FAILURE OF LOW MOLECULAR WEIGHT DEXTRAN INFUSIONS IN SCLERODERMA

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Of the many treatments used in scleroderma (progressive systemic sclerosis), none has so far been shown to alter the fundamental course of the disease (see review Bywaters and Scott, 1965).

Although corticosteroids may give symptomatic benefit in the early stages (Rodnan, Black, Bollet, and Bunim, 1956), prolonged therapy is unrewarding (Zion, Goldberg, and Suzman, 1955). Several other promising treatments such as relaxin (Jefferis and Dixon, 1962) and epsilon-aminocaproic acid (Hall and Scott, 1966) have not stood the test of a controlled study.

Since their introduction in the late 1940s, dextrans have come to occupy an important place in clinical medicine. Low molecular weight dextran increases peripheral circulation by reducing both blood viscosity and intravascular red cell aggregation (Gelin and Zederfeldt, 1960) and an extensive literature has accumulated on its use in peripheral vascular disorders (Powley, 1964).

Digital ischaemia is a prominent feature of scleroderma, yet scanty information is available on the use of low molecular weight dextran in this disease. Holti (1965) convincingly demonstrated that intermittent infusions temporarily improved digital ischaemic phenomena in ten out of twelve patients with scleroderma and noted that "these patients claimed to be remarkably better in themselves with an increased exercise tolerance and softening of their indurated facial skin".

Using Holti's technique, Denis (1967) found a similar circulatory improvement in five of seven patients. In addition joint stiffness improved in some patients, dysphagia lessened in one, and facial telangiectasis in another. Kantor (1966) treated five scleroderma patients with single dextran infusions; in one the skin texture "improved about 50 per cent.", and in the remainder "a decided softening of the acral skin" was noted.

Scleroderma is not primarily a vascular disease. Although dextran may temporarily improve the digital circulation, the important question of whether the course of progressive systemic sclerosis itself is

influenced needed to be resolved in a carefully controlled clinical evaluation.

Material and Methods

Six patients with scleroderma were selected for this study, the duration of disease ranging from early (6 months) to late (29 years), and the severity from mild and static to rapidly progressive (Table I, overleaf). All six showed clinical evidence of digital ischaemia including pulp pitting and atrophy (Fig. 1) and painful digital ulceration.

Fig. 1.—Pulp pitting and atrophy.

TABLE I
DETAILS OF PATIENTS

Case No.	Age (yrs)	Sex	Type of Scleroderma	Details	Previous Treatments
1	44	Female	Advanced progressive	Raynaud's phenomenon 16 yrs Scleroderma fingers 4 yrs, face and trunk 3 yrs Diarrhoea 4 yrs Facial telangiectasis MCP erosions	Triiodothyronine and decaserpasyI
2	56	Female	"CRST syndrome" (calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasis)	Raynaud's phenomenon 29 yrs Scleroderma hands 28 yrs Painful digital ulcers, calcinosis with ulcerating calcium plaques (Fig. 2) Contractures knees, elbows Widespread telangiectasis	Corticosteroids Versenate
3	40	Female	Early mild "acrosclerosis"	Raynaud's phenomenon 4 yrs Scleroderma fingers 4 mths Pulp necroses fingers (Fig. 1)	Cervical, lumbar sympathectomy Triiodothyronine and decaserpasyI
4	57	Female	Acute onset, rapidly progressive	Generalized scleroderma 6 mths Contractures wrists, elbows, ankles, and fingers (hand models, Fig. 4)	Corticosteroids
5	56	Female	Progressive, with generalized oedema	Scleroderma hands, face, and trunk, 2 yrs Intradermal (Fig. 3) and subcutaneous oedema Prominent arthritis wrists, ankle Oesophageal and small bowel involvement	Triiodothyronine and decaserpasyI Vasodilators
6	56	Female	Steadily progressive generalized	Raynaud's phenomenon 2 yrs Scleroderma hands 1 yr, arms and face 8 mths Oesophageal and pulmonary involvement E.C.G. abnormal intraventricular conduction	Potaba Corticosteroids Triiodothyronine and decaserpasyI

Fig. 2.—Calcinosis.

Calcinosis (Fig. 2), extensive telangiectasis, and visceral involvement (cardiac, pulmonary, oesophageal, and intestinal) were all represented. Widespread intradermal oedema which retained the examiner's fingerprint (Fig. 3) was a feature in one patient.

After a preliminary study in four patients, two of these and two others were admitted to a trial in which each patient was given a course of either dextran or normal saline, the treatment being allocated in a double-blind fashion. In patients who received both substances, at least 3 months elapsed between courses.

Assessment

The effects of treatment were assessed before and a week after the course of infusions by the following methods:

- (1) Detailed symptomatic enquiry.
- (2) Hands: Grip strengths, jeweller's ring sizes, palm printing, or serial plaster models (Fig. 4) according to the degree of deformity.
- (3) Photographic recording of skin ulceration, telangiectasis, facial appearances, etc.
- (4) Joints and contractures: Ranges of movement, —assessment of pain and stiffness, serial joint radiographs.
- (5) Digital blood flow: Changes in finger tip temperature using radiometer measurement of radiant heat emission during standardized reflex body warming.
- (6) Serial chest radiograph, electrocardiograph, blood examination, and other investigations where appropriate.

