such a unique opportunity to explore and demonstrate the positive aspects of health care, and it is because promotive health care services can best be administered from health centres that these constitute a central focus for the teaching of social medicine.

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THE PROBLEM OF CHILBLAINS

WITH A NOTE ON THEIR TREATMENT WITH NICOTINIC ACID

BY

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Chilblains are relatively common in Britain and on the Continent of Europe, but are rare in Canada and the United States of America. The usual sites of the lesions are the dorsal aspects of the proximal phalanges of the hand, on the plantar aspect of the toes, along the inner border and dorsum of the great toe, and in the region of the heel and Achilles tendon. Chilblains may also occur on the ears, but in this site they resemble frost-bite rather than a true pernio-sis; Dubreuilh and Petges (1911) have even reported a case in which a chilblain occurred on the prepuce.

The first sign that a chilblain is developing is a local redness and irritation which comes on in bed or on sitting in front of a fire. The redness becomes more intense and the irritation increases, and if the chilblain is situated on a toe the joint feels stiff and slightly painful. The redness is gradually replaced by a cyanotic tinge and the irritation by pain; desquamation may supervene or bulla formation and ulceration may develop. In mild chilblains very little thickening and infiltration can be felt, but in severe multiple chilblains, such as may occur in the region of the Achilles tendon, there is marked thickening and induration and the skin feels icy cold to the touch. In older people a chronic type of chilblain may develop on the backs of the fingers. It is associated with hyperkeratosis and painful fissuring of the skin. Pain is a more dominant symptom than irritation.

Hallam (1931), in 100 consecutive cases, found 54 in the 0-10 years age group, 29 in the 10-20 years age group, and thereafter only 17 cases; Haxthausen (1930) noticed the more frequent occurrence of chilblains in women; and Wigley (1946) claims that chilblains are frequent between the ages of 5 and 15 years, rare after 20 years, and exceptional after 30 years.

Aetiology

There can be little doubt that cold plays a part in the aetiology of chilblains, although Leduc (1927) suggested that chilblains were first-degree burns due to the incautious exposure of numbed limbs to heat. Becker and Obermayer (1940) believe that the degree of cold is not the sole cause, and attempt to prove this point by stating that natives of India while studying in England do not develop pernio-ses. I questioned three Indian medical students and found that they were all suffering from chilblains. It is certainly correct, however, that there is another factor, as witness the fact that certain individuals may develop chilblains during a thaw when colder weather has left them unscathed.

Mackenna (1927) and Savill (1926) incriminate focal sepsis, such as infected teeth and tonsils, as a predisposing cause. Funk (1899) blames anaemia, but Jausion, Somia, and Meunier (1941) examined the blood in 17 of their 47 cases and found no abnormality apart from a moderate polymorphonuclear leucocytosis in five of them. Glandular dysfunction has its advocates: Embden (1922) and Juster (1927) claim good results with thyroid extracts, but Parkes Weber (1925) and Dore (1928) have not been able to confirm these results. Barber (1926) found the simultaneous administration of thyroid and large doses of iodine of great value; while, according to Hallam (1931), in a series of 1,275 patients 12 were suffering from myxoedema but were not subject to chilblains. On the other hand, 24 of these patients were under treatment for exophthalmic goitre; of these, three had suffered from chilblains only since the onset of the hyperthyroidism. More lately a woman doctor (1947) has suggested a hormonal basis in chilblains, as she has noticed that, although a chronic sufferer, she experiences relief during pregnancy. One of my patients noticed the same freedom from chilblains during her two pregnancies.

Wright (1897) advises calcium, but Percival and Stewart (1927) consider a hypocalcaemia improbable. Hallam (1931) found no benefit from the administration of vitamins A and D and calcium, and noticed no difference in the incidence of chilblains in 100 London school-children subjected to carbon-arc light through the winter as compared with control groups. Dr. J. T. Ingram, of Leeds, in a personal communication, said he had noticed that a certain number of patients who were being treated for lupus developed chilblains for the first time while taking calciferol.

