Acta Dermatovener (Stockholm) 55: 461–465, 1975

TREATMENT OF GENERALIZED SCLERODERMA WITH INHIBITORS OF CONNECTIVE TISSUE FORMATION

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Abstract. 103 patients suffering from generalized scleroderma were studied in order to assess the effect of treatment with inhibitors of connective tissue formation. 93 patients with generalized scleroderma were given D-penicillamine, benzylpenicillin–diethylamino-ethyl-ester hydroiodide, adrenal glucocorticoids, dextro-thyroxine, hydralazine, and "mixed treatment" (one or several of the drugs in consecutive courses, or concurrently). The effect of dextrothyroxine could not be evaluated in this study. No improvement could be seen after adrenocortical steroid therapy. Hydralazine seemed to be effective. D-penicillamine improved 25 of 34 treated patients; penicillin hydroiodide 12 out of 16. The dermal sclerosis of 6 patients regressed completely; in 16, sclerosis regressed with the exception of finger sclerosis; in 32, partial regression was registered; 20 had their progression arrested, but there was no regression; in 19 cases, there was no effect whatsoever. The prognosis seemed to be better for young than for old people. The age at onset was lower in the better groups. The higher the total dose, the better the results. The length of the treatment course is probably of some significaance. The short-lasting cases had better prospects than the longer lasting. Ten untreated patients of this material and 11 patients seen earlier showed continued progression. Side effects leading to discontinuation of the drugs were seen in a substantial number of patients, especially after D-penicillamine. Twelve deaths could not be related to the treatments.

Key words: Generalized scleroderma; Treatment; Penicillamine; Benzylpenicillin–diethylamino-ethylester hydroiodide; Hydralazine; Corticosteroids

Scleroderma is a systemic mesenchymosis or collagen disease, which involves the connective tissue as a biological system. The cells as well as the extracellular material are included in the pathological processes (2, 15). Ultrastructural evidence of disease activity is found mainly in the deep corium (15), and it seems that most progression takes place in this zone (2, 14) at the cost of the subcutaneous tissue, in which the fat gradually disappears and fibrotic (sclerotic) connective tissue supersedes. The sclerosis starts with an inflammatory process and ends up with an intensified production of acid mucopolysaccharides (*syn.* glycosaminoglycans) and collagen (20). Important stages are increased capillary permeability, edema formation, mucinous organization of the water, changing the latter into a gel, and, finally, fibrous organization. One water-binding acid mucopolysaccharide is hyaluronic acid. The presence of chondroitin sulphuric acids is necessary for the deposition of collagen fibrils. The last-mentioned materials are products of connective-tissue cells (4).

Collagen biosynthesis proceeds through a series of stages (6) including ribosomal biosynthesis of protocollagen, which is a polypeptide rich in proline and lysine, hydroxylation of these amino acids, catalysed by specific hydroxylases, and glycosylation of hydroxylysine, catalysed by galactosyl and glucosyl transferases. Cofactors required for the hydroxylation are Fe^{2+} ions, α-ketoglutarate, ascorbic acid and atmospheric oxygen. Cofactors required for the glycosylation are Mn^{2+} ions, uridine diphosphate galactose (UDPGal) and uridine diphosphate glucose (UDPGlu). Substances capable of interfering with these processes may logically be expected to impede the biosynthesis.

Years ago, in our search for drugs possessing the capacity to inhibit, in some way or other, the inflammatory process which proceeds to fibrosis and sclerosis, we started testing a great variety of substances for their influence on the synthesis of collagen and acid mucopolysaccharides in bone and skin cultures (5).

The following are the drugs which have been shown to inhibit the synthesis of connective tissues.

Adrenal glucocorticoids are known to inhibit the biosynthesis of acid mucopolysaccharides and col-

lagen, to reduce the amount of soluble collagen in relation to insoluble collagen, and hamper the extrusion of collagen molecules from the cells (1, 13). These hormones have been widely used in the treatment of scleroderma, but with little success.