Fig. 3.—Finger-printing on patient's skin.

Intravenous infusions of low molecular weight dextran (10 per cent. W/V in normal saline) were given according to the method of Holti (1965). Patients were admitted to hospital an average of four times at 3 to 5 week intervals to receive a continuous infusion of 2 l. dextran given over 48 hours on each occasion.

Fig. 4.—Plaster models showing degree of deformity before and after treatment.

Results

Table II summarizes the results of treatment in the six patients. Patients 2, 3, 5, and 6 received infusions the nature of which was unknown to them and the authors until after the final assessment. As a result of random allocation Patients 5 and 6 received courses of both dextran and saline. Five patients noted an increase in energy and sense of wellbeing with dextran, either after each infusion or as a result of the course. One of these, however, experienced the same subjective improvement with saline. Another volunteered that her hands felt looser and the skin softer for a few days after each dextran infusion, although the changes were not of a sufficient degree to be appreciated by observers.

The tendency to Raynaud's phenomenon and ischaemic finger pain or ulceration lessened with dextran in three of the four patients in whom this had been a major problem, but increased in the fourth. Measurement of augmented radiant heat emission from the finger tips frequently showed temperature differentials of greater than 0.5°C. in adjacent digits in keeping with the clinical signs of peripheral vascular insufficiency and serial readings

confirmed the patients' impression of increased finger warmth. On occasions the fingers were observed to become warm and pink after each dextran infusion, but this effect passed off before the next infusion 3 to 5 weeks later except in Patient 1 in whom benefit persisted over several winter months. Saline infusions did not influence the digital circulation in either of the two cases studied.

Photography confirmed that facial telangiectasis diminished in one patient but increased in another during the course of dextran infusions.

Visceral manifestations of systemic sclerosis were not improved with the possible exception of Patient 1 whose intake of codeine to control diarrhoea was halved during a course of dextran. However, at the same time, localized electrocardiographic T wave flattening first appeared, consistent with the development of sclerodermatous myocardial involvement. Patient 5 first developed dysphagia from radiologically-proven oesophageal scleroderma during a course of dextran infusions and this complaint lessened considerably 4 months later while she was receiving saline. Weight loss from intestinal malabsorption in this patient progressed throughout the period of observation.

TABLE II
RESULT OF TREATMENT

Case No.	Treatment	Subjective Changes	Objective Changes	Comments	Results
1	Dextran	More energy; fingers feel warmer; Raynaud's crises less frequent	Facial contracture and telangiectasis worsened E.C.G. localized T wave flattening developed Diarrhoea lessened Digital temperature improved Ischaemic ulcers healing	Migraine Transient rash Infusion difficulties	Prolonged improvement in digital circulation Scleroderma progressed
2	Dextran	Feels better; more energy; joints less painful	Hand function unimproved, further ulcerating calcium plaques Telangiectasis face lessened One elbow increased 10° in range Fingers colder		Deterioration in digital circulation Scleroderma unchanged
3	Dextran	Each infusion gave a 2-week "boost" in energy; ischaemic pain temporarily lessened	Digital temperature improved Sclerodactyly unchanged	Infusion difficulties	Temporary circulatory improvement only
4	Dextran	Hands feel looser and skin softer for a few days post-infusion	No change in hand deformity or digital temperature		No worthwhile benefit
5	Dextran	Feels better; more energy	Dysphagia developed Joint erosion progressed Scleroderma increased in limbs, face, and trunk Tendon crepitus first appeared		Disease progressed
	Saline	Feels better; more energy	Dysphagia improved Weight loss continued (malabsorption) Grip improved 30 per cent. but arthritis and sclerodactyly progressed		Disease progressed
6	Dextran	Increased wellbeing; ischaemic finger pain less	Steady progression of tissue stiffness	Hypersensitivity reaction Infusion difficulties	Temporary circulatory improvement Scleroderma progressed
	Saline	No change	Facial scleroderma progressed Axillary contractures lessened	Infusion difficulties	Scleroderma progressed

Sclerodermatous changes in the hands, limbs, face, and trunk either remained static or progressed during treatment with both dextran and saline and in no case did the course of the disease appear to be significantly influenced by these procedures. Patient 6 experienced a lessening of axillary contractures while her facial involvement steadily increased. At the conclusion of the study it emerged that the localized improvement coincided with saline infusions.

Practical difficulties emerged in giving repeated infusions to patients with tough skin and poor circulation. The problems of siting the needle in one patient precluded consideration of further therapy and in two others the difficulty of maintaining the infusion made them dread the next hospital admission. A solution was found in the use of infant scalp vein sets (Portex, 23 Gauge) inserted into small superficial veins and held in place by a plaster of paris shell. This method is recommended for similar procedures.

