

## DIFFUSE SCLERODERMIA: ITS FREQUENCY; ITS OCCURRENCE IN STONE-MASONS; ITS TREATMENT BY FIBROLYSIN—ELEVATIONS OF TEMPERATURE DUE TO FIBROLYSIN INJECTIONS.\*

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DIFFUSE SCLERODERMIA is a very rare condition. Dr. Phineas S. Abraham, the writer of the article on "Sclerodermia" in Allbutt and Rolleston's *System of Medicine*, in speaking of diffuse sclerodermia, states that M'Call Anderson had 2 cases in 11,000 diseases of the skin, and Crocker 2 in 10,000 cases. In 17,000 general medical cases seen in my hospital practice (8502 in-patients, 8638 out-patients) there were 7 cases of diffuse sclerodermia, and in 10,000 general medical cases seen in private practice, of which I have kept notes, there were 2 cases of diffuse sclerodermia.

The first point I wish to make is that, so far as these figures show, cases of diffuse sclerodermia come at least as frequently under the care of the general physician as under the care of the dermatologist—in 22,000 cases of diseases of the skin seen by M'Call Anderson and Crocker there were 4 cases of diffuse sclerodermia, while in my 27,000 cases of general medical disease there were 9 cases of diffuse sclerodermia.

The next point which I wish to make is the relatively frequent occurrence of diffuse sclerodermia in stone-masons. In my 9 cases of diffuse sclerodermia 5 were stone-masons and 1 was a copper-smith, who was accustomed to work with a cold chisel. The only apparent cause which I am able to suggest for the relatively frequent occurrence of diffuse sclerodermia in stone-masons is the holding of a chisel in the hand during cold weather. In all of these six cases (5 stone-masons and 1 coppersmith) the condition commenced in the hands. None of the patients had suffered from syphilis, so far as could be ascertained.

In his article on "Sclerodermia" in Allbutt and Rolleston's *System of Medicine*, Dr. Phineas S. Abraham makes no mention of the occurrence of the condition in stone-masons. He informs me that he knows of no writer who does so. I feel certain, however, that my own experience on this point cannot be peculiar. Perhaps some general physician who reads this article will be able to corroborate my experience. I have been so impressed with the occurrence of diffuse sclerodermia in stone-masons that in the last

\* Read before the Edinburgh Medico-Chirurgical Society, 4th February 1914.

three cases which have come under my observation I have correctly suggested the occupation of the patient as soon as I saw and felt the hands and *before I had asked him a single question.*

The next point to which I wish to refer is the marked improvement which resulted in some of my cases of diffuse sclerodermia from subcutaneous injections of fibrolysin.

In two of the cases the injections, which at first produced no disturbance of temperature and pulse, produced marked elevations of temperature. In both cases these temperature alterations were identical in character. I have employed fibrolysin in several other diseases. In a case of disseminated sclerosis a very high temperature (105·8° F.) followed an injection of fibrolysin. So far as I am aware, no one has previously directed attention to this point.

The last point which I have to note is the close resemblance in some of the clinical features of diffuse sclerodermia to Raynaud's disease. In almost all of the cases exposure to cold produced the same cold, blue, dead condition of the hands which is such a striking feature of Raynaud's disease. In four of the cases painless sores, which were very slow to heal, developed on the knuckles or finger-tips, apparently as the result of slight injuries. In Cases V. and VI. the tip of one of the fingers became gangrenous.

In one case (Case V.) which was shown to the Society the condition when I first saw it 14½ years ago was typically that of sclerodermia—the hands, face, feet, and thorax were affected. The hard, brawny, swollen condition of the hands and the hide-bound condition of the face and front of the chest have now in great part disappeared. The fingers have become bent in to the palm and the tips of several of them distorted as the result of trophic lesions, highly suggestive of Raynaud's disease. Further, bright red vascular spots, highly suggestive of xerodermia pigmentosa, have developed on the face, tongue, chest, back, and dorsum of the right hand. This is a very remarkable case.

Hæmatinuria was carefully inquired for but was not observed in any of the cases. In several of the cases pains, apparently rheumatic, and stiffness of the joints were complained of.

The thyroid was not enlarged in any of the cases.

The clinical features of diffuse sclerodermia are to my mind very suggestive of a trophic or vasomotor neurosis, but in none of the cases were any definite objective symptoms suggestive of syringomyelia or other definite nervous lesion detected.

