UNION CARBIDE

INTERNAL CORRESPONDENCE

UNION CARBIDE CORPORATION
CORPORATE APPLIED TOXICOLOGY
HEALTH, SAFETY AND ENVIRONMENTAL AFFAIRS DEPARTMENT
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To (Name) Mr. R. N. Wheeler
Division
Location
Area

Date June 4, 1984

Copy to Dr. B. Ballantyne - 511
Mr. M. R. Huffman - 511
Dr. W. C. Kuryla - 511

Subject

Dear Nick:

Attached is the retrieval from your search on the causes of sclerodeima. The search was run in Medline and all of it's backfiles which covers the medical literature back through the mid 1960's.

Feel free to call if there are any questions.

Very truly yours,

Shirley D. Conner

Shirley D. Conner
Senior Information Specialist
Toxicology Information Services

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Attachment

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Bates number VCC-020885 has been skipped

ATTACHMENT VIII

Severe disease requires immediate corticosteroid therapy, the mainstay of treatment. The other previously mentioned anti-inflammatory agents are not used in acutely ill patients because they are not as effective as corticosteroids. Prednisone is given before meals twice daily in divided doses to febrile patients and once daily to others. Alternate-day treatment is satisfactory for patients with hematologic and renal complications. The suggested doses are for adults, but children may require almost as much. Prednisone dosages for specific manifestations are as follows:

Hemolytic anemia—60 to 80 mg/day. The dose is increased to 100 to 120 mg/day if there is no clinical and laboratory improvement within several days or a week.

Thrombocytopenic purpura—80 mg/day. Platelets may not rise for 4 wk.

Severe polyserositis—40 to 60 mg/day. Response begins within days.

Renal damage—50 to 60 mg/day or 100 to 120 mg every other day. Improvement does not usually occur for 4 to 12 wk and may not be evident until corticosteroid dosage is reduced. (Alkylating agents such as nitrogen mustard are helpful in corticosteroid-resistant nephropathy; azathioprine is not helpful.)

Acute vasculitis—40 to 100 mg/day. Response usually appears within a few days, but gangrene of the extremities improves over several weeks.

Acute CNS damage—50 to 100 mg q 12 h. If there is no response in 24 to 48 h, a more physiologic glucocorticoid such as hydrocortisone 250 to 500 mg should be given IM or IV q 12 h; the dose of hydrocortisone is doubled every 24 to 48 h until 3000 mg is being given daily. The dose is maintained at that level for several weeks until the patient shows evidence of Cushing's disease. The dose is then tapered by 20% decrements every 4 days until a maintenance level is established.

In both mild and severe disease, after the inflammatory process is controlled, the minimal dose of corticosteroids and other agents necessary to suppress tissue inflammation must be determined. This is usually done by decreasing the dose by 10% at intervals varying with how fast clinical improvement occurred. In the presence of fever and arthritis, for example, the dose can be reduced at weekly intervals; in the presence of thrombocytopenia or renal disease (both of which respond more slowly to initiation of therapy), reductions should be made every 2 to 4 wk. Rebound (temporary flare) and relapse tend to occur in the system which had the most recent exacerbation. Response to therapy is measured by relief of symptoms and signs, rise in Hct, or improvement in other laboratory tests. Since positive antinuclear antibody and LE cell tests and elevated ESR may persist despite clinical remission, these parameters should not be used as guides to therapy.

General medical management is also important. Intercurrent infection, often complicating the disease and easily mistaken for some of its manifestations, should be treated vigorously. The usual measures to combat heart failure and renal insufficiency must be taken in addition to using anti-inflammatory agents. Close medical supervision is imperative during surgical procedures and pregnancy. Elimination of emotional stress, physical fatigue, any implicated drugs, and excessive sun exposure, and avoidance of such sensitizing agents as nonessential medication may inhibit exacerbations of SLE.

PROGRESSIVE SYSTEMIC SCLEROSIS
(PSS; Scleroderma)

A chronic disease of unknown cause, characterized by diffuse fibrosis and vascular abnormalities in the skin (scleroderma), articular structures, and internal organs (especially the esophagus, intestinal tract, lung, heart, and kidney). The disease may occur in a mild form compatible with long life, or cause early death due to cardiac

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failure, fulminating renal disease, pulmonary complications, or intestinal malabsorption and cachexia. PSS is more common in women and comparatively rare in children.

Symptoms and Signs

The most common initial complaints are Raynaud's phenomenon and insidious swelling of the acral portions of the extremities with gradual thickening of the skin of the fingers.Polyarthralgia is also a prominent early symptom. In some cases, muscle weakness indistinguishable from polymyositis ("scleroderma tomyositis") may be the dominant presenting feature. Visceral disturbances are occasionally the first manifestation of the disease.

Induration of the skin tends to be symmetric and may be confined to the fingers (sclerodactyly) or distal portions of the upper extremities (acrosclerosis), or affect most or all of the body. As the disease progresses, the skin becomes taut, shiny, and hyperpigmented; the face becomes masklike; telangiectases appear on the fingers, face, lips, and tongue. Subcutaneous calcifications develop (calcinosis circumscripta), more commonly in women, usually on the fingertips and over bony eminences. Biopsy of indurated skin shows an increase in compact collagen fibers in the reticular dermis, epidermal thinning, loss of rete pegs, and atrophy of dermal appendages.