The dextran itself was not universally well tolerated by patients. A hypersensitivity reaction in the form of fever and generalized rash developed in one woman with a history of allergy to other agents. In another, migrainous attacks, to which she was otherwise infrequently subject, accompanied two out of five infusions and transient generalized pruritis with a fine macular rash occurred once although the causal relationship was not established with certainty.

Discussion

Dextrans are the polysaccharides formed by *Leuconostoc Mesenteroides* cultured in a sucrose-containing medium (Ricketts, 1961). The British Pharmacopoeia contains three dextrans with average molecular weights 150,000 (Dextran 150 B.P.), 110,000 (Dextran 110 B.P.), and 40,000 (Dextran 40 B.P.).

The relative properties of dextrans are largely dependent on their molecular weight (Gronwall, 1957). Low molecular weight dextran increases blood flow in the microcirculation by means of a disaggregating effect on human erythrocytes (Gelin and Ingelman, 1961), a reduction in whole blood viscosity at low flow rates in excess of the effect of haemodilution (Gregersen, Peric, Usami, Chien, Chang, and Sinclair, 1963), and an increase in intravascular volume leading to increased venous return and cardiac output (Schenk, Delin, Domanig, Hahnloser, and Hoyt, 1964). The duration of action depends mainly on the renal threshold for dextran which is around molecular weight 50,000.

In view of the established place of dextran in the treatment of peripheral vascular disorders, it is reasonable that this agent should be suggested for use in scleroderma in which a regular feature is digital ischaemia due to intimal thickening of the digital arteries and peripheral microthromboses. Previous reports (Holti, 1965; Denis, 1967) and our own experience confirm that peripheral tissue perfusion is enhanced in at least 50 per cent. of patients although the benefit is usually transient.

However, ischaemia accompanies but is not the cause of scleroderma and the improvement in circulation with dextran, although welcome, does not necessarily presage an improvement in the sclerodermatous involvement of tissues. Encouraging initial reports, such as that of Klein and Harris (1955) on the use of chelation with sodium versenate, have later proved to be disappointing in other treatments in cases of scleroderma, and the results of this study suggest that this will be so with dextran.

Therapeutic assessment in scleroderma is fraught with difficulties. Subjective responses may be influenced by the desire of both patient and physician to see improvement in a disease in which previous treatments have proved valueless. Temporary hydration of the tissues with resulting softening may follow dextran infusions and natural fluctuations of the disease can further confuse assessment. Furthermore, this is a dramatic form of treatment. It involves infusions and periods of confinement to bed in hospital. This may introduce placebo responses unrelated to the basic course of the disease.

The use of saline control infusions has illustrated these aspects. One patient experienced the same subjective benefit with both saline and dextran. She felt better and was pleased with both treatments in spite of an obvious progression in her disease. Dysphagia first appeared during dextran infusions and subsided with saline. A modest improvement in one of the complaints of another patient, axillary contractures, coincided with a course of saline infusions. This may ordinarily have been ascribed to the treatment being evaluated.

Low molecular weight dextran is essentially a safe treatment, but acute renal failure (Morgan, Little, and Evans, 1966) and hypersensitivity have been reported; one patient in this study developed hypersensitivity. Furthermore, the treatment is expensive (a course of infusions costs £32) and demanding in hospital bed space, patient attendance, and medical time.

Although the number of patients in this study is small, objective evaluation suggests that no alteration

in the course of the disease of practical value is likely to be achieved by dextran infusions. Nevertheless, the peripheral circulation is improved in most patients and in a few this may persist for a prolonged period (Holti, 1965). In the occasional patient with disabling ischaemic pain and digital ulceration, who has responded well to an initial infusion of dextran, repeated infusions perhaps during each winter may well be worthwhile, but our experience suggests that the skin and visceral involvement with scleroderma will be unaffected.

Summary

Six patients with scleroderma of various patterns, duration, and severity have been treated with periodic infusions of low molecular weight dextran under controlled conditions.

Although temporary improvement to the digital circulation may occur, the course of the underlying disease appears to be unchanged.

This treatment may, however, have a place in the management of the peripheral ischaemic phenomena accompanying scleroderma.

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La faillite des infusions de dextran à poids moléculaire peu élevé dans le traitement de la sclérodermie

RÉSUMÉ

Six malades atteints de sclérodermie de différents types, de durée et de sévérité variables ont été traités par des infusions périodiques de dextran à poids moléculaire peu élevé sous des conditions contrôlées.

Malgré qu'une amélioration temporaire de la circulation digitale peut avoir lieu, le cours de la maladie même semble inchangé.

Ce traitement peut pourtant avoir une place dans le traitement du phénomène ischémique périphérique accompagnant la sclérodermie.

Falla de las infusiones de dextrán de poco peso molecular en la esclerodermia

SUMARIO

Seis pacientes con esclerodermia de varios tipos y duración y severidad variables han sido tratados con infusiones periódicas de dextrán de poco peso molecular en condiciones controladas.

Si bien pudiera ocurrir mejora temporal en la circulación digital, el curso de la enfermedad misma parece inalterado. Este tratamiento podría, sin embargo, ser útil en la terapia del fenómeno isquémico periférico que acompaña a la esclerodermia.