The clinical features of the nine cases which have come under my observation are detailed in the following table and notes:—



# CASES OF DIFFUSE SCLERODERMIA.

No.	Initials.	Age.	Sex.		Occupation.	Hospital Practice.		Private Practice.	Part Affected.					Complications.	Treatment.	Result.
			M.	F.		In-P.	Out-P.		Hands.	Feet.	Face.	Thorax.	Abdomen.			
1	Miss F.	65	1		None.			1	1	1				Rheumatic pains in hands, feet, knees, etc.	Warmth; iodide of potassium.	Died 5 years later from cystitis.
2	D. K.	36	1		Stone-mason.		1		1	1	1	1		Pigmentation of skin; muscular pains in fingers, wrists, shoulders, knees, and hips.	Warmth; iodide of potassium; thyroid extract; arsenic; opium.	Slight temporary improvement. Died 2½ years later from pericarditis.
3	D. M.	43	1		Stone-mason.		1		1					Sores on knuckles.	Warmth; morphia.	Some improvement.
4	A. H.	44	1		Coal-miner.	1			1					Hard swelling (? osteo-arthritis) head of right ulna, and pain and swelling of metacarpal and phalangeal joints.	Warmth; alkaline baths; menthol oil.	I. S. Q.
5	R. M.	35	1		Stone-mason.	1			1	1	1			Scars on knuckles; rheumatic pains in shoulders, elbows, and hips; pigmentation of skin; telangiectases, etc.	Warmth; thyroid extract; quinine; cod-liver oil.	Marked temporary improvement.
6	J. M <sup>l</sup> .	57	1		Merchant.			1	1	1	1	1	1	Gangrene of tip of forefinger exactly resembling the lesion of Raynaud's disease.	Warmth; arsenic; iodide of potassium.	Died 15 months later—sudden pulmonary oedema.
7	J. D.	26	1		Stone-mason.	1			1		1?			Sores on knuckles.	Warmth; fibrolysin.	Marked improvement.
8	J. L.	46	1		Coppersmith.	1			1					Rheumatic pains and creaking in shoulders, ankles, and thighs.	Warmth; fibrolysin.	Marked temporary improvement.
9	J. S.	55	1		Stone-mason.	1			1	1	1	1		Creaking in wrists, elbows, knees, and ankles.	Warmth; fibrolysin.	Marked improvement. Died 8 months later.

Note.—In all cases massage and passive movements were employed.

CASE I.—Miss F., aged 65, seen in consultation on 28th December 1892.

*Complaints.*—Pain and stiffness in hands and legs; inability to walk; shooting pains in hands and fingers, and burning sensation in the feet.

*Duration.*—Three years; commenced with a bulla resembling pemphigus over the outer side of one leg.

*Condition when Seen.*—Right hand stiff and swollen; skin of hands, especially palms, very hard and dense; movement of fingers impaired. Left hand affected in same way, but in a less degree than right. Legs bent and rigid; knee-jerks cannot be elicited.

The condition appears to be a combination of scleroderma and peripheral neuritis.

*Treatment.*—All treatment has failed. Sulphonal gives sleep.

*Subsequent Progress.*—Patient died five years later from cystitis.

CASE II.—D. K., aged 36, stone-mason, seen as an out-patient at Edinburgh Royal Infirmary on 13th April 1894.

*Complaints.*—General weakness; stiffness and coldness of the hands; pains in shoulders, wrists, fingers, hips, and knees.

*Previous History.*—A healthy man until eighteen months ago, when fingers began to feel cold and dead; he thought they were frost-bitten. The coldness of the fingers was first noticed after curling and lying out in the cold all night while intoxicated. Before the onset of the disease was a robust, healthy man.

*Family History.*—Good.

*State on Admission.*—Hands feel heavy, dense, hard, and cold; skin of hands and fingers hide-bound; little and ring fingers in each hand contracted; skin of palms hard, dense, cold, and clammy; fingers pointed. Hands get blue on the least exposure to cold. Movements of fingers and wrists restricted. Sores on knuckles of little, ring, and forefinger of right hand, and on little finger of left hand; these sores have been present for twelve months and have not healed. Skin of face looks thin and drawn. Skin of body generally is so much pigmented that the doctor (Dr. Reid) who sent the patient to the Infirmary suggested that he might be suffering from Addison's disease.

No visceral disease.

Sensations to heat, cold, and touch normal over the body, though somewhat impaired over the hands. Urine has never been porter-coloured.

*Treatment.*—To keep parts warm; avoid exposure to cold; iodide of potassium.

*Progress.*—13th June 1894, seen again at Edinburgh Royal Infirmary much *in statu quo*. Iodide to be discontinued; thyroid extract (5 grains, three times daily) substituted.



18th July 1894.—Thyroid treatment produced little or no improvement although the dose was doubled by Dr. Reid. The patient says he felt better under the iodide than the thyroid.

19th July 1895.—In April last had an attack of pleurisy with effusion; the chest was tapped. The sclerodermia is more marked; face more affected; cannot close his lips so as to hold his pipe. Skin over the body generally, and especially over the upper part of the chest (manubrium sterni), affected. Feet and legs affected to some extent, much less than the hands and arms. Ulcers on knuckles still from time to time present; the least injury, he says, leads to the formation of a sore.

Has tried arsenic and opium in addition to the thyroid and iodide. The only thing which does him good, he says, is keeping the parts warm. Antimony and the constant current suggested.

The patient died on 26th October 1896. The immediate cause of death was pericarditis. Dr. Reid informs me that the sclerodermia gradually increased and became very marked on arms, face, and chest; the movements of the chest-wall were much impaired and painful. Dr. Reid suggests that the sclerodermatous condition of the chest-wall was perhaps concerned in the production of the pericarditis.

