THE PROBLEM OF CHILBLAINS, WITH A NOTE ON NICOTINIC ACID AND ITS USE IN THEIR TREATMENT.

Macleod and Muende (1940a), Goldsmith (1936a) and Haxthausen (1930a) give excellent accounts of the blood vessels of the skin and their innervation. For the purpose of this thesis the following brief description is given.

Deep to the corium lie the skin arteries which anastomose to form a subdermal plexus from which branches are given off and travel in a direction perpendicular to the plane of the skin; as these vessels pass towards the papillae they lose their muscular coat about the middle of the corium, and the contractile elements of Rouget make their appearance. In the subpapillary region these vessels send out branches at right angles to form the subpapillary network from which the capillaries supplying the papillae arise. These arterial capillaries empty into venous capillaries having a relatively large diameter and draining into a subpapillary venous network; it is this network

which gives most of the colour to the skin. In the mid-dermal region there is a second venous plexus which drains by relatively straight, thin-walled vessels into the subcutaneous veins In addition to this arrangement there is an accessory arterio-venous mechanism called the glomus. This anastomosis may be found at any level in the corium but occurs most commonly in the region of the superficial plexus. The arterial segments of the anastomosis have very thick walls composed of myo-epithelial cells and surrounded by a network of nerve fibrils; their lumen is very narrow. It is suggested that the function of the glomus is to regulate the temperature and pressure of the interstitial tissue.

The constrictor nerve supply to the arteries and arterioles derives from the sympathetic system. The dilator nerves for the skin vessels of the limbs leave the cord through the posterior nerve roots and run to the periphery without making contact with the sympathetic chain. If the sensory nerves are excited distal to the ganglia flushing of the skin occurs. The fibres concerned belong to the posterior

root system degenerating when the root ganglia are removed but not when the roots are cut between the cord and the ganglia. Hirt (1928) showed that the spinal ganglia contained autonomic nerve cells, some of which send long processes to the periphery and probably act as efferent vasodilators to the vessels of the skin.

Woollard (1926) states that the plexuses found on the arteries are of two kinds; medullated (sensory) supplying the smaller arteries and arterioles and non-medullated (sympathetic). The sensory fibres supply the adventitia of the vessel walls and send branches to the Pacinian bodies and sensory nerve endings, and he has shown that the same sensory fibre may, by division, supply the arteriolar wall and special sensory nerve endings, forming a short axon reflex arc. Bruce quoted by Goldsmith (1936b) thinks that a stimulus can ascend such an afferent nerve fibre to a bifurcation and then go over into the other branch to dilate the arteriole. Lewis (1927a) and Carrier (1922) have shown that the contraction of the minute vessels (subpapillary venous plexus) appears

to be the direct result of stimulation of their walls and occurs independently of nervous reflexes. Ebbecke (1917) observed the latent contraction of the minute vessels after stroking the skin in which the nerve supply had long been lost. Goldsmith (1936c) points out that the marginal crenations of the flare of Lewis' Triple Response of the skin correspond to the area supplied by a single arched arteriole and therefore deduces that this is the most peripheral vessel that dilates due to nerve action and the smallest that possesses a muscular coat.

As a result of some simple experiments involving the immersion of the hands in water at 115°F. and water at 45°F. the writer came to the conclusion that in the hands, at least, the superficial vessels dilate and contract entirely passively as a result of temperature changes. It was found impossible by the inspection of the colour of the skin to estimate whether the hand was warm or cold. The increased redness of the skin which developed, without a preceding pallor, on immersing the hands in cold water was thought to be due to passive venous congestion induced by the fact that the circulation

was considerably slowed on account of the vasoconstriction of the subcutaneous arteries, and the increased redness of the skin, apparent on immersing the hands in hot water, was thought to be due to the increased blood flow resulting from vasodilatation.

DISTRIBUTION, OCCURRENCE AND DESCRIPTION OF CHILBLAINS.

Becker and Obermayer (1940) state that 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 on the dorsal aspects of the proximal phalanges of the hand, on the plantar aspect of the toes, along the outer border of the small toe and 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 perniosis; Dubreuilh and Petges (1911) have even reported a case of a chilblain occurring on the prepuce.

Barber (1926a) divides chilblain sufferers into two types: the fat, phlegmatic and mentally dull type with a dry skin and the thin nervous type with vasomotor instability; in the present series of cases this classification was not observed.

The first sign that a chilblain is developing is a local redness and irritation which comes on in bed at night 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 bullae formation and ulceration may develop. In acute cases the process described may take two or three days leaving a feeling of soreness which may persist for several weeks. In chronic milder cases the cyanotic stage may never be reached and the irritation and redness may persist during the winter. 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 Tendo Achilles in susceptible persons, there is marked thickening and induration and the skin feels icy cold to the touch. This type of chilblain shows an infiltrated central area of a yellowish red colour, which blanches readily on pressure, surrounded by a brighter red zone; as the chilblain ages a cyanotic tinge becomes manifest, the infiltration spreads more deeply and greater pressure is necessary to cause blanching and the irritation of the initial stage gives way to pain. It is interesting to note with this type

of chilblain that no new chilblain will develop on the same site until the expiration of two or three weeks (case 6).