Dextro-thyroxine counteracts the release of thyrotrophic hormone from the pituitary as much as or even more than the L-isomer (16) and without accelerating the metabolism of tissues. Since thyrotrophic hormone stimulates the formation of acid mucopolysaccharides in the tissues and, in the presence of growth hormone, also collagen formation, and since a condition of this kind is found in scleroderma, an inhibition of thyrotrophic hormone activity might be expected to inhibit the sclerodermic process. The drug has been used with some success by the author (3).

Benzylpenicillin-diethylamino-ethyl-ester hydroiodide interferes with the incorporation of proline and lysine into the protocollagen molecule (Blumenkrantz & Asboe-Hansen, unpublished). It has a strong affinity for lung, brain and skin. The drug has been used clinically by Ottolenghi (18) and Øhlenschlæger and Tissot (21) for localized and generalized scleroderma.

Certain chelating agents inhibit the above-mentioned hydroxylation and glycosylation processes by metal chelation. D-penicillamine chelates ferrous and manganous ions, inhibits the incorporation of proline and lysine in the protocollagen molecule, as well as their hydroxylation, and also inhibits glycosylation of hydroxylysine. It binds aldehydes involved in cross-linkages, and increases soluble collagen in relation to the insoluble fraction (7, 19).

Certain amino acids influence collagen biosynthesis by metal chelation or by interfering with specific carrier systems and transport mechanisms (8). In addition, *L-Dopa* (9), *Diphenylhydantoin* (10), *Chlorpromazine* (11), *Procainamide* (11), *Hydralazine* (11) and *Dihydralazine* (12) are agents acting, in different ways, as inhibitors of the biosynthesis of collagen and acid mucopolysaccharides. This group of drugs is now on clinical trial as therapeutics for scleroderma in this clinic. The experiment is not yet completed, but the time may now be ripe to give a report on the preliminary experience in the treatment of scleroderma with inhibitors of connective tissue formation.

MATERIAL AND METHODS

A total of 103 patients (80 female, 23 male) suffering from generalized scleroderma were hospitalized for investigation at regular intervals over a 15-year period. All facilities of this department were used for this study, including laboratories of histopathology, electron microscopy, biochemistry, physiology, immunology and pharmacology. Laboratory studies on blood cells, enzymes, proteins, metals, inorganic salts, metabolites and serologic reactions etc. were regularly made as well as studies on cells, inorganic salts, creatine, protein, glucose, collagen and mucopolysaccharide metabolites, etc., in urine. In addition, other biological fluids, excreta and tissues were regularly examined. The biosynthesis of collagen and acid mucopolysaccharides was studied by incorporation of ^{14}C-labelled proline, lysine and glucosamine. Function tests were carried out to check organ integrity, especially of lungs, gastro-intestinal tract, kidneys, pancreas, endocrine organs and liver. Electrocardiogram and X-ray examinations were resorted to in an effort to disclose changes in internal organs (oesophagus, gastro-intestinal tract, lungs, serous membranes, mycocardium, calcinosis, etc.)

Most patients treated with the drugs as well as the "untreated" had physical and other supportive treatment.

The patients were followed up with a view to elucidating etiology, pathogenesis, pathology, biochemistry, clinical course, prognosis and treatment. This paper deals with the results of treatment. The drugs used were as follows.

D-penicillamine (Dimethylcysteine®, PA). Patients received a daily dose of 450–2 400 mg of PA capsules, divided into three daily doses for 2 months to 5 years (average 2 1/3 years).

Benzylpenicillin–diethylamino–ethyl–ester hydroiodide (Leocillin®, PI). Patients had one daily intramuscular injection of 500 000 international units for 10 days up to a total of 5 million IU.

Adrenal glucocorticoids (Prednisone, CS). Patients had three daily doses of steroid tablets. The total daily dose varied between 7.5 and 50 mg.

Dextro-thyroxine (Dethyron®, DT). was given as tablets of 4 mg once or twice daily.

Hydralazine (Apresoline®, Hy). A total of 75–100 mg was divided in three or four daily doses of tablets.

Mixed treatment. A group of patients had two or several of the above-mentioned drugs either in consecutive courses or two or several drugs concurrently.

Sixty-three (63) patients were treated with PA, 44 with PI, 6 with DT, 13 with Hy and 21 with CS.