CASE III.—D. M., aged 43, stone-mason, seen as an out-patient at the Edinburgh Royal Infirmary on 28th January 1895.

*Complaint.*—Coldness and stiffness of the hands.

*Duration.*—Three years.

*Apparent Cause.*—Exposure to cold. Fingers became so cold at his work that he was unable to hold the chisel, and the hammer fell out of his hand. Soon after the condition (coldness and stiffness in the hands) developed, sores appeared without any apparent cause on some of the fingers; there was little or no pain; the nail of the right forefinger came off.

*State on Admission.*—Both hands cold, dense, hard, blue or whitish-blue if exposed to cold; skin of palms dense, hard; skin of fingers smooth, tightly stretched, cannot be pinched up. Scars of old ulcers on some of the knuckles and finger-tips. Movements of fingers much impaired.

Sensibility to touch, heat, and cold normal over body generally, slightly impaired over the hands. Urine never dark in colour.

No visceral disease.

*Treatment.*—Warmth; liquor morphinæ hydrochlor. (4 minims, subsequently increased to 8 minims, three times a day).

23rd February 1895.—Slightly better; hands do not feel so cold; sores healed.

*Subsequent Progress of the Case.*—Not known.

CASE IV.—A. H., aged 44, married, coal-miner, admitted to the Edinburgh Royal Infirmary on 29th June 1897.

*Complaints.*—Stiffness of the fingers and wrists, pain and swelling in the fingers of both hands, more especially the right.

*Duration.*—Right hand four years, left hand two months.

*History.*—Before the present condition developed enjoyed good health. About four years ago was dragged on his hands and knees by a waggon for six yards; the right hand was injured; the back of the hand became swollen, the swelling extended to the wrist and metacarpo-phalangeal joints. There was considerable pain in the wrist and back of the hand and fingers, burning in character, with stiffness and soreness of the joints. Was off work for three months. After recovery worked for twelve months; the condition then recurred without obvious cause, and he was again off work for three months; since then has worked two or three days a week. Two months ago the left hand became similarly affected, and he has been unable to work. Has been exposed to cold and weather going to and returning from his work.

*State on Admission.*—Fairly well nourished; not very muscular; has got much thinner during the past four years.

The morbid appearances are entirely confined to the hands and wrists. The right hand is much more affected than the left. Both hands have a waxy, smooth appearance; the skin feels very hard, is tacked down to the subcutaneous tissue and cannot be pinched up. Hands feel very cold, and the patient states that at times he feels the cold very severely. The movements of the hands and wrists are much impaired.

There is a hard swelling over the head of the right ulna, the metacarpal and phalangeal joints are swollen and somewhat painful, the nails are brittle and speckled over with white spots, the palm and fingers are contracted. The muscles of the forearm, more especially the extensor muscles, are somewhat atrophied.

The patient states that at times reddish spots appear on the back of his hands and last for four or five days; the spots are circular in shape and about one-third of an inch in diameter. There is no visceral disease.

*Treatment.*—Warmth; alkaline baths and menthol oil were applied to the hands with passive movements.

*Result.*—Some improvement in the movements of the fingers and wrists and disappearance of the pain on movement; little change otherwise.

Discharged 15th July 1897.

CASE V.—R. M., aged 35, married, stone-mason, admitted to Edinburgh Royal Infirmary on 8th October 1898.

*Complaints.*—Coldness and stiffness in hands and feet, stiffness in legs, stiffness in face.

*Duration.*—Two years.



*Previous History.*—Enjoyed excellent health until two years ago when he began to suffer from cold hands and feet; a year ago noticed stiffness in the legs and arms. Works in the open air and is much exposed to the weather.

*Home surroundings good. Family history excellent.*

*State on Admission.*—Healthy-looking man, but muscles rather wasted. Height, 5 ft. 9 ins.; weight, 10 st. 1 lb. Skin of whole body dark in colour, smooth, and dry. Nipples not pigmented. Hands, feet, forearms, legs, shoulders, and face markedly affected with diffuse sclerodermia.

The condition began in the hands. The face was affected twelve months ago.

The hands feel heavy and cold, like frozen india-rubber; they become markedly blue on exposure to cold. The points of the fingers are glazed and shrunken, fingers slightly flexed into the palm; the skin is thin and tightly stretched over the hands and fingers, which are pointed; the nails are long and narrow; there is a transverse groove in the nail of the forefinger of the right hand and a longitudinal groove on that of the little finger of the left hand.

The movements of the fingers and wrists are markedly impaired.

The skin of the forearms is markedly affected; skin of the upper arms normal; skin over both shoulders markedly affected. He cannot raise his arms above his head. Face is markedly affected, skin tightly stretched and feels stiff, especially over the nose, cheeks, and lower part of the forehead; says he has difficulty in opening the mouth, as in yawning, owing to the tightness of the skin. The ears are much affected, blue and cold; skin thin, glazed, and tightly stretched.

The feet are similarly affected to the hands but in a much less marked degree.