In older people a chronic type of chilblain lesion may develop on the backs of the fingers. It is associated with hyperkeratosis and painful fissuring of the skin and a considerable degree of swelling. Pain is a more dominant symptom than irritation. Haxthausen (1930b) noticed the more frequent occurrence of chilblains in women; Hallam (1931) in 100 consecutive cases found 54 cases in the 0-10 years age group, 29 cases in the 10-20 years age group and thereafter only 17 cases. 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 etiology of chilblains, although Leduc (1927) suggested that chilblains were first degree burns due to the incautious exposure of numbed limbs to heat. It is hard to justify this theory in view of the fact that several patients in a sanatorium who had no access to fires or hot water bottles developed chilblains. 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 perniones. Three Indian medical students were questioned regarding this point and it was found that they were all suffering from chilblains. It is certainly correct, however, that there is another factor. This is evident from the fact that of a group of persons subjected to similar climatic and environmental conditions, such as in a sanatorium, only a few develop chilblains; and from the fact that in the case of certain individuals a change of weather, even to a milder type (case 6), may precipitate an attack of chilblains when

more severe weather had left them unscathed. The site of chilblains, occurring as they do, not at the tips of the fingers as frostbite commonly does, but more proximally, is further evidence that the degree of cold is not the only cause.

Mackenna (1942) and Savill (1926) incriminate focal sepsis, such as infected teeth or tonsils, as a predisposing cause. Funk (1899) blames anaemia but Jausion, Somia and Meunier (1941) did 17 blood examinations in their series of 47 cases and found no abnormality apart from a moderate polymorphonuclear leucocytosis in 5 of the cases. 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 (1926b) finds the simultaneous administration of thyroid and large doses of iodine of great value while Hallam (1931) in a series of 1275 patients found 12 suffering from myxoedema, none of whom were subject to chilblains; on the other hand 24 of these patients were under treatment for exophthalmic

goitre of whom 3 had suffered from chilblains only since the onset of the hyperthyroidism. Gans (1924a) suggests a dysfunction of the hypophysis, and Barber (1926c) postulates a pluriglandular upset, but Haxthausen (1930c) points out that treatment with ovarian extracts and preparations of the parathyroid and hypophysis glands and pluriglandular products have not produced convincing results. More lately a woman doctor (1947) has suggested an hormonal basis in chilblains as she has noticed that although a chronic sufferer she experiences relief during pregnancy. One of the cases to be presented (case 3) noticed the same freedom from chilblains during her two pregnancies.

Wright (1897) advises calcium but Percival and Stuart (1927) consider a hypocalcaemia improbable. Mr. A.D.Rhodes, Northern Pharmaceuticals, Bradford, says that the biochemical investigation of chilblain sufferers does not support a low blood calcium and Dr. H.M.Walker, Glaxo laboratories, Middlesex, states that there is no evidence of a calcium deficiency in perniosis. 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 a 100 London School children subjected to carbon arc light through the winter compared with control groups. Dr J.T.Ingram of Leeds, in a personal communication, said that he had noticed that a certain number of patients who were under treatment for lupus developed chilblains for the first time when taking calciferol. Lewis (1941b) states that an altered blood coagulation time is not found with constancy in chilblain sufferers.

Many writers believe that there is an association with tuberculosis. Bazin (1861) included chilblains in his "scrofulides benins" and Rasch (1898), Hutchinson (1900), Permin (1903) and Haxthausen (1930a) stress this association. Darier (1928) alleges that a chilblain is an actual tuberculide and Jausion, Somia and Meunier (1941) in a review of 47 patients suffering from chilblains found 37 who reacted positively to tuberculin skin tests. On the other hand Hagen (1922) considers that sufferers from chilblains have a "vasoneurotic constitution"; Unna (1896a) maintains that pernio occurs solely on angioneurotic

skin areas and Van Leeuwen (1925) was struck by the high proportion of his allergic patients, chiefly asthmatics, that presented over sensitiveness to tuberculin. Barber (1926*d*) states that the suggestion,made chiefly by French writers, that chilblains should be considered a superficical form of erythema induratum and therefore a tuberculide cannot be accepted. Dr. Ingram, in a personal communication, also stated his disbelief in the tuberculous basis of chilblains.

Hallam (1931) found the incidence of chilblains in different groups of patients as follows:-
Casualty patients (Sheffield Royal Infirmary) 5.3%
Medical patients (Sheffield Royal Infirmary) 9.2%
Tuberculous Patients (Sheffield T.B.Dispensary) 13.2%
Winner and Cooper-Willis (1946) in a survey of servicewomen (A.T.S) estimated that 50% of their sample will have, at one time or another, suffered from chilblains by the time they reach the age of 40 years.