Many writers believe that there is a tuberculous diathesis in chilblain sufferers, but Barber (1926) denies this. The past and present incidence of chilblains in 217 men suffering from tuberculosis and undergoing treatment in a sanatorium was found, on personal interview, to be 19.8%. In cases of pulmonary tuberculosis the incidence was 18.6% and in non-pulmonary 24.4%. Their ages ranged from 4 to 63 years. The slightly higher incidence in the non-pulmonary cases may be due to the fact that their average age was considerably less than the average age of the pulmonary cases and that their movements were more restricted. These figures do not, however, prove the relationship between tuberculosis and chilblains, for Winner and Cooper-Willis (1946) estimated that 50% of their sample of Service women (A.T.S.) will at one time or another have suffered from chilblains by the time they reach the age of 40.

It was not found possible to obtain any correlation between the observed peripheral circulation and the incidence of chilblains. Many patients with red congested hands and lowered bodily metabolism, as evidenced by undue intolerance to low temperatures, were found never to have suffered from chilblains. Neither was any relation discovered between patients who often suffered from "dead fingers"

and those who suffered from chilblains. A patient who had a severe degree of Raynaud's disease for two years before lumbar ganglionectomy had to be performed, and who complained of cold feet both summer and winter, never developed chilblains; and an old lady who refused insulin treatment for her diabetes and as a result developed gangrene of the toes of one foot remained free from chilblains.

Andrews (1946), on the other hand, claims that even moderate exposure may produce chilblains in people predisposed by poor peripheral circulation. Hallam (1931), however, found 14 patients with arteriosclerosis in his series of 1,275 cases, and none of them suffered from chilblains; he remarks that in Raynaud's disease chilblains are not commonly seen, and notes how seldom chilblains occur in the aged even when serious organic disease is present.

Pathology

The gross pathology of the chilblain lesion is a vasoconstriction of the subcutaneous arteries and larger arterioles associated with a vasodilatation of the superficial minute vessels.

Microscopically the lesion has been described by Hodara (1896), who found the skin vessels full of blood and dilated, with thickened walls. In the vessels there were hyaline masses of white blood cells without actual thrombosis; the cutis showed dense inflammatory infiltrations of round cells, in which plasma cells were absent, and oedema of the connective tissue. Kyrle (1915) confirmed these observations, and Gans (1925) found thrombi in late cases of chilblains with alteration of the endothelium; the stratum corneum was thickened and the stratum granulosum occasionally so. In the connective tissue there were proliferation of the connective tissue cells and a considerable perivascular infiltration of lymphocytes. Hallam (1931) claims that a histological examination in the early stages shows a rapid degeneration of the small vessels accompanied by perivascular infiltration: this is not a mere transudation of serum, as some writers state, but a sudden and severe damage affecting the vessels of the papillary layer of the cutis. Diapedesis of red cells may also take place.

Pathogenesis

Many theories have been evolved to explain the pathology of the chilblain lesion. Harris, Lewis, and Vaughan (1929) think that cold urticaria is due to a dermolysin present in the blood which unites with the skin cells at low temperatures and lyses them on rewarming, setting free histamine; and Goldsmith (1936) suggests that this mechanism plays a part in the formation of chilblains. Unna (1896) maintains that there is a high degree of venous tone and a normal or very low arterial tone in perniosis; and Parrisius (1921) supposes that there is a spasm of the subcutaneous veins, as witness the slow return of blood to an anaemic spot caused by pressure on a perniotic area.

Lewis (1941) later elaborated his theory of the liberation of H-substance from the skin cells as a result of damage by cold; however, this theory does not seem to explain why severe degrees of cold may produce no lesion when moderate degrees cause chilblains in the same individual. It does not explain why persons who develop frost-bite do not at the same time develop chilblains, and it has been found impossible to produce chilblains experimentally by the injection of histamine or by the application of carbon dioxide snow. Simmons (1945) states that the spasm of the vessels in chilblains leads to suboxygenation of the tissues, which of itself gives rise to further vascular spasm; and Gellhorn (1943) points out that continued deficiency of oxygen supplies and blood stagnation in-

crease capillary permeability and lead to dropsical exudations. Sequeira, Ingram, and Brain (1947) claim that erythema pernio is the outward sign of the inability of the skin, including its small blood vessels, to adapt itself to low temperature.