The feet became affected two months later than the hands; they became cold and numb, and he did not feel the ground when they were cold; he then began to complain of weakness and stiffness in the legs, and consequent difficulty in walking. He gradually got weaker and weaker until he was unable to walk. The skin of the legs is slightly affected, the calves feel tight and stretched, and are apt to pain him in walking. The skin of the abdomen, thorax, and thighs is unaffected.

The skin of the body generally is yellowish-brown in colour (markedly pigmented).

He complains of numbness in the fingers and feet when exposed to cold. There are no objective disturbances of sensation.

The tendon reflexes are somewhat diminished; superficial reflexes all distinct.

Scars, the result of old ulcers, which he says were very slow in healing and which developed spontaneously, are present on the

metacarpophalangeal joints of the 1st, 2nd, and 4th fingers of the right, on the 1st and 2nd fingers of the left hand, on the distal phalangeal joints of the 1st and 2nd fingers of the right hand, and on the 1st, 2nd, 3rd, and 4th fingers of the left. The sores on the fingers began to develop twelve months after the disease commenced.

Three scars are present on the sole of the left foot and two on the left ear. These scars exactly resemble the lesions which are seen in Raynaud's disease and in some cases of syringomyelia.

The patient has never suffered from dead fingers nor passed dark, porter-coloured urine.

Blood—red corpuscles 3,800,000 per cubic millimetre, whites 5800, hæmoglobin normal. Blood film shows nothing abnormal. No visceral disease.

*Treatment.*—Warmth; thyroid extract, quinine, and cod-liver oil.

*Result.*—Temporary improvement. Discharged 7th January 1899.

*Readmitted 8th February 1899 and discharged 15th February 1899, in statu quo.*

Seen as an out-patient 12th August 1903. Is worse. The terminal phalanges of the fingers are permanently flexed; face very pinched; complains of pain and difficulty in swallowing. The veins over the chest and arms are very prominent. No definite signs of aneurysm or intra-thoracic growth.

*Seen at Chalmers Hospital on 4th February 1914.*—His condition is markedly changed since last seen ten and a half years ago. The sclerodermatous condition is less marked, but the fingers of the right hand are now much more contracted. The slightest exposure to cold makes the hands turn blue; he says that the hands are painful when cold.

The fingers of the right hand are flexed into the palm and cannot be straightened; the palm feels hard, dense, and contracted (Figs. 1 and 2). The tip of the right thumb is ulcerated, the nail is partly destroyed and detached. This ulcer has been present since July; it is now healing. Before the ulcer developed, the tip of the thumb became black. The nails of the 1st, 2nd, and 3rd fingers of the right hand are very long, thin, narrow, pointed, and curved. The nail of the 3rd finger is absent; it was detached recently as the result of a sore which formed on the end of the finger. The skin on the back of the right hand is thin, but is not tied down and fixed; the condition of the back of the hand is very different to what it was ten years ago. There are some spots (telangiectases), small in size, on the back of the right hand.

The left hand is less affected than the right; most of the fingers can be partly straightened (extended). The little finger is rigidly flexed, skin very thin and shiny, the nail very long and narrow. The nails of the other fingers of the left hand are curved. The skin of the fingers is tightly stretched. On the back of the left hand the skin is fairly normal as compared with that of the right.



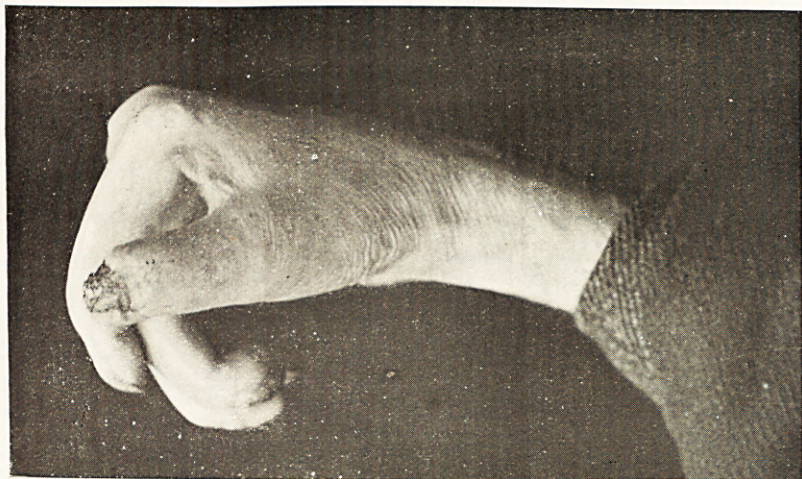


FIG. 1.—Right hand in the case of diffuse sclerodermia described in the text, showing ulceration of the tip of the right thumb and contraction of the fingers.