The incidence of chilblains, past and present, 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 tuberculosis the incidence was 24.4%. The ages ranged from 4 to 63 years. The slightly higher incidence in the non-pulmonary cases may be due to the fact that movement is more restricted by splinting in bone tuberculosis and therefore the circulation is not so well stimulated by muscular movement. It should be emphasised that even the mildest and most transient cases were included in this survey. It is worthy of note that a few of the patients interviewed volunteered the information that their chilblains only developed during their stay in the sanatorium. One such patient stated that he had spent the Winter in the sanatorium on three separate occasions and on each occasion developed chilblains although he never suffered from them in his own home.

These figures compare favourably with Winner and Cooper-Willis' estimated incidence in servicewomen. Of the cases to be presented in this paper only one, a woman of 39 years (case 6), gave a history of tuberculosis in childhood, and none had active tuberculosis. 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, and very cold extremities were found never to have suffered from chilblains. Neither was any relationship found between patients who frequently suffered from "dead fingers" and chilblain sufferers. A patient who suffered from a severe degree of Raynaud's disease for two years before lumbar ganglionectomy was performed and who complained of cold feet both Summer and Winter, never developed chilblains and an old lady who refused insulin treatment for 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 in people predisposed by poor peripheral circulation even moderate exposure may produce chilblains. Hallam (1931), however, found 14 patients with arteriosclerosis in his series of 1275 and none of them suffered from chilblains; he remarks that in Raynaud's disease chilblains are not commonly met with and notes how seldom chilblains occur in the aged even when serious organic disease is present. In the same series he found 86 suffering from some form

of heart disease and of these 15 (17.4%) had recent chilblains, and he suggests that the frequency with which chilblains are met with in disorders of the heart is due to the lessened propulsive force causing slowing of the blood stream and interfering in some way with the nutrition of the superficial vessels. Collens and Wilensky (1939) state that the picture of the chronic chilblain is produced by the repeated exposure to cold causing an increased irritability of the vessels to subsequent exposure. It is also possible for one exposure to a requisite degree of cold to cause a chilblain - Hallam (1931) also supports this view.

PATHOLOGY.

The gross pathology of the chilblain lesion is a vasoconstriction of the subsutaneous 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 (1925b) 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 was 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. Haxthausen (1930e) describes small haemorrhages into the skin of the lesion.

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 (1936d) suggests that this mechanism plays a part in the formation of chilblains. Parrisius (1921) supposes that there is spasm of the subcutaneous veins in perniosis as witness the slow return of blood to an anaemic spot caused by pressure on a perniotic area; Haxthausen (1936f) admits that there may be a general contraction of the subcutaneous veins in perniosis but claims that this contraction can play but little part in the pathology of the condition. Unna (1896b) maintains that there is a high degree of venous tone and a normal, or very low, arterial tone in perniosis.

Lewis (1941c) later elaborated his theory of the liberation of H-substance from the skin cells as a result of damage by cold and did several experiments

to prove his contention; however this theory does not seem to explain why severe degrees of cold may produce no lesion in an individual when moderate degrees cause chilblains in the same individual. It does not explain why persons who develop frostbite do not at the same time develop chilblains, and it has been found impossible to produce chilblains experimentally by the injection of histamine or the application of carbon dioxide snow. Goldsmith (1936e) said that pruritus can hardly be ascribed to the setting free of histamine, since a wheal caused by pricking-in histamine does not itch; this has been confirmed by the writer. In fact Watson (1941) claimed a certain degree of success in the treatment of chilblains by the local injection of histamine. The local application of carbon dioxide snow for 90 seconds on the fingers of several persons, a procedure that must have caused a considerable amount of damage to the skin cells, failed to produce a lesion even remotely resembling a chilblain.

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 increases capillary permeability and leads 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 certain experiments were done by the writer.

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. for 3 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. It has been shown that 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 reasonable to assume that oedema of the corium had caused pressure on, and partial collapse of, these veins. Macleod and Muende (1940b) state that when a skin irritant is chemical or thermal the chemotactic agent is either the irritant itself or poisonous products eliminated by the epidermal cells in response to it. The irritant may cause a swelling of the connective tissue cells to such an extent as to interfere with their nutrition and cause cellular degeneration.

Another experiment was done in which the left hand of a normal individual was placed in water at 115°F. for 5 minutes and the right hand in water at 42°F. for 5 minutes, after drying both hands the temperature of the left hand was found to be 85°F. and the right 60°F. The individual was then placed in a room with the air

temperature at 56°F. and the following results were obtained:-

	After 10 Mins.	After 20 Mins.	After 30 Mins.
Temperature of left hand.	76°F.	74°F.	70°F.
Temperature of right hand.	62°F.	63°F.	64°F.

