

THE NEUROLOGICAL AND ENDOCRINOLOGICAL ASPECTS OF ICHTHYOSIS, CHRONIC INDURATIVE ECZEMA AND SOME OF THE MINOR FORMS OF SO-CALLED TROPHIC CHANGES IN DERMAL TISSUES\*

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INNERVATION OF THE DERMAL TISSUES

The skin and its appendages, including the nails, hair and pigment bodies, the pilomotor muscles, and the sweat glands; likewise the subcutaneous tissue and bones, are subject to many changes effected through the vegetative nerves. The subcutaneous tissue and bones belong to what has been termed by some writers the "passive" tissues because of their peculiar lack of secretory and motor function.

The skin and its appendages is supplied by both the sympathetic and the parasympathetic components of the vegetative system. There is sympathetic innervation to all these structures. The parasympathetic innervation, however, is more limited and indefinite except in case of a few body areas.

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The preganglionic fibers which pass upward to the cervical sympathetic ganglia carry impulses for vasoconstriction, pilomotor action, sweat secretion, pigment control and the nutrition of the hair of the face and head; also trophic control for the subcutaneous tissue and the bones of the face and head. This is evident from the changes produced by removal of the cervical ganglia. The vasodilator fibers and fibers for sweat inhibition for the face and head come from cranial parasympathetics. As far as known pilomotor action for the face and head depends entirely upon the sympathetics. For the remaining portions of the body, with the exception of the genitalia, vasoconstriction, as well as vasodilatation, pilomotor action and sweat secretion—both activation and inhibition—are due to the sympathetic nerves alone. For the external genitalia the vasodilator fibers and the sweat inhibiting fibers course in the sacral nerve of the parasympathetics.

Vasomotor, pilomotor and sweat reactions are all independent of each other; so we must recognize different systems of neurons presiding over each of these functions.

Aside from the sensory impulses which may be picked up from the skin and its appendages to produce reflex action in dermal structures we have impulses which arise in the internal viscera and also in the higher centers of the brain. These structures are particularly influenced by such emotional stimuli as fear, pain, anger and shame.

Not only are the dermal structures under the influence of the vegetative nerves but they are also subject to the influence of various products of the glands of internal secretion, such as that of the thyroid, pituitary, adrenals and gonads. They also are the possessors of automaticity in action, by which we mean action on the part of the cells themselves without the intervention of nerves or other outside stimuli. Without outside stimuli internal respiration may be carried on and the cells are able to protect themselves from injurious substances which tend to enter through their limiting membranes, and they are able to get rid of substances of a harmful nature which are formed within the cells themselves. Through the nerves and internal secretions, however, their action is integrated and correlated with other structure of the body. There is a very close relationship between the skin and its appendages and certain endocrine se-

cretions. Particularly is this shown in the pigment changes in adrenal insufficiency and at times in pituitary disorders; and more commonly in the changes in the skin and subcutaneous tissue, and the hair in myxedema, and in hypothyroid states of a lesser severity.

#### COMMON PATHOLOGICAL CONDITIONS AFFECTING THE DERMAL STRUCTURES

Dermal structures are subject to many pathologic changes of both hyper- and hypo-active types. Such are vasomotor disturbances; atrophy and hypertrophy of the skin and subcutaneous tissues; dryness, scalliness, induration and fissures of the skin; dryness, early grayness and loss of hair; changes in the nails, and hyper- and an-hydrosis. Hypertrophy and rarefaction of the bones also occur at times. Although the bones do not belong to the dermal structures they are influenced by and through the same vegetative systems.

The explanation of such clinical manifestations is often found in the domain of pathologic changes in the physiologic mechanism of the vegetative nervous system and hyper- or hypo-function of the glands of internal secretion. Many of these pathologic manifestations are of a trophic nature, which fact brings up the question of whether or not there are nerves whose sole function is trophic. Many writers have been satisfied to believe that all trophic changes in these structures can be explained on the ground of changes in the vasomotor nerves, but the argument is raised against this that anemia of the skin, no matter how marked, does not produce atrophy. Anatomy and physiology so far offer no answer to this question, but clinical observation seems to suggest that trophic nerves are a possibility. It is quite probable, however, that trophic changes in these structures may be produced by action directly upon the cells without the intervention of nerves and without changes in glandular secretion, such as that of the thyroid.

In my experience in the treatment of tuberculosis, I have been much interested in the condition of the skin and its appendages. The skin is often dry and scaly, and the hair dry and brittle, with a tendency to fall out and to become prematurely gray. Sometimes pigment changes are present and local atro-

phies are very common. There are also pilomotor manifestations, changes in sweat secretion and alteration in the nails.

