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THE MECHANISM OF THE NEURAL SIGNS AND SYMPTOMS OF LEPROSY

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The clinical signs of leprosy include, besides other things, hypopigmentation, anidrosis, keratosis, depilation and anesthesia in patches of skin, or anesthesia and trophic changes in extremities apart from skin lesions. All these signs are generally ascribed to the degeneration of nerves. There is no doubt that degenerative changes do take place in the peripheral nerves and their branches, and that many of the clinical signs of leprosy are produced as a result of those changes. However, I find difficulty in explaining all the manifestations mentioned on the basis of nerve degeneration alone.

As early as 1930 I noticed that sensation might return suddenly in an anesthetic skin area when it became red and thick under "reaction."¹ Conversely, it was noticed that when nonanesthetic, erythematous, thickened patches subsided they sometimes became anesthetic. Since then several other anomalous conditions have been observed that cannot be explained satisfactorily on the basis of nerve degeneration alone.

For one thing there is often seen marked disproportion between the clinical signs in a patch and the obvious involvement of the associated nerves, and also disproportions between the different signs themselves. For example, there may be little or no sensory change in a patch with gross thickening of the associated nerve, or marked sensory change may be found in a patch with little or no nerve thickening. Moreover, the degrees of anesthesia, hypopigmentation, and other changes in a patch may vary considerably. If all these changes were due to the degeneration of the nerves, how can we explain the wide variations seen?

Similar disproportion between the nerve trunk involvement and the signs produced may be found in polyneuritic cases: (a) A considerable

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¹ This was made the subject of a query in *Leprosy in India* (²), and Dr. Muir, the editor at that time, agreed that this change was possible although not satisfactorily explained. He himself had observed similar return of sensation a few weeks after the injections of ethyl hydnocarpate in anesthetic patches.

thickening of the nerve trunk may be associated with either no anesthesia or deformity (Text-fig. 1), or only anesthesia and no deformity (Text-fig. 2), or rarely, only deformity and no anesthesia (Text-fig. 3).² (b) There may be glove-like anesthesia but only some of the nerves supplying the part may be thickened while the others are not. (c) In spite of thickening of multiple nerves, the anesthesia may be limited to a small area (Text-fig. 4).



TEXT-FIG. 1. Anesthetic patch on left wrist. Thickening of the left ulnar trunk and a branch of medial antebrachial cutaneous nerve. No secondary anesthesia in the hand, and no deformity. (Case No. 7001.)

TEXT-FIG. 2. Anesthetic patch at the base of left ring finger. Ulnar trunk thickened. Secondary anesthesia on the dorsum of the hand and the little finger, but not in the ring finger. No deformity. (Case No. 7222.)

TEXT-FIG. 3. Anesthetic patch on left ring finger. Ulnar trunk thickened. No secondary anesthesia on the hand. However, the little and ring fingers were bent (as indicated by the reversed-S symbols). (Case No. 7110.)



TEXT-FIG. 4, A & B. Left ulnar, median, and radial nerves are thickened. Only part of left hand is anesthetic. (Case No. 7318, front and back aspects.)

Furthermore, the same disproportion may be seen in cases improving under treatment. For example, sensation, pigmentation and hair growth

² This last condition was also seen in Case (b), Rameswar Rana, of Reference 3.

may be restored in a patch while the nerve supplying the patch remains as thick as before. The hyperpigmentation and excessive hair growth sometimes seen after local injection of hydnocarpus oil cannot possibly be explained on the basis of restoration of nerve function. In polyneuritic cases the return of sensation may not be in anatomical order.

Because of these difficulties it was decided to undertake a study of the matter, and the findings are reported here. Since the signs to be discussed are most prominently found in the type of leprosy known as neural or tuberculoid, the investigation has been concerned mainly with cases of this type. Before going into that, however, some of the pertinent highlights of the anatomy and physiology of the skin and its nerve and vascular supply will be reviewed briefly.

ANATOMY AND PHYSIOLOGY

It is to be borne in mind that the corium of the skin consists of reticular and papillary layers, and that the papillary layer consists of numerous highly sensitive and vascular eminences. The nerves of the skin terminate partly in the epidermis and partly in the corium. The various accessory organs are supplied with nerve fibers except the sebaceous glands (14).

Our knowledge of the functional significance of the sympathetic system is very incomplete, and most of the available information concerns the efferent rather than afferent components. The sympathetic fibers often constitute one-third of the cutaneous nerves.