After one hour the left hand was still warmer by 1°F. During the experiment both hands exhibited a high colour.

The results of this experiment show the considerable time required for arterial spasm to relax in a cool atmosphere. Schröder (1944) demonstrated an abnormally slow response to warming in the skin of subjects disposed to chilblains, and Haxthausen (1930g) states that the spasm of arteries persists for a considerable time even in a warm atmosphere.

For the third experiment the venous return from one hand was stopped by means of a tourniquet and the hand immersed in cold water at 45°F. for 6 minutes - no cyanosis developed in the hand; with the tourniquet

still in position the hand was then immersed in hot water at 115°F., cyanosis developed and was very well marked after 4 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 6 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 therefore prevents the elimination of the waste products of cellular metabolism.

It was thought 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 chilblains.

In an attempt to confirm this theory of the production of irritating metabolites by the action of cold, further experiments were done:-

1. The veins in the arm were occluded by means of a tourniquet and the hand was then immersed in hot water at 115°F. - no tingling was felt even after 10 minutes immersion.
2. The arm and forearm were exsanguinated by raising the limb above the head and by vigorously massaging towards the heart. A tourniquet was then applied to occlude both the arteries and veins and the hand then immersed in cold water at 45°F. for 3 minutes - no tingling developed. The tourniquet was left in place and the hand

transferred to hot water at 115°F. - no tingling developed, neither did tingling develop on releasing the tourniquet.

3. The veins in the arm were occluded and the hand immersed in cold water - slight tingling was felt after 6 minutes. The hand was then immersed in hot water at 115°F. and the tingling persisted and became more intense.

4. The hand, with no tourniquet on the arm, was immersed in cold water at 45°F. - slight tingling developed after 6 minutes. The hand was then immersed in hot water at 115°F. and the tingling intensified after 15 seconds and lasted for a further 5 seconds.

   This same phenomenon was also observed after only 2 minutes immersion in cold water.

It follows from these experiments that the tingling experienced was not due to congestion and

local pressure on the nerves because no tingling was felt in experiment 1.; neither was it referred due to the pressure of the tourniquet because no tingling was felt in experiment 2. and the tingling experienced in experiments 3 and 4. came on after the same period of immersion in cold water. The tingling could not have been due to the return of nervous sensation after numbing as the result of the immersion in cold because no tingling was experienced in experiment 2.

As a result of these experiments it was concluded that cold acting on the skin does cause the production of irritating metabolites and it was felt that the absence of tingling, which was a feature of experiment 2. was due to the fact that little if any blood was present in the skin and therefore no metabolites were capable of being formed by the skin cells.

The nature of these 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 oxalo-acetic 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 done: the arm and forearm were exsanguinated and a tourniquet applied to occlude both the arteries and veins. The hand was then immersed in cold water at 45°F. for 2 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.

On the basis of this hypothesis it would seem clear that the pathogenesis of chilblains is the following:- Exposure to cold causes a vasoconstriction of the subcutaneous arteries and interference with cellular metabolism, with the result that metabolites are formed. On warming the part, if the arterial spasm relaxes, the metabolites are removed into the general circulation and no lesion develops; if, however, the arterial spasm does

not relax the circulation is not re-established; more metabolites are formed because of the increased cellular metabolism in the warm atmosphere, causing irritation, oedema of the corium and interference with venous drainage, and thus establishing a vicious circle. This explains the bright red colour noticed in developing chilblains which later deepens and becomes cyanotic when the arterial spasm relaxes.

In certain individuals, although the arterial spasm produced by cold persists for a longer time than normal, their vital cellular activity may be impaired with the result that even on warming, insufficient metabolites are formed to cause an inflammatory reaction and therefore a chilblain does not develop.

It is claimed that this theory explains the apparent anomalies met with in the reaction to cold of certain individuals. For instance it explains why arterial spasm alone, as in Raynaud's disease or "dead fingers", may not cause chilblains; it also explains why severe degrees of cold may not cause chilblains in an individual and yet a thaw may; in the first case cellular activity

is depressed by the severe cold and sufficient metabolites to cause perniosis are not formed.

To sum up a chilblain will only result if cold causes arterial spasm and an upset of the balance between vital cellular activity and venous drainage.

This theory receives some support from the observations of Gellhorn (1943) who states that within normal limits the metabolic rate is directly related to the temperature of the body, and of Hallam (1931) who notes that in a susceptible individual a chilblain commences to make its appearance about 18 hours after exposure to cold of the requisite severity.