The disease may be limited for a varying period of time to the so-called **CREST syndrome** (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia). Other visceral changes (including pulmonary hypertension due to vascular disease of the lung, and a peculiar form of biliary cirrhosis) eventually develop, but the course of this form of PSS is often remarkably benign.

Friction rubs develop over the joints (particularly the knees), tendon sheaths (tendinitis), and large bursae due to fibrin deposition on synovial surfaces. Flexion contractures of the fingers, wrists, and elbows result from fibrosis of the synovium and periarticular structures. Trophic ulcers are common, especially on the fingertips and overlying the finger joints.

Esophageal dysfunction is the most frequent visceral disturbance and eventually occurs in most patients. Dysphagia, acid reflux due to lower esophageal sphincter incompetence, and peptic esophagitis with possible ulceration and stricture are common. Hypomotility of the small intestine may be associated with severe malabsorption resulting from anaerobic bacterial overgrowth. Pneumatosis intestinalis may occur following degeneration of the muscularis mucosa and entry of air into the submucosa of the intestinal wall. Characteristic large-mouthed sacculations develop in the colon and ileum due to atrophy of the smooth muscle of these segments. Biliary cirrhosis has occurred in individuals with the CREST syndrome.

Defective gas diffusion resulting from fibrosis of the lungs causes restrictive and obstructive ventilatory disease. Pleurisy and pericarditis with effusion may occur. Pulmonary hypertension may develop as a result of longstanding lung disease or intimal hyperplasia of small pulmonary arteries. Cardiac arrhythmias, conduction disturbances, and other ECG abnormalities are common. Cardiac failure may develop and tends to be chronic and to respond poorly to digitalis.

Severe renal disease may develop as a consequence of intimal hyperplasia in renal arteries and is a major cause of death in PSS. It is usually signaled by the abrupt onset of accelerated or malignant arterial hypertension that is soon followed by rapidly progressive and irreversible renal insufficiency. Antihypertensive medications are usually ineffective, and bilateral nephrectomy may be required to control the blood pressure; successful renal transplantation has been reported in a few cases.

Rheumatoid factor tests are positive in a third of the patients; serum antinuclear (speckled pattern) or antinucleolar antibodies are present in 60%.

Mixed connective tissue disease occurs in patients with scleroderma and other evidence of PSS who also show clinical and serologic features of SLE, including fever, pleurisy, pericarditis, myositis, anemia, leukopenia, marked hypergammaglobulinemia, and positive LE cell reactions. Patients with this syndrome have extremely high titers of ribonucleoprotein antibodies.

Localized forms of scleroderma are usually benign and occur as circumscribed patches (morphea) or linear sclerosis of the integument without systemic involvement; antinuclear antibodies are often found in the latter condition.

Prognosis

The course of PSS is variable and unpredictable. It is often only slowly progressive. Most patients eventually show evidence of visceral involvement. Prognosis is poor if cardiac, pulmonary, or renal manifestations are present at diagnosis.

Treatment

There is no specific treatment. No drug has proven valuable in adequately controlled trials or is generally considered effective. Corticosteroids may be helpful in patients with disabling myositis or mixed connective tissue disease. D-Penicillamine and various immunosuppressive agents are being studied for use in PSS. Vasodilators and sympathectomy may induce temporary improvement in Raynaud's phenomenon. Reflux esophagitis is relieved by frequent small feedings, antacids after meals and at bedtime, and having the patient sleep with the head of the bed elevated. Tetracycline 1 Gm/day orally, or another broad-spectrum antibiotic, suppresses intestinal flora and may alleviate symptoms of intestinal malabsorption. Physiotherapy may be helpful in preserving muscle strength but is ineffective in preventing joint contractures.

POLYMYOSITIS; DERMATOMYOSITIS

A systemic connective tissue disease characterized by inflammatory and degenerative changes in the muscles (polymyositis) *and frequently also in the skin* (dermatomyositis), *leading to symmetric weakness and some degree of muscle atrophy, principally of the limb girdles, and, often, to a skin rash.* The conditions share certain clinical findings with RA or progressive systemic sclerosis (PSS); less frequently, with SLE or vasculitis.

Classification of the several types of myositis, though not uniformly agreed upon, includes central muscle weakness (1) alone (polymyositis) or (2) with cutaneous lesions (dermatomyositis); (3) either form in adults with an associated malignancy; and (4) either form in children with an associated diffuse vasculitis of the bowel.

Etiology and Incidence

The etiology is unknown. The myositis may be caused by hypersensitivity or an autoimmune reaction since deposits of IgM, IgG, and the third component of complement have been found in the blood vessel walls of skeletal muscle. Viruses may play some role since picornavirus-like structures have been found in muscle cells, and tubular inclusions resembling the paramyxovirus nucleocapsid have been identified by electron microscopy in myocytes and endothelial cells of vessels in the skin and muscle. The association of a tumor and dermatomyositis suggests that the neoplasm may incite myositis as the result of an autoimmune reaction directed against a common antigen in muscle and tumor.

The disease is not rare. Similar in incidence to muscular dystrophy, it is less common than SLE or PSS, but more common than polyarteritis nodosa. The