In an attempt to elucidate further the problem of the pathogenesis of chilblains I carried out certain experiments

Present Investigation

It was noticed that considerable pressure with a glass slide on an established chilblain was necessary to cause blanching, and that on the release of pressure the colour was only slowly re-established. If the same experiment was carried out on the skin of a hand that had been immersed in water at 45° F. (7.2° C.) for three minutes it was found that blanching occurred readily, but that, as in the first experiment, the colour was only slowly re-established. Since in both cases the subcutaneous arteries were in spasm, as witness the coldness of the skin—for Krogh (1922) has shown that the skin temperature is dependent on the rate of blood flow—it follows that in the case of the chilblain there must have been interference with venous drainage. The veins draining the subpapillary venous plexus are thin-walled and pass through the corium in close relation to the collagen bundles, and it is not unreasonable to assume that oedema of the corium can cause pressure on and partial collapse of these veins. This mechanism may cause interference with the nutrition of the connective-tissue cells, with consequent cellular degeneration.

In another experiment the venous return from one hand was stopped by means of a tourniquet applied round the arm, and the hand was then immersed in cold water at 45° F. for six minutes: no cyanosis developed in the hand. With the tourniquet still in position the hand was then immersed in hot water at 115° F. (46.1° C.): cyanosis developed, and was well marked after four minutes. The hand was then returned to the cold water, with the tourniquet still in position, and it was noticed that the cyanosis started to disappear, and at the end of six minutes had been replaced by a bright-red colour. This experiment was repeated on three occasions with the same result. It was thus concluded that the cold had in some way caused a breakdown or dissociation of the carboxyhaemoglobin responsible for the cyanosis. This took place when the venous drainage from the part was occluded.

As has been shown, the venous drainage from a chilblain area is at least partially occluded and the skin temperature is initially very low; therefore it would seem that cold interferes with the formation or causes the breakdown of carboxyhaemoglobin and thus prevents the elimination of the waste products of cellular metabolism. It was felt that these waste products, if allowed to remain for any length of time in the tissue spaces or capillaries, would cause irritation and damage to the tissues resulting in the inflammatory reaction which has been shown to be the basis of the pathology of a chilblain. Several other experiments were done with this theory in mind, and further support was gained for it.

The nature of these waste products, or metabolites, is open to speculation, but they may well be the products of catabolism such as carbon dioxide and lactic acid, or they may be the products of incomplete anabolism such as oxaloacetic acid, fumaric acid, or succinic acid, because enzyme activity is either limited or arrested by cold and therefore the action of the dehydrogenases will be impaired.

One more experiment was performed: the arm and forearm were exsanguinated and a tourniquet applied to occlude both the arteries and the veins. The hand was then immersed in cold water at 45° F. for two minutes and the

tourniquet was then released. It was noticed that the colour returned to the fingers very much more slowly than in a control experiment with the hand in warm water. It was thus concluded that cold can cause spasm of the subcutaneous arteries without the intermediary of metabolites.

To sum up on the basis of this hypothesis it would appear that the pathogenesis of chilblains is the following:

Exposure to cold causes a vasoconstriction of the subcutaneous arteries and interference with cellular metabolism resulting in the formation of irritating metabolites. On warming the part, if the arterial spasm relaxes the metabolites are removed and no lesion supervenes. If, however, the arterial spasm does not relax within a reasonable time more metabolites are formed at the site because of the increase in cellular metabolism due to warming the part; this causes irritation, oedema of the corium, and thus interference with venous drainage, setting up a vicious circle and producing a chilblain. Thus a chilblain will result only when cold causes arterial spasm and there is an upset of the balance between vital cellular activity and venous drainage.

It is claimed that this theory explains the many and varied anomalies of chilblain production.

Treatment

The best treatment of chilblains is undoubtedly prevention, and to this end warm clothing should be worn, a certain amount of exercise taken, and a liberal diet provided.