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 and rolling them round the fingers and claimed good results for this treatment; 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 (1930h) 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; Grunbaum

(1920) and Stein (1928) advise diathermy and Lenk (1922) advises 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 or methyl salicylate have their advocates and Wigley (1946) advises dressing ulcerated chilblains with penicillin. Brack (1940) used dihydro-imidazole; Grossman (1926) advises inducing artificial fever by means of aolan and novoprotin. Dr. H.M.Walker of Glaxo Laboratories, Middlesex, in a personal communication, claims that the value of Vitamin D_2 in colloidal form (5,000 units of calciferol and 5 mgms. of calcium oleate per cc.) in the treatment of chilblains is not due to its calcium content but due 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; he advises keeping the elastic bandage on all night and recommends that this treatment be continued for six weeks. In 24 cases so treated he achieved complete success in 21 cases after 5-7 days. Simmons (1945) treated chilblain sufferers by a paravertebral sympathetic block using 20 ccs. of a solution containing amethocaine 1/1,000 and adrenaline; of 8 cases so treated 6 remained cured throughout the winter.

Whitfield (1921) recommends nitroglycerin 1/200 gr. and erythrol tetranitrate 1/50 gr. thrice daily; Grover (1926) advises injections of sodium cacodylate prophylactically . He gives three injections of 3/4 gr. made up in ampoules at intervals of two days and claims good results; he got the idea from an Armenian doctor. Lefèvre, Dubarry and Halle (1942) treated 85 cases with intravenous fluoresceine (5%) and recorded failures in 9.42%. The first four injections were given daily, and then the injections were given every two days and ultimately twice a week. Improvement usually was noticed after two injections. They think that

fluoresceine acts by virtue of its selective vasodilator action on the terminal vessels and quote M. Baillart for confirmation.

Jausion, Meunier and Somia (1941) used up to 600 mgms. of nicotinamide per day in their treatment of chilblain sufferers; they administered it both orally and by injection and by this method claimed they could cure mild cases in one week, moderate cases in two weeks and severe cases in three weeks. The only untoward effects noticed during treatment were occasional slight headaches, tickling of the skin and sleeplessness unassociated with tiredness, but they seldom had to interrupt treatment on that account. Unfortunately Winner and Cooper-Willis (1946) quote these French workers as using vitamine P, which is a flavone and is referred to as citrin or hesperidin, while in point of fact vitamin PP or nicotinamide was used by them. Andrews (1946) says that in the treatment of chilblains nicotinamide 50 mgms. and calcium gluconate 2 gms. are used with occasional benefit. Watson (1941) injected each chilblain with 0.5 ccs. of histamine and caused immediate intense

irritation locally with subsequent alleviation. He also used Beetoxin ointment but his results are not very convincing.

The writer having observed the vasodilator action of nicotinic acid 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 1943-1944 to attempt the treatment of chilblains, which has for so long been unsatisfactory in general practice, by means of the oral administration of tablets containing 50 mgms. of nicotinic acid for adults and 25 mgms. of nicotinic acid for children under 10 years of age. 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 - 1947 has proved so severe and unremitting and the results of treatment so successful that it was decided to place on record this method of treatment. It should be pointed out that the writer

was unaware of the fact that French workers had been using nicotinamide for the treatment of chilblains as early as 1941.

No reference in the literature has been found, however, of the treatment of chilblains with nicotinic acid.

The usual dosage administered was for an adult 50 mgms. and for a child 25 mgms. of nicotinic acid in tablet form thrice daily immediately after meals; by this means the incidence of flushing was greatly reduced. In severe cases with considerable thickening and infiltration the dose was increased, but on no occasion was it found necessary to exceed 300 mgms. per day. It was found that relapse was common on the cessation of the tablets and, as will be shown, advantage was taken of this fact to assess the value of the treatment. It therefore follows that taking nicotinic acid a considerable time before the onset of the chilblains in an attempt to build up a reserve is of little value.

PRESENTATION OF CASES.

The cases to be presented are unselected and consecutive and were collected in the normal routine of general practice.

Twenty seven cases were treated of which 21 were female and 6 were male. The ages of the females ranged from 4 years 5 months to 75 years and of the males from 1 year 10 months to 52 years. The incidence and distribution of chilblains in 15 year age groups for males and females is shown in table I.

TABLE I.

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

TABLE II

Ages in years.	Cured.	Improved.	No difference.
0 - 14	2	1	-
15 - 29	4	1	-
30 - 44	7	3	1
45 - 59	1	2	-
60 - 75	-	4	-

These results are summarised in table III as regards females and males.

TABLE III

	Females.	Males.
Cured.	12	3
Improved.	10	3
No difference.	1	-

All the patients were asked if these tablets were the best treatment that had been tried and 26 answered

"Yes" and only one answered that they had made no difference. That is a failure rate of 3.7%.

The one failure was a female telephonist aged 30 years who suffered from very severe chilblains of the hands and feet. Her work may have mitigated against a cure. She was only given 150 mgms. of nicotinic acid per day and it was felt later that the dose should have been increased.

Six of the cases gave a past history of a serious illness. The illnesses recorded were: Infantile paralysis, Diphtheria, Abdominal tuberculosis, Cholecystectomy, Pneumonia and Bilateral quinsies.