Untreated. Ten (10) patients had no treatment whatsoever for various reasons (i.e. objections to treatment, fear of experimenting, allergy to or intolerance of the drugs, lack of confidence in the treatment). These patients were followed-up in addition to a group of 11 patients with generalized scleroderma (acrosclerosis) seen in this clinic in earlier years.

Realizing that collagen has a very slow turnover rate (17), the administration of one drug was maintained for at least one and mostly for several years, provided discontinuation was not imposed by serious side effects. If this was not the case, treatment went on uninterrupted. The period of observation was at least one year.

A general clinical observation was the basis upon which

the severity was evaluated. Joint contractures were measured. The degree of sclerosis was judged from the firmness of the skin. Evaluation of the folding of skin and subcutis, shrinkage and restriction of mobility, microscopical measuring of the dermal thickness, histopathology, and electron microscopy, were carried out to help grade the activity of the disease.

Patients with scleredema adultorum, scleromyxedema and mixed mesenchymosis including sclerodermic lesions were excluded from this study.

RESULTS

Ninety patients had acrosclerosis (systemic sclerosis with Raynaud-like vascular crises); 13 had diffuse progressive sclerosis (systemic sclerosis without vascular crises).

All patients had sclerosis of the dermis and subcutaneous tissue. 37 had sclerosis of the oesophagus, 22 fibrosis of the lungs. Other sclerodermic lesions are listed in Table I.

In 7 cases, a strict regression of oesophageal sclerosis and, in 4, a regression of pulmonary sclerosis could be demonstrated with certainty. In one case, lung symptoms were aggravated despite treatment, although lung function, as indicated by tidal volume, ventilation capacity, analysis of arterial blood, etc., was unchanged.

The effects of treatment on dermal sclerosis were categorized into five different groups. The grades from 0 to 4 had the following meaning (Table II).

Table I. *Symptoms and complications*

Dermal sclerosis	103
Oesophageal stricture and spasms	37
Hiatal hernia	4
GI tract fibrosis	8
Lung fibrosis	22
Impaired renal function	3
Hypertension	6
Myocardial fibrosis	2
Sjögren syndrome	8
Myxedema	1
Diabetes mellitus	7
Pericardial and pleural fibrosis	1
Pneumonoconiosis	1
Arthritis	3
Periarthrosis humeri	2
Myopathy	4
Lupus erythematosus (chronic discoid)	3
Calcinosis (Thiebierge-Weissenbach syndrome)	5
Necrobiosis lipoidica (without diabetes)	1
Malignancy[a]	4
Deaths[b]	12

[a] Cancer of uterus, lung, ovary, skin.
[b] Septicemia, myocardial infarction, renal insufficiency, cancer of lungs, uterus, ovary, hypertension, pneumonia, brain hemorrhage, G.I. hemorrhage.

Table II. *Ninety-three patients with generalized scleroderma treated with various drugs*

The material is grouped according to the results of treatment

Grade	PA	PI	CS	DT	Hy	Mixed	Totals
0	3	1	6			9	19
1	6	3		1		10	20
2	14	6			1	11	32
3	8	3			2	3	16
4	3	3					6
Total	34	16	6	1	3	33	93

0 Continued progression; no effect whatsoever.
1 Progression arrested; no regression of the sclerosis.
2 Progression arrested; distinct regression objectively demonstrated (tissues softer, mobility increased, etc.).
3 Sclerosis no longer traceable; the dermis has regained its normal thickness or is even atrophic; digital sclerosis persists.
4 Complete cure.

Ten untreated patients of this material and 11 earlier seen in this department experienced continued progression, though with static periods. In old age the aggravations became rarer and less severe. No non-treated patients experienced spontaneous cure.

Adrenocortical steroids did not by themselves improve any of the patients treated (Table II).

The effect of dextro-thyroxine cannot be evaluated by these studies, as only one received this drug as the sole medicine. Five patients had DT in combination with other drugs (Table II).

Three patients treated with hydralazine alone were considerably improved, and Hy was included in 10 of the mixed courses that resulted in an improvement of the scleroderma (Table II).

Penicillin hydroiodide gave marked improvement in 12 out of 16 treated patients (Table II).