Such conditions have usually been ascribed to the fever; but this does not explain. They may be classed, physiologically, as disturbances in the various mechanisms of the skin and its appendages—vasomotor, pilomotor, sweat and trophic; consequently they are representative of an altered function in the vegetative systems which control these structures. Especially are some of these changes found in hypofunction of the thyroid gland. Whether the changes met in tuberculosis are due to hypofunction of the thyroid; or partly this and partly to a disturbance in the vegetative nerves, particularly the sympathetics, and changes in the cells themselves, we are not able to say, for all of these systems show evidence of injury during the course of a long-drawn-out clinical disease accompanied by toxemia. This is not peculiar to tuberculosis, but is found in many states of chronic toxemia and also in states of malnutrition.

This clinical picture, so often met in tuberculosis, led me to become interested in more serious manifestations in the dermal structures. It seemed reasonable that the same underlying pathologic physiology might be present in other dermal affections of a trophic nature, such as ichthyosis and chronic eczema.

*Ichthyosis.* Ichthyosis is described as a hypercornification, the skin being susceptible to irritation, eczema and kindred conditions. In patients suffering from ichthyosis the hair of the scalp and brows is usually dry and lusterless. The skin as a rule loses its elasticity, so that at times fissures develop. The subaceous and coil glands of the skin usually show a deficiency in secretion. The skin is dry, scaly, inelastic and thickened.

Ichthyosis usually appears soon after birth, although in some instances it develops later in life. There seems to be a definite hereditary tendency. It has been suggested that the condition was probably due to toxins, and yet there has been no real definite toxin suggested. More recently it has been considered as due to a hypothyroid state, or a disease of the nerves, yet all of these suggestions have been characterized by indefiniteness.

That these dermal manifestations depend upon inherent characteristics of the individual is apparent when it is noted that they usually develop at or soon after birth, and that often

there is a familial relationship as shown in Cases 3 and 5 herein reported.

An interesting and suggestive characteristic of ichthyosis is that it changes with weather. It is usually milder in the summer and more severe during the colder season; in fact, patients suffering from ichthyosis usually stand cold poorly. Sometimes the milder cases entirely disappear during the summer time. This has been ascribed to the fact that the patient perspires in the summer, which moistens the skin and causes it to assume a normal condition; but this increased sweating is more probably simply another evidence of an improvement in the physiological control of these structures in summer.

*Chronic Eczema* is a dermal infection, recurrent in nature, in which there is marked irritability of the skin with itching and induration, and in which the skin sometimes shows marked folding and creasing. There seems to be a hereditary factor in its etiology.

In attempting to assign a cause to such pathological conditions as ichthyosis and the chronic form of eczema, likewise the minor dermal changes herein described as noted in chronic tuberculosis, the relationship to the vegetative nervous system at once forces itself to the fore, because all functions of these structures which are affected are presided over by vegetative nerves. The relationship to weather conditions suggests very definitely the relationship of the disease to those factors which control metabolism, because the disease is worse in cold weather when greater metabolic activity is acquired.

Increased energy requirements in winter is met by increased activity of all those mechanisms which increase energy: the sympathetic nerves become more sensitive and the energizing glands of internal secretion, particularly the thyroid, more active.

It has been pointed out by Kendall that more thyroid secretion is circulating in the tissues in the winter and thus meets the extra energy requirements of the cold. In case of a deficiency in secretion it can be readily understood how this increased demand fails to be met, how metabolism lags and how the patient is unable to supply the extra amounts necessary for maintaining normal conditions in the tissues. As a result the

skin becomes dry, scaly and lusterless, and the patient endures cold badly.

## REPORT OF CASES

The following cases will illustrate some of the points made in this paper, particularly as regards suggestions of etiology.

*Case I.* K. O., Japanese, aged 17, entered the Pottenger Sanatorium February 6, 1922, suffering from acute caseous tuberculosis, involving both upper lobes, with high fever. He also had a marked ichthyosis which had appeared soon after birth, the skin being dry, thickened and scaly. It resembled the scales of a fish. Large and small scales were continuously thrown off. The patient always suffered from cold.

In spite of active tuberculosis he was put on thyroid, beginning with 1 gr. and increasing to 2 gr. daily. Calcium chloride, 10 cc. of 5% solution, was given once a week from July 16 to October 5, 1925. The patient improved very greatly. The large scales disappeared. The skin did not become entirely smooth but smoother than it had ever been and also somewhat moist. The tuberculosis also improved greatly. The patient formed a small cavity in the right lung and a large cavity in the left. He became fever-free and gained considerably in weight.

*Case II.* F. M. G., aged 68, was suffering from far advanced tuberculosis with cavities in lung, high temperature, also tuberculosis of the larynx with ulceration. He had very marked ichthyosis which had existed from birth. The skin was dry, scaly and was continuously thrown off in large scales. This condition existed over the entire body. He suffered from cold and always wore woolen union suits, even in summer.

