically benign, but may result in a sterile pneumoperitoneum, which should be treated conservatively with bowel decompression, supplemental nasal oxygen, and intravenous antibiotics to reduce excessive gas formation by intestinal micro-organisms.

COLON

The most common symptom of large intestinal hypomotility is constipation, which is treated successfully with stool softeners and increased dietary bulk to stimulate emptying. Anorectal muscular incompetence results in rectal seepage and prolapse, which are uncommon but may be incapacitating and uncorrectable. Pessaries have been designed but often become dislodged. Several surgical procedures have been proposed, but the tissues involved are atrophic and are difficult to suture. A perineal approach is favoured because intra-abdominal surgery often results in ileus.⁹⁰ Wide mouthed sacculations of the colon are asymptomatic, but rarely may perforate and cause a diverticular abscess or generalised acute bacterial peritonitis.

Lung

Acute, symptomatic pleuritis is treated with non-steroidal anti-inflammatory agents and, rarely, corticosteroids are required. It is likely that a chronic inflammatory process (macrophages, lymphocytes) precedes and influences the development of pulmonary interstitial fibrosis. If such inflammation is detected (by gallium scan, bronchoalveolar lavage, or open lung biopsy), and if pulmonary function is deteriorating, intervention is indicated. For example, if high cell counts are found on lavage (>20 million cells per millilitre), especially with an increased proportion of lymphocytes (>10%), concomitant treatment with high dose corticosteroids (prednisone 60 mg/day) and any one of several immunosuppressive drugs may be justified.⁹¹ D-Penicillamine has been shown in two studies to retard progression of lung disease in treated compared with untreated patients,^{92 93} but the changes noted may be more statistically than clinically significant. All patients with interstitial fibrosis are at increased risk from bacterial pneumonitis; they should be protected with influenza and pneumococcal vaccines and treated promptly and vigorously with antibiotics if bronchitis or pneumonia develops.

Secondary pulmonary arterial hypertension can result from longstanding pulmonary fibrosis and is usually low grade and slowly progressive. Far more ominous is the development of 'primary' pulmonary hypertension, which occurs in a small proportion (5%) of patients with limited cutaneous changes, is accelerated in pace, and almost uniformly fatal after two to four years. Rapidly worsening exertional dyspnoea (over several months) and severely reduced diffusing capacity for carbon monoxide are clues to this diagnosis before evidence of right ventricular dysfunction. Vasodilators are ineffective as the problem appears to be non-inflammatory subintimal proliferation of arteries and arterioles rather than vasospasm.⁹⁴ Care should be taken to exclude multiple pulmonary emboli and association with anti-cardiolipin antibody; both of these underlying conditions may be stabilised by the use of anticoagulation. Late in the course of primary pulmonary hypertension there is often hypoxia with minimal exercise or at rest and anginal-like substernal chest pain or sudden death due to ventricular arrhythmia. Supplemental oxygen is needed both at night and during daytime activities. Single lung or heart lung transplantation is a theoretical option which has not as yet been pursued in patients with systemic sclerosis.

Heart

Acute pericarditis is unusual in systemic sclerosis, but is treated with non-steroidal anti-inflammatory drugs or, if necessary, with corticosteroids in standard doses. Pericardiocentesis is rarely required for impending or actual tamponade.

Myocardial involvement is almost always due to widespread fibrosis, which leads to left ventricular hypokinesis and congestive heart failure. There is some speculation that repeated episodes of coronary arterial spasm may contribute to myocardial fibrosis. The clinical role of vasodilators, such as calcium channel blockers, is unproved, but it has been shown that pretreatment with nifedipine can prevent thallium perfusion defects after cold challenge.⁹⁵ Ventricular, nodal, and supraventricular arrhythmias may be extremely difficult to control and can be fatal. As in other cardiomyopathies there is increased sensitivity to digitalis, and greater reliance is placed on dietary sodium restriction and diuretics. Myocarditis is rare in scleroderma, and has been reported only in association with polymyositis affecting skeletal muscle; here corticosteroid treatment is clearly indicated.

Secondary causes of heart disease include left heart failure due to 'renal crisis' with malignant systemic arterial hypertension or right heart failure due to one of the several pulmonary problems discussed above. In these instances, treatment of the primary problem is indicated, if possible.

Kidney

New, potent antihypertensive drugs and improved dialysis procedures and care have

dramatically reduced mortality in scleroderma renal disease.⁹⁶ In particular, the angiotensin converting enzyme inhibitor captopril is the drug of first choice. However, even more important than treatment is anticipation. It is crucial to identify the patient at high risk, who generally has rapidly progressive, diffuse cutaneous disease of less than three years' duration.⁹⁷ Although most of these subjects already have affected truncal skin, some very early in disease have more limited but also rapidly increasing skin changes and often palpable tendon friction rubs. These patients must be followed up closely for the development of symptoms (headache, blurred vision) or signs (hypertension, proteinuria, azotaemia, or microangiopathic haemolytic anaemia) which herald renal disease. Any patient classified as having diffuse disease, who has the onset of arterial hypertension during the course of scleroderma, should have stimulated plasma renin levels obtained and, if these are increased should be given an angiotensin converting enzyme inhibitor.⁹⁸ It is rare that blood pressure cannot be controlled by captopril alone or in combination with other agents, such as minoxidil, hydralazine, or propranolol.^{99 100}

Unfortunately, a number of patients have progressive renal insufficiency and ultimately require dialysis despite prompt and complete blood pressure control. Poor vascular access and reduced peritoneal clearance have been claimed to be limitations of haemodialysis and peritoneal dialysis, respectively, but in our experience these problems are not common. A number of patients continuing treatment with captopril have been able to discontinue dialysis after four to 15 months,¹⁰¹ an occurrence virtually unheard of before the availability of angiotensin converting enzyme inhibitors. If no return of renal function occurs after 18–24 months, renal transplantation should be considered as in many instances it has been performed successfully.¹⁰²

Summary

Proper classification of patients into diffuse cutaneous and limited cutaneous subsets and the anticipation of complications are the keys to the management of subjects with systemic sclerosis (scleroderma). Patients with early diffuse disease and rapidly progressive skin thickening are at highest risk of developing serious disease of the internal organs (intestine, lung, heart, kidney) and should be considered for disease modifying treatment. The targets of the disease and sites of possible intervention are vascular endothelium (vasoprotective agents), mononuclear cell subsets (immunosuppressive agents), and fibroblasts (colchicine, D-penicillamine). A number of new agents with sound scientific rationale are currently undergoing therapeutic trials. Much can be done to improve the lifestyle of those with scleroderma. The most dramatic recent development is the ability to reverse kidney disease by the prompt use of angiotensin converting enzyme inhibitors and modern methods of renal dialysis and transplantation. Scleroderma is not a hopeless disease.

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