Seven patients thought that food rationing had made the chilblains worse, sixteen denied this and four were doubtful.

Four patients blamed a change in the weather such as a thaw as the cause of chilblains; one blamed sitting still for along time; two blamed sitting in front of the 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 occasionally sufferers.

Two patients complained of occasional cracks at the corner of the mouth and one of a sore tongue, but it was difficult to relate these symptoms to any systemic deficiency of the vitamin B complex.

Two patients noticed improvement after taking one tablet; five noticed improvement after treatment for 3 days; ten after 4 days; six after 7 days and three were indefinite.

Only three patients thought that the chilblains affected their general health.

The answers to other questions are summarised in table IV.

TABLE IV.

	YES.	NO.
Did the tablets cause flushing?	12	15
Do you get short of breath on exertion?	6	21
Do you get cold feet?	22	5
Do you get "dead fingers"?	9	18
Do the chilblains interfere with your work?	7	20
Do the chilblains interfere with your sleep?	8	19
Do the chilblains ever ulcerate?	4	23

In eight patients who were asked to stop taking the tablets after the chilblains disappeared or were considerably improved the chilblains returned and on taking the tablets again, they were again either cured or considerably improved.

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 tablets containing 50 mgms of nicotinamide thrice daily for four days without result; they were then

re-treated with nicotinic acid: improvement was noted after one day and cure after three days.

Jausion (1941) on the other hand is convinced that vitamin PP (l'amide nicotinique) by mouth cures most cases of chilblain in doses of 40-50 centigrams per day. Using these large doses other French workers, already quoted, noticed that tingling of the skin developed and it is probable that, although Dilling (1944) says nicotinamide does not cause vasodilation, this tingling was sufficient to stimulate the peripheral circulation.

Jausion (1941) claimed that, as a result of his success with nicotinamide, there must be a dietetic factor in the aetiology of chilblains, but the writer claims that his positive results with nicotinic acid in doses of 150 mgms. per day and his negative results using the same dosage of nicotinamide rules out this hypothesis.

Seven of this series of 27 cases are presented in more detail.

Case 1 .

Female shop assistant aged 34 years. This lady suffered very severely with chilblains every year on her feet and the back of her legs. She has not noticed that they have been any worse since food rationing was introduced. Her fingers frequently go "dead" and she suffers from cold feet in the winter. She has tried many remedies without success. She felt that the chilblains made her rather irritable but they did not keep her from sleeping. Sitting in front of a fire made them worse. She has had no serious illnesses and does not get short of breath on exertion. The chilblains frequently fissure and bleed. During the frost she notices that they are tense and painful but if she manages to get her shoes on, and thus constrict them, they become relatively comfortable. However, the worst time is the thaw when the chilblains inflame, swell and become extremely painful.

She received treatment with 50 mgms. of nicotinic acid in tablet form three times daily after food; no flushing or other untoward symptoms appeared. She

noticed that one tablet relieved the chilblains for a time and on continuing the tablets she obtained complete relief. Shen then stopped the tablets and when the thaw commenced and the chilblains started to burn and itch she again took the tablets and was again relieved after one day.

She gave one tablet to a fellow sufferer whose chilblains were affected mostly by the frost and she said her feet felt more comfortable 5 minutes after taking it.

I finish with a quotation from a letter she wrote to me: "I would like to thank you for the relief the tablets have given me. Nothing I have had before has had any result and I was almost resigned to having trouble every winter."

Case 2.

Female dispenser aged 28. This lady has suffered from chilblains on her toes and the ball of her foot every winter for the last ten years. She thinks they have been worse since food rationing was introduced. She suffers from cold feet and her fingers go "dead" periodically. She does not get short of breath on exertion. She had infantile paralysis when she was 10 years old but no residual palsy resulted. The chilblains are not ulcerated but they show desquamation.

Previously she has tried ointments of various kinds with indifferent results. She blames the frost for the onset of her chilblain and does not associate their onset with damp weather. Sitting in front of a fire causes an intolerable itching.

She was treated by the oral administration of 50 mgms. of nicotinic acid thrice daily after food and in three days all subjective symptoms had disappeared and the chilblains were obviously healed.

She continued taking the tablets for 5 days. The chilblains returned in a modified form in three weeks and

disappeared again on taking the tablets.

The tablets did not cause flushing but she complained that they made her constipated.

Her own verdict on the tablets was: "They are marvellous".

Case 3.

Housewife aged 35 years. This lady has suffered from chilblains every winter since 1939 except on two occasions when she was pregnant. The chilblains occur on her feet and in the region of the Tendo Achilles.

On examination with a glass slide no punctate haemorrhages were seen but it was noticed that they blanched with difficulty on pressure and slowly regained their colour. She blames food rationing for making them worse. She never suffers from "dead fingers" but her feet are usually very cold. Her chilblains never ulcerate but they show a fine desquamation.