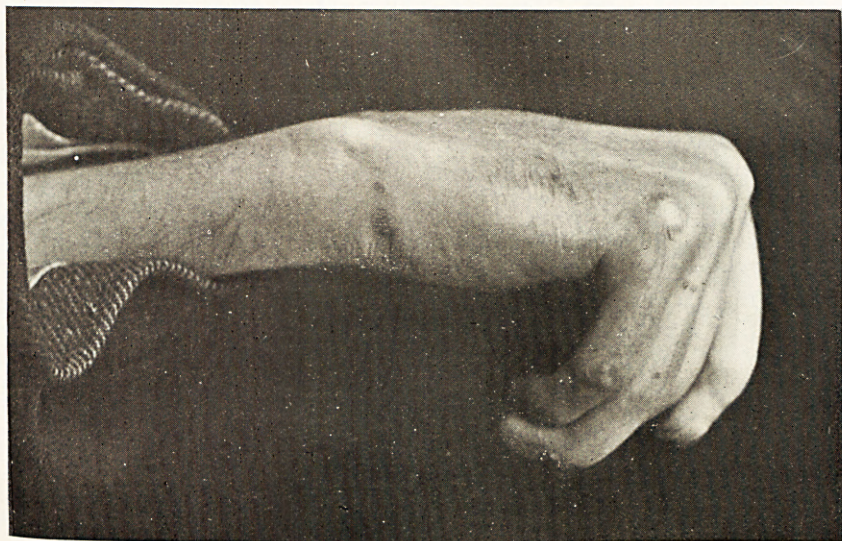


FIG. 2.—Right hand in the case of diffuse sclerodermia described in the text, showing contraction of the fingers.

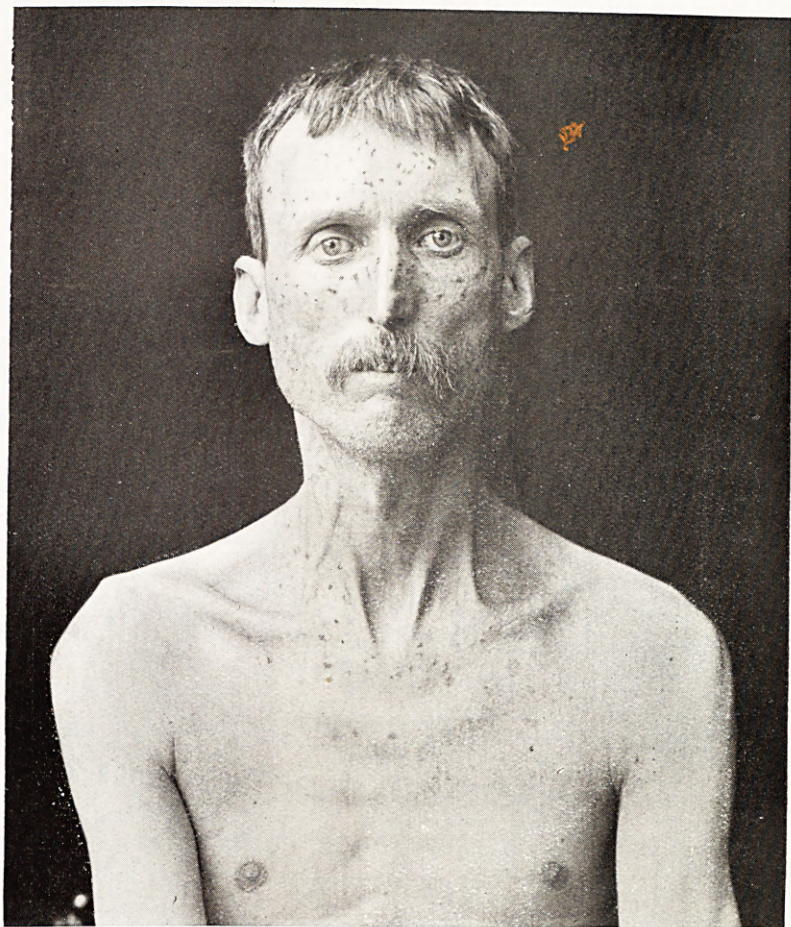


FIG. 3.—Case of diffuse scleroderma described in the text, showing the vascular lesions on the face, neck, and upper part of the chest.



The face is thin ; he can open his mouth much more freely than he used to do. The sclerodermatous condition of the face has to a large extent disappeared.

Numerous bright red vascular spots (telangiectases) are present on the forehead, nose, and cheeks (Fig. 3) ; they are of various shapes. On pressure the colour disappears from these spots. There are a few small red spots on the tongue, more especially on the right side. The appearance of the face is suggestive of xerodermia pigmentosa.

The skin of the ears is thin and tightly stretched.

Over the neck and upper part of the thorax multitudes of small arborescent vessels are seen, red in colour. Over the front of the chest, more particularly over the left side, there are several red vascular areas, not so bright as on the face, distinctly arborescent ; on pressure the colour disappears from these spots.

There are a few vascular red spots over the back.

Feet are slightly swollen, the skin is hard, and they get blue on exposure to cold. From time to time he has had sores on the back of the toe joints.

The skin of the abdomen is natural.

The thyroid cannot be felt ; it is apparently atrophied. The nipples are not pigmented.

His general health is, he says, good ; he sleeps well. His appetite is fair, his bowels regular.

There is no difficulty in making water, but every now and again, perhaps for a fortnight at a time, it comes away without his knowing it and he wets himself.