He was put on treatment while in the sanitarium—four and one-half months. Thyroid was given, 2 gr. daily, beginning after the patient had been in the sanatorium two weeks. This was continued during his stay except during a two-weeks period when he was having a severe attack of singultus. At the same time he was given calcium chloride, 10 cc. of 5% solution, every four days. He improved very greatly. The scales almost entirely disappeared from the body; the skin became quite smooth and somewhat moist, and the patient declared that it was the first time he had had any relief during his life.

*Case III.* J. R., aged 28, had dry scaly skin since birth, being worse in winter than in summer. Face and hands chapped easily during cold weather. There was no itching. On exposure to the sun the skin burned and blistered easily but did not tan.

*Family History.* The father's height was 6 feet; weight, 210 pounds; his skin was soft. The mother was 5 feet 10 inches in height, and weighed 220 pounds. Her osseous system was well developed. Her skin had a tendency to dryness. One brother died of pneumonia; one died from accident at 3½ years. One brother, aged 15, has dry scaly skin; one brother, aged 21, has scaly skin on exposed surfaces; one brother, aged 27; one sister, aged 25, and one sister, aged 9, all have a slight tendency to dryness.

Physical examination of the patient showed skin uniformly dry and scaly over the entire body, with some small indurated folds on flexor surface of the arms. Scales in the nature of thin white flakes show both on exposed and unexposed surfaces. The hair was coarse but not unduly dry, and the scalp scaly.

The patient was suffering from extensive far advanced tuberculosis with cavities and fever.

*Medication.* Thyroid, 1 gr. daily for two months and 2 gr. daily for six months, together with calcium chloride, 10 cc. of 5% solution every four days during entire period—eight months, were administered. The skin condition improved markedly and at present it is soft and smooth and shows practically no scaling.

*Case IV.* J. F., aged 24, suffered from asthma up to the age of 17 years. He entered the Pottenger Sanatorium, suffering from moderately active tuberculosis, May 21, 1925. He was discharged February 27, 1926. His skin over both exposed and unexposed parts of body had always been dry and leathery. The eyebrows were scanty. He stood cold badly. On account of the dryness and scalliness of the skin he had always been sensitive.

He was treated by thyroid and calcium chloride; thyroid, 1 gr. daily from June 21, 1925, to August 29, 1925; 2 gr. daily August 29 to December 1, 1925, and 3 gr. daily from December 1, 1925, to date of discharge, February 27, 1926. He is still taking it. Calcium chloride, 10 cc. of 5% solution was given every four days from July 13, 1925, to February 27, 1926.

The skin improved very markedly. The scales disappeared; the skin became soft and moist, and the surface looked about the same as those of ordinary individuals. This was the first relief the patient had had since this condition started as a child.

*Case V.* Mrs. G. H., aged 26, began having trouble with her skin at the age of 11. This took the form of inflammation with induration and itching, confined to arms and neck. The first attack lasted one year. At the age of 16 she was troubled with the condition from June to December. She had had two x-ray treatments a week in mild doses and improved. At the age of 21 the trouble returned and persisted for some time, beginning with papules which broke, forming pustules and scales. The lesions were very changeable: Sometimes only redness with intense itching; at other times, induration. She scratched lesions in sleep and caused excoriation of the skin. Keeping the arm under the bed covers or protected by clothing increased the symptoms. She always noted that the symptoms were worse when she was nervous and at the menstrual periods. From June to December, 1921, she took 18 x-ray treatments without improvement. These resulted in burns of the skin with telangiectasis. She noticed that the condition was always worse in winter.

I first saw the patient May 1, 1923, at which time the skin over the face and flexor portions of the arms was very thick and thrown into folds. Itching was extremely intense. The skin was dry, scaly and leathery. Excoriations from scratching were present on the arms from the elbow to the wrist. The vessels of the face and arms were dilated as a result of x-ray treatment. She showed scantiness of the external third of the eyebrows and a dry skin over the body; she withstood cold badly, giving the impression of a definite hypothyroidism. She also had a tendency to hay fever.

*Family History.* Her father was 6 feet tall and weighed 190 pounds. He had a large frame and was always active. There was no early grayness. He died of heart trouble at 53. The mother's height was 5 feet 8½ inches; weight, 182 pounds. She was of large frame but did not appear fat. She had no skin trouble. One brother was 5 feet 5 inches tall and weighed 170 pounds at the age of 42. A sister was 5 feet 5 inches tall and weighed 142 pounds at the age of 39. They had no skin abnormalities. The patient has one child 3 years old who weighs 40½ pounds. She has a slight tendency to dryness of the skin and itching. The condition improved following the use of thyroid. The difficulty returned in cold weather but yielded again to increase in the amount of thyroid.