She has had no serious illnesses and does not get unduly short of breath on exertion. Previously she has tried calcium by the mouth and several ointments locally with no result.

She noticed improvement after three days, taking 50 mgms. of nicotinic acid thrice daily, and continued for a further four days. The chilblains did not return after the cessation of treatment.

On first taking the tablets she noticed a flushing

of the skin and irritation, both of which became less marked on continuing with the tablets. She also noticed an undue sleepiness during treatment. She would fall asleep in her chair in the evenings - a thing she had never done before.

Case 4.

Housewife aged 40 years This lady has suffered from chilblains on the toes and heels since 1940 and thinks food rationing has been a contributory cause. Previous treatment with ointments was unsatisfactory. The interest in this case lies in the fact that she noticed improvement after taking 9 tablets of 50 mgms. of nicotinic acid and in the fact that the chilblains reappeared on the cessation of the treatment to disappear just as rapidly on restarting treatment.

The chilblains were allowed to redevelop and her treatment was then changed to 50 mgms of nicotinamide thrice daily in tablet form. Although she took these tablets for four days she noticed no effect on the chilblains but on changing to 50 mgms. of nicotinic acid thrice daily she noticed improvement in one day and a complete cure in two days.

Case 5.

Business woman aged 42 years. This lady suffers every year with chilblains on her toes. She does not think that food rationing has made them worse. The chilblains never ulcerate. She was cured in 4 days with 50 mgms. of nicotinic acid taken thrice daily. Previous treatment with a camphor ointment had caused but little improvement. The chilblains returned on stopping the treatment to disappear on retaking the tablets. The chilblains were allowed to redevelop and tablets containing 50 mgms. of nicotinamide were then substituted and taken thrice daily for four days without improvement.

On reverting to nicotinic acid tablets, relief from the irritation was experienced after taking 2 tablets, and the swelling of the feet disappeared after three days.

Case 6.

Housewife aged 39. This lady suffered from very severe chilblains of the toes and Tendo Achilles region which came on every year. On examination the small toe and great toe were very red, congested and slightly infiltrated and thickened. The Tendo Achilles region exhibited numerous nodular chilblains with a considerable amount of deep infiltration. The recent chilblains were very irritable and showed a slightly raised yellowish-red centre with a surrounding zone of a franker red. The older chilblains were cyanotic and were not raised appreciably above the level of the surrounding skin. The recent chilblains blanched on pressure more readily than the older ones but regained their colour slowly. On palpation the skin of this region was icy cold. The chilblains on the back of the leg tend to ulcerate. No punctate haemorrhages were seen on examination with a glass slide.

Three tablets of 50 mgms. of nicotinic acid per day did not seem to have any effect on the chilblains but they made her definitely more tolerant to cold. The

dose was increased to 6 tablets per day and improvement was noted after two days. She persevered with the tablets and the undoubted improvement was maintained but the thickening and slight soreness persisted. It was felt that the considerable thickening and infiltration present mitigated against the complete success of the treatment and it was felt that if treatment had been started before the chilblains developed the results would have been wholly successful.

This lady suffered from "abdominal tuberculosis" when she was 9 years old.

Taking six tablets a day caused a slight frontal headache each afternoon and she complained of feeling sleepier than usual. She noticed that the flushing she experienced initially on taking the tablets did not develop after three days' treatment.

Case 7.

Cobbler aged 52 years. This was a very bad chronic case of chilblains of all the fingers of both hands. The skin was hyperkeratotic and showed fissuring. The fingers were considerably swollen and congested and obviously must have interfered with his work as a cobbler.

Previously he had tried calcium tablets with but little success. He had never suffered from a serious illness but noticed that lately he had been getting slightly short of breath on exertion.

He was advised to take four tablets of 50 mgms. of nicotinic acid daily; after taking 10 tablets he noticed improvement and he continued taking the tablets until the swelling subsided; the fissures healed in a week. After healing had taken place the skin was still hyperkeratotic and dry and so he was advised to massage his hands with a lanolin cream.

On examining his hands with a glass slide a few small punctate haemorrhages were seen.

POINTS FROM OTHER CASES.

One lady aged 30 years who started to develop a chilblain in bed and was unable to sleep because of the intense irritation took one tablet containing 50 mgms. of nicotinic acid and obtained complete relief in five minutes. Another lady noticed that her feet, which were the site of well developed chilblains, felt more comfortable five minutes after taking a tablet. A housewife, aged 34 years, who suffered from dry skin and whose hands fissured badly every winter so that she could not bear putting them in water noticed that the fissures were completely healed after the treatment for her chilblains.

Two patients noticed that they did not feel the cold nearly so much during their treatment as they had done previously. The writer suggests that this phenomenon is due to a "stoking up" of skin-cell metabolism resulting from the vasodilatation of the subcutaneous arteries.