The difficulty in swallowing which he complained of when last seen ten years ago, lasted for some years and then disappeared ; there has been no difficulty in swallowing for the last seven years.

He is thin ; the muscularity of the arms is poor, of the legs fairly good. He says that he sweats very little.

CASE VI.—Mr. M.L., aged 57, merchant, seen in consultation on 7th January 1906.

*Complaints.*—Stiffness of hands, arms, face, chest, lower part of abdomen, and thighs.

*Duration.*—One year.

*Apparent Cause.*—None.

*Condition when Seen.*—Skin over the whole body is hide-bound except over the calves ; the hands are more affected than any other part. Skin pale, cold, dense, tightly stretched over the fingers, which are pointed. The patient states that he feels the cold very much ; his general health is good. There is some numbness in the hands and feet, and at times a dull aching pain.

No visceral disease. The urine has never been dark coloured. No symptoms of Raynaud's disease. Nothing abnormal detected in con-

nection with the nervous system. Sensation to touch, pain, heat, and cold normal.

*Treatment.*—Arsenic and iodide of potassium.

*Result.*—Patient remained much *in statu quo* until 1st April 1907, when he was attacked with sudden dyspnoea and the expectoration of blood-tinged, copious, frothy sputa, and died in ten minutes. The condition was obviously acute pulmonary oedema in a patient affected with sclerodermia. For some days before the attack of dyspnoea he had complained of headache and sickness, but there was no elevation of temperature.

During the year 1906 the tip of the forefinger of the left hand became gangrenous—resembling the lesion seen in Raynaud's disease.

CASE VII.—J. D., aged 26, stone-mason, admitted to Edinburgh Royal Infirmary on 23rd February 1909.

*Complaint.*—Numbness, stiffness, and coldness of hands.

*Duration.*—One year.

*Apparent Cause.*—Exposure to cold during work. Right hand first affected. Patient says he had to cycle to his work, a distance of five miles, in cold frosty weather, and the metal handles of cycle used to be exceedingly cold; this, and holding a cold chisel in his hand, he thinks, is the reason why the hands became affected first.

*State on Admission.*—Hands of a dead leaden-violet colour; on exposure become much more blue. Skin of the hands feels firm, dense, and very cold; it resembles a frozen corpse or a piece of frozen india-rubber. Palms feel cold, hard, and moist; skin tightly stretched over the fingers and devoid of wrinkles; fingers are pointed. Movements of fingers and wrists are considerably impaired; parts are hide-bound. Patient cannot close his fist. Joints of fingers somewhat enlarged. Three sores, two at the base of the nails of first and second fingers of left hand, one on the extensor aspect of the metacarpo-phalangeal joint of right thumb, are present.

Skin of forearms and face affected.

Says that he is very sensitive to cold; has never passed dark-coloured urine.

No visceral disease. Nervous system normal.

*Treatment.*—Warmth; fibrolysin injections.

*Result.*—Marked improvement; the patient was discharged on 30th May.

As a result of the fibrolysin treatment marked elevations of temperature occurred.

The preparation used was a solution of fibrolysin (200 milligrams of thiosinamine (Merek) and 200 milligrams of salicylate of sodium dissolved in 3 c.c. distilled water). Of this solution 30 minims (containing 120 milligrams of thiosinamine) were injected into the upper arm; the injection was repeated every second day.



The first seven injections were not attended by any alteration in temperature and pulse; after this, each injection was followed by a very considerable rise in temperature and pulse. *Between 14th March and 3rd April* the highest temperature noted was  $102.4^{\circ}$  F. The injection which was made on 3rd April (which consisted of 20 instead of 30 minims of the solution) was followed by a temperature of  $103.4^{\circ}$  F. and a pulse of 112.

After this considerable rise in temperature the fibrolysin injections were discontinued—from 4th to 14th April inclusive no fibrolysin was given; during this period the temperature and pulse were, practically speaking, normal.

The question arose whether these rises in temperature were the result of septic poisoning (septic decomposition which had occurred in the solution of fibrolysin which was being employed). Consequently a fresh solution (Mereck's) in sealed glass capsules was obtained. Of this solution 50 minims (containing 200 milligrams of thiosinamine) were injected on 15th April; this was followed by a still greater rise of temperature, viz.  $104.4^{\circ}$  F.

The fact that the injection of a different and aseptic solution of fibrolysin was also followed by very marked rises in temperature negatived the supposition that the rises in temperature which followed the injections of the solution first employed were due to septic poisoning. This view was corroborated by the fact that in two other cases in which the same solution of fibrolysin as that which produced the rises in temperature in the case of sclerodermia was used no temperature or pulse alterations resulted from the injections.

On 19th April 16 minims of the original solution, containing 60 milligrams of thiosinamine, were injected; this was again followed by a very high temperature ( $104.2^{\circ}$  F.). On 22nd April 8 minims of the original solution, containing 30 milligrams of thiosinamine, produced a temperature of  $103.8^{\circ}$  F.

On 24th April distilled water was injected instead of the fibrolysin. The patient was not, of course, told that the nature of the injection had been changed. There was no rise of temperature. The possibility that the elevations in temperature were merely nervous was consequently excluded.