*Menstrual History.* The patient was regular until 1925. Since then she has flowed every 18 days. The skin condition was a little worse toward end of the period.

*Treatment.* Desiccated thyroid was given, 1 gr., daily from May 1 to May 14, 1923; 2 gr. daily from May 14, 1923, to February 4, 1924. This seemed to relieve the condition very satisfactorily until February. From February 4 to March 13, 1924, 3 gr. daily was given. With this dosage the skin cleared and became soft and pliable, but showed signs of recurrence in March, 1924. Four gr. daily was given from March 13 to March 27, 1924, when the patient began to experience slight tremors. Thyroid was then withheld for a short period and then resumed with 3 gr. daily, which amount the patient has taken until the present time. She was also given calcium chloride, 10 cc. of 5% solution, from 2 to 3 intravenous injections a week, from May 1, 1923, to March, 1924. Calcium injections were stopped from March, 1924, to March, 1925. In the spring of 1925 two injections a week were given, and during February and March, 1926, one injection a week was given. Since March, 1923, calcium lactate (20 gr. daily) has been taken by mouth.

As a result of the treatment the skin condition has been markedly improved; the skin has become more moist; the itching decreased and shortly disappeared entirely. The induration has also gradually disappeared, and at the present time the skin shows little evidence of former induration. The thickness which is present is accentuated by the results of the x-ray treatment. Also the excessive nervousness has disappeared. It was noted on September 12, 1923, that the patient had gained 3½ pounds in weight. Hair was then present and normally distributed over the forearms, and the skin had lost much of its leathery appearance. March 26, 1926, except for slight relapses during the winter months each year, the patient has remained in a very satisfactory condition. These relapses quickly disappear under an increased amount of thyroid and the resumption of the intravenous injections of calcium chloride.

#### DISCUSSION

In the treatment of the above cases ointments and soothing baths, which are usually employed, were purposely omitted. This was an experiment to determine if those measures that are known to influence the neurocellular mechanism presiding over these dermal tissues would produce a favorable response. The manifest difficulties surrounding the treatment of these patients will be evident to all. Part of them were suffering from far-advanced, active tuberculosis. All but one had tuberculosis. Furthermore, the prolonged toxemia had a tendency to cause conditions similar to the ones that we were trying to treat. Foods containing large quantities of calcium should be employed during treatment, and the proteins, which hasten its elimination, should be avoided; but in tuberculous patients such a diet could not be followed. There is no doubt that the improvement in the patient's general condition had some influence in causing the

skin lesions to respond, but that it was not the main factor is made clear by the fact that in all instances the skin affections were present prior to the time the patient had tuberculosis.

I cannot believe that these dermal affections are purely hypothyroid in nature; for, if they were, we would expect a more complete yielding to the administration of thyroid preparations than occurs. In other instances of thyroid deficiency, even cretinism and myxedema, there is a more rapid and more complete response. In case of the patients reported herein, however, the response was not complete in a single instance. We found that thyroid alone would not keep the skin in as good condition as thyroid with calcium added. This was noted even though the thyroid was pushed to the point of causing increased heart action and nervous instability. We also found that while calcium by the mouth, which was given between the series of intravenous injections, was advantageous, it had to be supplemented ever now and then by intravenous administration, especially when relapses occurred. A point indicative of the intimate part played by the nerves is the fact that all of the various mechanisms, trophic, sweat, vasomotor, pilomotor, and even the subcutaneous fat distribution are affected.

The relapses occur during times of nerve stress and when the weather becomes cold. The former are times when nerve imbalance is accentuated; the latter when thyroid deficiency shows most markedly and the calcium content of the cells is relatively low. So it seems justifiable to assume that these lesions do not represent a pathologic condition of one phase of vegetative control to the exclusion of others, but rather a general disturbance in all: the nerves; the endocrine organs, particularly the thyroid; and the automaticity of the cell itself, particularly as it depends upon its ionic content, its permeability and reactivity.

We note that these mild instances of dryness and scaliness of the skin which are met in chronic tuberculosis improve when the patient's nutrition improves and the general physiologic balance is restored. We assume that nerve, endocrine and cell balance are all improved when this condition has been attained. We also at times see the hair become oily and even regain some of its color when health has been regained. The vasomotor and sweat anomalies met in patients suffering from a long-drawn-

out toxemia also disappear with recovery. That these lesions are in part due to the general process of wasting in tuberculosis may be true; but it is desirable to define them more accurately if possible, and this may be done by a careful study of their physiologic control. It is possible that there is a close etiological relationship between these minor changes noted in tuberculosis and the more severe lesions represented by ichthyosis and chronic eczema cited above, even though the former is apparently caused by a disease process while the latter is apparently due to inherited factors.

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