The number of special measures advocated is legion, but in the main their object has been to improve the local circulation of the affected limbs. Jacquet and Debat (1914) advise raising the hands and actively flexing the fingers several times; McAll (1946), during his internment in China, came across a means of exercising the fingers by playing with two walnuts in the one hand. Bathing the affected parts in hot and cold water alternately has been recommended, and Whitfield (1921) suggests bathing the chilblains in a 5% salt solution at a temperature of 38° C. to relieve the irritation. Haxthausen (1930) has used carbon-arc light filtered through a water filter to exclude the non-luminous heat rays and has also applied carbon dioxide snow for short periods; Steimann (1926) used ethyl chloride locally; Grünbaum (1920) and Stein (1928) advise diathermy; and Henk (1926) recommends one-third of an erythema dose of x rays filtered through an aluminium filter. Price (1933) suggests massage, galvanic and faradic stimulation, and Spiethoff (1933) advises Grenz rays; Dore (1928), on the other hand, has tried arterial sympathectomy with unconvincing results. Stimulating ointments containing such substances as iodine, camphor, phenol, turpentine, and methyl salicylate have their advocates. Wigley (1946) advises dressing ulcerated chilblains with penicillin. Brack (1940) used dihydro-imidazole; Grossman (1926) advises the induction of artificial fever by means of "aolan" and "novoprotin." Dr. H. M. Walker, of Glaxo Laboratories, in a personal communication, claims that the value of vitamin D (5,000 units of calciferol and 5 mg. of calcium oleate per ml.) in the treatment of chilblains is not due to its calcium content but to the fact that it is a colloid suspension containing negatively charged colloids which have a specific stimulating action on the reticulo-endothelial system.

Herxheimer (1942) advocates a modification of Bier's method of passive congestion, and Simmons (1945) treated chilblain sufferers by means of a paravertebral sympathetic block using 20 ml. of a solution containing amethocaine 1/1,000 and adrenaline. Whitfield (1921) recommends nitroglycerin 1/200 gr. (0.32 mg.) and erythrol tetranitrate 1/50 gr. (1.3 mg.) thrice daily; Grove (1926) advises prophylactic injections of sodium caedylate; Lefevre, Dubarry, and Halle (1942) treated 85 cases with intravenous

fluorescein, and had to record failure in only 9.4%. Jausion, Somia, and Meunier (1941) used up to 600 mg. of nicotinamide daily in their treatment of chilblains; they administered it both orally and by injection, and by this method they claimed they could cure mild cases in one week, moderate cases in two weeks, and severe cases in three weeks. Watson (1941) injected each chilblain with 0.5 ml. of histamine; this caused an immediate and intense irritation locally, with subsequent alleviation.

Having observed the vasodilator action of nicotinic acid I decided to use it in the treatment of the cold congested hands and noses from which so many young children suffer in the winter; the results were dramatic. It was then decided in the winter of 1943-4 to attempt the treatment of chilblains, which has for so long been unsatisfactory in general practice, by the oral administration of nicotinic acid. The results were most gratifying, not one failure being recorded. In the following winter similar results were obtained, but it was felt that the weather had not been severe enough nor the chilblains bad enough to assess the real value of this treatment.

The winter of 1946-7 proved so severe and unremitting and the results so successful that it was decided to place this method of treatment on record. The basic dose of nicotinic acid administered was for an adult 50 mg. and for a child 25 mg. thrice daily immediately after meals; this tended to reduce the incidence of flushing, and no doubt caused a prolongation of the vasodilator action of the nicotinic acid. In severe cases the dose was increased, but in no case was it found necessary to give more than 300 mg. a day.

Relapse was common when the nicotinic acid was withdrawn, and advantage was taken of this fact to assess the value of the treatment. In eight patients who were asked to stop taking nicotinic acid as soon as their chilblains were cured or considerably improved, the chilblains returned but were promptly relieved by further treatment. Two patients who were cured by the administration of nicotinic acid were asked to stop treatment and to wait until the chilblains returned. They were then given nicotinamide in similar doses (the substitution was unknown to them), but no improvement resulted; they were then again treated with nicotinic acid with complete success.

It follows from this that it is of no prophylactic value to administer nicotinic acid for a long time before the advent of the chilblain season in an attempt to build up some sort of reserve. It also follows that nicotinic acid does not act primarily by virtue of its enzyme action, as the radical of coenzymes 1 and 2, otherwise nicotinamide, in similar doses should have effected as satisfactory a cure.

Presentation of Cases

The cases presented are unselected and consecutive, and were collected in the normal routine of general practice. Detailed notes were made of 27 cases so treated, of which 21 were female and 6 male. The incidence and distribution of chilblains in 15-year age groups for males and females is shown in Table I.