On 26th April 4 minims of the solution, containing 16 milligrams of thiosinamine, produced a temperature of  $101^{\circ}$  F. On 28th April 20 minims were followed by a temperature of  $102^{\circ}$  F.; and on 3rd May 20 minims were followed by a temperature of  $101^{\circ}$  F.

The injections were then discontinued until 18th May. The temperature again remained normal during the period that the fibrolysin was not employed.

On 18th May 15 minims of the solution produced a temperature of  $102^{\circ}$  F.; on 22nd May 15 minims produced a temperature of  $99.4^{\circ}$  F.;

on 25th May 30 minims of the solution were not followed by any rise of temperature; on 27th May 40 minims produced only a temperature of 100° F.

From these statements it will be seen:—

1. That the first seven injections produced no temperature alteration.
2. That a marked rise in temperature followed each dose of the remedy which was subsequently given different solutions being from time to time employed.
3. That the patient seemed to become accustomed to the remedy; on 27th May a large dose—40 minims—produced a comparatively slight effect.

In Figs. 4 and 5 the alteration in temperature and pulse which followed the injections of fibrolysin are shown.

In Fig. 4 the course of the temperature, taken every hour for twenty-four hours after an injection of fibrolysin, is shown.

At 9.15 P.M. on 28th April 80 milligrams of thiosinamine were injected; this was followed by a slight fall. Then at 3 A.M. (on 29th April) a marked and sudden rise occurred, the temperature reaching 103° F. at 7 A.M.; after this there was a gradual fall, the temperature becoming normal at 11.30 P.M. on 29th April.

Several observations of this kind were made; in all of them the temperature curves were practically the same as that represented in Fig. 5.

At the time this patient suffering from sclerodermia was being treated, the same solution of fibrolysin was given subcutaneously to several other patients in the wards. In one of these a very marked elevation of temperature resulted after an injection. The patient, a man, aged thirty-four, was suffering from disseminated sclerosis.

On 18th, 22nd, 23rd, 26th and 28th April 20 minims of the same solution as was used in the stone-mason's case were injected, without any elevation of temperature being produced.

On 2nd May 30 minims of the same solution produced a very high temperature—105.8° F.

Why the injection on 2nd May (although it was rather a larger dose than had been previously given—30 instead of 20 minims of the solution) should have been followed by such a marked temperature disturbance, while the previous injections produced no temperature alteration, I am unable to say.

One of my former house-physicians wrote me on 12th May 1909, saying: "I happened to mention to the house-surgeon here (Paddington Green Children's Hospital, London) that in one of your cases of sclerodermia a sudden rise of temperature occurred after the injection



of fibrolysin. He tells me he had once a case (not a case of sclerodermia) in which a similar rise of temperature took place."

CASE VIII.—J. L., aged 46, coppersmith, admitted to Edinburgh Royal Infirmary on 3rd March 1911.

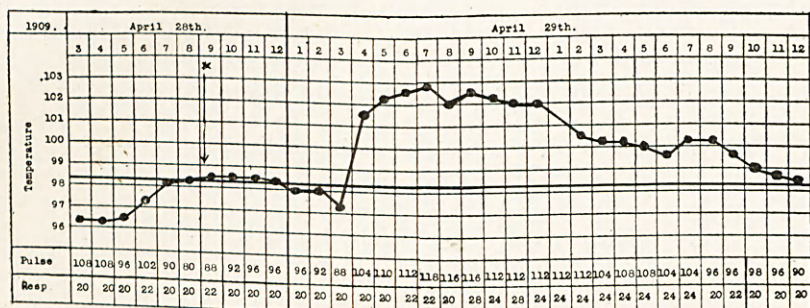


FIG. 4.

*Complaints.*—Stiffness of hands, pains in hands, shoulders, thighs, and knuckles.

*Duration.*—Three months.

*History.*—Stiffness in hands first felt three months ago—he found

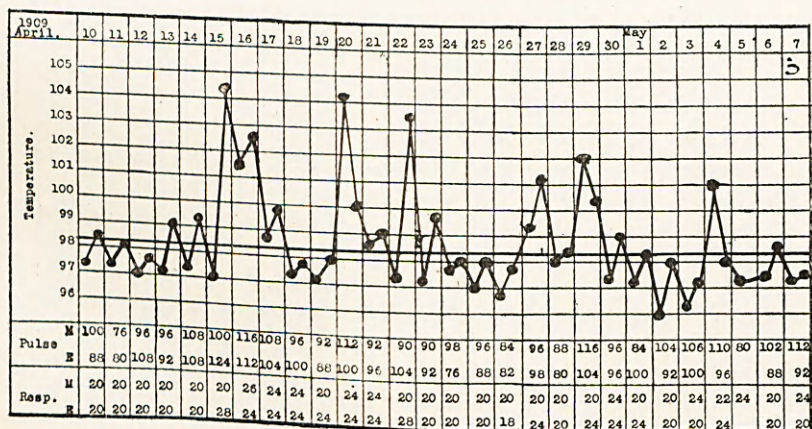


FIG. 5.

he could not grip his hammer and chisel properly; at this time there was some stabbing pain in the palms and fingers. Had to give up work six weeks ago. Has also complained of pains in shoulders, thighs and ankles. Until this illness commenced was a healthy man.