D-penicillamine improved 25 out of 34 treated.

Complete recovery was observed in 6 out of 93 treated patients (Table II). Three of these had PA, while 3 had PI. Four had acrosclerosis, while 2 had diffuse sclerosis. All were relatively fulminant.

A total of 54 patients showed regression; 20 had their progression arrested; 19 were not helped at all (Table II).

Table III. *Average total dose of PA in all five groups*

Grade	Total dose (g)
0	98
1	471
2	910
3	1 125
4	1 075

Table IV. *Approximate duration of treatment (years, average. Accuracy ½ year)*

Grade	PA	CS	DT	Hy	Mixed
0	2	6.3			2.5
1	2.4		5		4.2
2	2.6			2	8
3	2			3	9.2
4	2.5				

Table V. *Number of courses of PI*

Grade	Average number
0	1
1	2
2	2.7
3	3.2
4	6

Table VI. *Age at start of treatment*

Grade	Years, average
0	51.2
1	56.0
2	43.9
3	32.3
4	22.6

Table VII. *Age at onset*

Grade	Years, average
0	46.0
1	50.1
2	35.4
3	31.0
4	21.5

Table VIII. *Approximate duration of disease at start of treatment*

Grade	Years, average
0	5.1
1	6.9
2	8.7
3	7.8
4	2.4

A considerable total dose was used in most of these experiments. It is inferred from the findings (Table III) that the higher the total dose, the better the result. The length of the treatment course may be of some significance, although this is not evident for the PA group (Table IV, V).

Four patients with acute diffuse scleroderma appeared to be highly sensitive to treatment with PA and PI.

The best results were seen in the younger patients (Table VI). The age at onset was also lower in the better groups (Table VII). The prospects of patients with a shorter disease history were better than for those with a long one (Table VIII).

In a substantial number of patients an improvement was evident at an early point of the PI courses, while strict improvement was generally seen much later after the start of treatment with PA.

Side-effects were frequently seen during treatment

Table IX. *Side-effects of* D-*penicillamine*

Gastrointestinal symptoms	10
Rash	10
Pemphigus foliaceus	1
Hypogeusia, ageusia	10
Leucopenia	3
Thrombopenia	2
Fever	8
Joint pain	1
Muscular weakness	1
Impaired liver function	1
Proteinuria	5
Coronary attack	1
Extrasystoles	2
Fainting	1
Vertigo	1
Sweating	2
Lymphadenitis	1
Polyneuritis	1
Pneumonia	3
Nose-itch	1
Weight-loss	1
Epididymitis	1

with PA and CS, while PI, DT and Hy rarely produced untoward symptoms.The main side effects of CS were the well known hypercorticism symptoms. PI produced exanthema (1), zoster (2), thrombopenia (1) and epidermolysis of the legs (2). Hy produced a lupus syndrome in one patient, and DT extreme exhaustion in one patient. The side effects noted in patients under PA treatment are listed in Table IX. In 31 instances such symptoms led to discontinuation of the drug. However, several patients resumed the treatment at a later date, with varying success. Four patients developed malignancies. Twelve died within the period. None of the deaths could with certainty be related to the treatment.

DISCUSSION

These results need further confirmation, but there can be no doubt that scleroderma can be arrested and even be improved and cured. Although efforts were made, it was difficult to evaluate regression or progression of internal changes. In some cases, however, objective evidence of improvement could be registered. The sclerosis of fingers, which was often found in acrosclerosis, was relatively recalcitrant. The reason is probably the firm fusion of the fibrotic dermis with tendons, joint capsules and periosteum, as is sometimes found. Similar lesions were rarer and less severe around the elbow, shoulder, and other joints. Calcinosis did not respond favourably to the treatment.

The reasons why several drugs were used in a considerable group of patients are various. One was our misjudgement, at an early stage of the period, of the long-term chances of the drugs. Another point was that one or several drugs had severe side effects, which led to a switch to a different agent.

There is no explanation for the observation that a favourable response to PI treatment could be demonstrated early, sometimes almost immediately, while the effect of PA treatment was seen much later. Different points of attack might be suggested.

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Received August 14, 1975

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