TABLE I.—Incidence and Distribution of Chilblains

Ages in Years	Female	Male	Hands	Feet	Hands and Feet
0-14	2	1	—	2	1
15-29	5	—	—	4	1
30-44	10	2	—	11	1
45-59	—	3	—	1	2
60-75	4	—	2	1	1

The results of treatment arranged in 15-year age groups is shown in Table II. Cases were considered to be improved if *all* subjective symptoms such as irritation and pain were

TABLE II.—Results of Treatment

Age in Years	Cured		Improved		No Difference	
	Female	Male	Female	Male	Female	Male
0-14	2	—	—	1	—	—
15-29	4	—	1	—	—	—
30-44	6	2	3	—	1	—
45-59	—	1	—	2	—	—
60-75	—	—	4	—	—	—
Total	12	3	8	3	1	—

abolished, but they were not counted as cures unless there was no evidence of chilblains on examination. Observations were made on results only during the severe weather.

Every patient was asked if this was the best treatment so far tried, and 26 responded in the affirmative; this gives a failure rate of only 3.7%. The one failure was a female telephonist aged 30, who suffered from very severe chilblains of the hands and feet. Her work may have militated against a cure. She was given only 150 mg. of nicotinic acid daily, and in the light of further experience it was felt that the dose should have been increased.

Four patients blamed a change in the weather, such as a thaw, for the onset of their chilblains; one blamed sitting still for a long time; two blamed sitting in front of a fire; sixteen blamed cold weather and frost; four blamed cold weather and damp. All but two said sitting in front of a fire made the chilblains worse. Fifteen were chronic sufferers and got chilblains practically every year; of these eight were cured and seven improved. Nine were sufferers for the first time: of these six were cured and three improved. The others were only occasional sufferers.

Two patients complained of occasional cracks at the corners of the mouth and one of a sore tongue, but it was difficult to relate these symptoms to a systemic deficiency of the vitamin B complex. Two patients noticed improvement after taking only 50 mg. of nicotinic acid; five noticed improvement after treatment for three days, ten after four days, six after seven days, and three were indefinite.

It is interesting to record that two patients found that they could tolerate the cold with much greater comfort during treatment; this may have been due to a "stoking up" of skin-cell metabolism resulting from the vasodilatation of the subcutaneous arteries.

Untoward effects noticed during treatment were of little significance and were only transitory: constipation was recorded in three cases, sleepiness in two, slight headache in two, and transient flushing and mild irritation of the skin in twelve.

Conclusions Regarding Treatment

On the basis of the action of nicotinic acid—namely, vasodilatation—it stands to reason that this treatment cannot be expected to benefit to any great extent chilblain sufferers who have pronounced arteriosclerosis or other condition of the peripheral circulation which interferes with the vasodilatation of the skin vessels. Nevertheless it is felt that nicotinic acid has a specific action on chilblains, and that the very vast majority of chilblain sufferers will benefit from this treatment.

Treatment should start as soon as the first sign of a chilblain makes its appearance and should be continued, possibly in reduced dosage, until the chilblain season has passed.

Summary

The problem of chilblains is discussed as regards their aetiology and pathogenesis. It is claimed that nicotinic acid, given orally, has a specific effect on chilblains. Twenty-seven cases are quoted to prove this, and it is suggested as the treatment of choice in general practice owing to its ease of administration and its freedom from serious untoward effects.

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HYPOTHALAMUS AND PITUITARY GLAND

WITH SPECIAL REFERENCE TO THE POSTERIOR PITUITARY AND LABOUR

BY

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Marañón (1947) reported the case of a woman who had diabetes insipidus with an associated uterine atony, and discussed the light that this and similar cases throw on the mechanism of labour. Two important facts emerge from a study of such cases: (1) that lesions of the hypothalamus or neurohypophysis which produce diabetes insipidus may also interfere with the mechanism of parturition, and (2) that similar lesions which produce interference with the secretion of the posterior lobe of the pituitary gland (as evidenced by the diabetes insipidus) do not necessarily interfere with the activity of the anterior lobe of the pituitary (as shown by normal menstrual cycles and pregnancy). It is felt that a summary of recent work dealing with these points may be of interest in view of Marañón's paper.