*Family History.*—Unimportant.

*Social Condition.*—A coppersmith. Has to put his hands in cyanide

of potassium, muriatic acid, and vitriol. Works a good deal with a hammer and cold chisel.

*Condition on Admission.*—Small man, well built, healthy looking. Hands and fingers slightly swollen; skin hard, shiny, tightly stretched, cannot be pinched up; some tenderness on pressure over the palms; movements of fingers much impaired. The sclerodermatous condition is confined to the hands. The patient complains of aching pains in shoulders, ankles, and thighs; on movement, creaking is well marked in shoulders and ankles.

No visceral disease. No evidence of any disease of the nervous system. Urine has never been dark coloured.

*Treatment.*—Warmth; fibrolysin injections.

*Result.*—Decided improvement in condition of hands.

16th April.—Discharged distinctly better.

6th June 1911.—Readmitted. Pains in ankles; knees and shoulders worse; some swelling of wrists. Sclerodermatous condition of the hands is much *in statu quo*.

*Treatment.*—Hot-air baths; guaiacol carbonate, 5 grains, three times daily.

19th June.—Discharged improved.

CASE IX.—J. S., aged 55, stone-mason, admitted to Chalmers Hospital on 10th June 1913.

*Complaints.*—Coldness and stiffness of hands; stiffness of face, arms, chest, legs; shortness of breath on exertion; occasional attacks of sickness and diarrhoea.

*Duration.*—One year.

*Apparent Cause.*—Exposure to cold.

*History.*—The numbness in the hands was first felt after clearing out some cold spring water from a drain.

July 1912.—Attack of pleurisy; in bed four or five days (confined to the house a fortnight). After this hands got worse; after exposure to cold became blue and discoloured. Stiffness of fingers developed; feet and toes became similarly affected (cold and stiff). About Christmas 1912 lost his appetite and was troubled with stomach; vomited occasionally. Rheumatic pains in ankles, legs, shoulders, and chest developed in March 1913; there was also occasional looseness of the bowels. Until the present illness commenced was a very healthy man.

*Family History.*—Unimportant.

*Condition on Admission.*—Slightly-built man. Height, 5 ft. 4 ins.; weight, 9 st. 3 lbs. Expression of face immobile. Marked dryness of skin of body and of hair. Does not perspire except over the hands and feet, which feel cold and moist.

Marked sclerodermatous condition present on hands, arms, face, chest, scalp, buccal mucous membrane, and feet.

The hands are most markedly affected; after the slightest exposure



to cold they become blue. Hands feel heavy, hard, and dense; skin lardaceous, tightly stretched, thin over the fingers, which are pointed; skin cannot be pinched up over the hands, front of the chest, scalp, thighs, and feet. Movements of parts greatly impaired. The cheeks feel brawny.

On movement, creaking felt in elbows, wrists, fingers, knees, ankles, and toes.

No visceral disease. Blood normal. No evidence of disease of the nervous system. Urine normal; never has been porter-coloured.

Sensation to touch, pain, heat, and cold normal all over the body.

*Treatment.*—Rest in bed, warmth, light diet; fibrolysin injections, thyroid extract, iodide of potassium, and arsenic.

On 16th June thyroid extract (5 grains twice daily, increased to 5 grains three times daily, on 22nd June) was prescribed. On 3rd July the thyroid extract was discontinued.

On 4th July iodide of potassium (10 grains three times daily) and arsenic (2 drops of the liquor arsenicalis) prescribed.

*Result.*—Very marked improvement. Sclerodermatous condition of skin became markedly less, movements of affected parts much freer.

9th September 1913 discharged very much improved.

*Elevations of Temperature following Injections of Fibrolysin.*—In this case the same alterations in temperature and pulse which were seen in Case VII. followed some of the injections of fibrolysin.

In several instances a blood count was made immediately before an injection, and during the subsequent rise of temperature. The only alteration found was a slight diminution of the red corpuscles, a decided increase in the polymorphs, and a diminution in the small mononuclear white corpuscles.

*Additional Note.*—Patient died suddenly from heart failure on 23rd February 1914; post-mortem examination showed a condition of chronic interstitial myocarditis.

## A BIOMETRIC ANALYSIS OF SOME INSEMINATION-LABOUR AND MENSTRUAL-LABOUR CURVES IN CERTAIN MAMMALIA.

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In a previous communication\* I showed that from Tessier's statistics as to the insemination-labour duration in ewes, from Earl Spencer's in cattle, and from von Winckel's and Reid's

\* "On the Duration of the Interval between Insemination and Parturition in Certain Mammals as Studied by Biometric Curves, with Special Reference to the Calculation of Labour in Human Pregnancy," *Edin. Obstet. Trans.*, xxxviii. 107; *Edin. Med. Journ.*, 1913, xi. 291.