The untoward effects noted during treatment were constipation (three cases), sleepiness (two cases), slight headache (two cases) and temporary flushing and irritation (twelve cases)

CONCLUSIONS REGARDING TREATMENT.

It is felt that nicotinic acid has a specific action on chilblains and that the very vast majority of chilblain sufferers will benefit considerably from treatment with nicotinic acid.

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

The dosage recommended is 50 mgms. of nicotinic acid orally thrice daily immediately after food for adults and half that amount for children under ten years. The dosage in resistent cases can be increased very considerably; the Lancet (1938) stated that the maximum and minimum dose of nicotinic acid has not been determined. Indeed up to 1500 mgms. have been given daily without producing toxic symptoms, and Spies (1938) found that 100 mgms. of nicotinic acid can be given five times a day quite safely.

The untoward symptoms produced in a few susceptible people during treatment are mild and of no significance.

Because of its safety and ease of administration it is suggested that this treatment should be the method of choice in general practice.

NICOTINIC ACID.

Nicotinic acid, which has been known as a chemical compound since 1876, was found in 1937 to cure black tongue in dogs and in the same year was used successfully in the treatment of Pellagra in man.

Nicotinic acid is pyridine-3-carboxylic acid and is one of the water soluble vitamins of the B complex; it is converted in the body, most probably in the erythrocytes, into nicotinamide, which is the enzymatically active radicle of coenzyme 1 (diphosphopyridine nucleotide) and coenzyme 2 (triphosphopyridine nucleotide) and thus plays an indispensable part in the transfer of hydrogen from triose to the oxygen of the blood. As Mitchell (1943) has pointed out it is essential for tissue or cellular metabolism.

Joliffe and Most (1943) suggest that 18 mgms. of nicotinic acid per requirement unit is a satisfactory intake although they admit that the quantitative data concerning human requirements are incomplete. The Committee on Food and Nutrition of the National Research

Council of America advise increasing this amount to 23 mgms. per day in the case of nursing mothers. Marrack (1946) points out that the main natural sources of nicotinic acid are meat, tinned green peas, wheat germ, turnip, greens and kale.

Sutton and Sutton (1942) state that nicotinic acid may cause transient vasodilatation, flushing, itching, urticaria, dizziness and vomiting.

The writer has been unable to discover in the literature the precise mode of action of nicotinic acid as a vasodilator so certain experiments were done in an attempt to elucidate this problem.

If 50-100 mgms. of nicotinic acid are ingested on an empty stomach a typical reaction develops within 5-10 minutes in the vast majority of people; irritation is first felt at the nape of the neck or in the occipital region and is followed in a minute or two by an obvious flush and a feeling of warmth; the irritation and flush spread forward along the scalp and towards the cheeks. The other regions involved are commonly the wrists, the anterior aspect of the arm, the shoulder girdle, the front of the chest and the front of the thighs in that

order. In less susceptible persons only the nuchal and facial region may be affected while in more susceptible persons the irritation and flushing may extend into the fingers and feet. The sensation of warmth subjectively is very like that produced by rubbing an irritating liniment, such as Sloan's, into the skin, and objectively the skin feels warm. The whole condition passes off in 10 - 20 minutes. Although the skin of the face may show very marked flushing the conjunctivae are only minimally, if at all, injected. In view of the nature of the spread of the flush and the fact that it was preceded by a feeling of irritation it was felt that nicotinic acid must act peripherally on the sensory organs of the skin and on the skin vessels. To prove this hypothesis nicotinate sodium (nicotinic acid, British Drug Houses) was injected intradermally into volunteers; at the same time 0.2 ccs. each of histamine, nicotinamide and saline, as a control, were injected into the same volunteers. The typical reaction of redness and wheal developed in 3 - 4 minutes after the histamine injection and showed crenations at its margin; it lasted for 30 minutes. No reaction was observed after the nicotinamide and saline injections,

but following the nicotinic acid injection a flush developed in 8 - 10 minutes and lasted for 20 minutes. The flush measured two inches across and the dilatation of the superficial vessels was well seen at the borders of the erythema where they showed as a reticulation. In one person injected a marked linear spread of the erythema was noticed spreading towards the heart along the course of a vein and extending for two and a half inches from the site of injection. Evidence of a negative nature i.e. that nicotinic acid does not act centrally on the nervous system, is supplied by Stokes (1944) who noted that spasm of the coronary arteries is not relieved by the administration of nicotinic acid.

As a result of these experiments it was concluded that nicotinic acid did act locally on the skin to produce vasodilatation, and it is suggested that the presence of nicotinic acid in the tissue fluid, carried there by the blood stream, causes irritation of the sensory end organs and a consequent vasodilatation of the subcutaneous arteries via the short axon reflex already mentioned.

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 strongly recommended as the treatment of choice in general practice owing to its ease of administration and its freedom from serious untoward effects.

A brief note on nicotinic acid and its probable pharmacodynamics is appended.

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