Besides others, the skin has a receptive function. It receives four main modalities of sensation, i.e., touch, cold, warmth and pain, through special receptors or free nerve-endings. There are still other types of sensation, but the selection of these four fundamental modalities for the classification of cutaneous sensation is a compromise between simplicity and confusion (1). It is stated (1^0) that, although endeavor has been made to associate a particular function with each type of end organ, the results are as yet inconclusive.

Regarding the peripheral nerves, it is to be borne in mind that each nerve fiber is ensheathed by a delicate connective-tissue layer (endoneurium), that each bundle of these fibers (funiculus) in surrounded by a sheath (perineurium), and that the larger nerves comprise several funiculi held together by a loose areolar connective-tissue structure (epineurium) which contains numerous blood vessels which supply the nerve structure, sensory fibers distributed to the nerve trunks (nervi nervorum), lymphatics and fat cells. The blood-vessels that supply a nerve terminate in a minute plexus of capillaries which pierce the perineurium and run for the most part parallel with the nerve fibers.

Three types of sensory impressions are conveyed from the periphery by the sensory fibers, namely, deep sensibility, protopathic sensibility, and epicritic sensibility. A nerve exerts a "trophic" influence on all the structures to which it is distributed (21), but, contrary to the long-held belief that there is a specific set of nerve fibers concerned with this matter, it is now regarded as unlikely that any nerve influences the nutrition or growth of tissues except by altering the blood supply (18). It is doubtful if special trophic nerve fibers exist (9).

APPLIED ANATOMY AND PHYSIOLOGY

Hypopigmentation .- Regarding the formation of skin pigment (melanin), one view is that it takes place in the basal-cell layer of the epidermis; the other is that

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it is produced by certain specialized cells of the corium, the melanoblasts, and reaches the basal cells by lymphatic drift. Its formation is closely bound up with protein metabolism, melanin or its precursor being a derivative of protein (tyrosin) decomposition under the influence of adrenalin and pituitary hormones. But in leprosy there is usually no interference with protein metabolism, and the hypopigmentation is localized, not generalized. It is therefore probably due to local interferences with pigment formation (1^1) .

Keratosis.—This is due to dysfunction of the sebaceous glands, of unknown causation. These glands are not under the influence of any nerve. It is believed (¹⁸) that their activity depends on their blood supply.

Anidrosis.—The sweat glands are under the influence of the secretomotor fibers of the sympathetic system. Therefore, there may be anidrosis if there be degeneration of the sympathetic nerve fibers.

Depilation.—This condition, also, is not explained. Degeneration of the fibers from the sympathetic nerves that supply the arrector pili muscles leads only to nonerection of hairs, they being motor fibers. The fibers which surround the hair shafts and hair bulbs are sensory, and their degeneration may cause anesthesia but not depilation.

Anesthesia in the skin lesion.—Obviously, loss of sensation is caused by some changes in the nerve, but this point will be discussed in detail later.

Secondary anesthesia, muscular paralysis, etc.—These changes are likely to be caused by the degeneration of mixed nerves (sensory and motor), a matter also to be discussed later.

EXPLANATIONS OF DIFFERENT WORKERS

The explanations that have been offered by various workers for the conditions under discussion will now be examined.

Hypopigmentation, depilation, anidrosis, keratosis.—Conditions of this type have been ascribed to (a) cellular infiltration, (b) involvement of peripheral sensory nerves, and (c) involvement of the sympathetic nerves.

(a) Cellular infiltration: Some workers believe that cellular infiltrations mechanically obstruct the functions of the melanoblasts and of the sweat and sebaceous glands, and that in consequence the various structures concerned are ultimately destroyed. Other workers do not support this view. It does not satisfy in cases where the cell infiltration is slight and loosely distributed, while on the other hand in lepromatous macules there is usually no anidrosis and keratosis in spite of dense cell infiltration.

(b) Degeneration of peripheral sensory nerves: It is said that this change, besides producing anesthesia, also causes the other conditions under consideration. In that case one would expect anesthesia and the other signs to go together when the peripheral nerve is involved, but in practice one does not often find a complete correlation of these signs and symptoms.

(c) Degeneration of sympathetic nerves: This is said to cause these various conditions except hypopigmentation. It has already been pointed out that depilation and keratosis cannot be explained on this basis. Moreover, degeneration of sympathetic nerves causes vasodilatation, which is not found in hypopigmented patches.

Anesthesia in a patch.—Anesthesia of a macule may be due to (a)

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degeneration of the peripheral sensory nerve, or (b) degeneration of the terminals of that nerve.

(a) Degeneration of the nerve: In a typical case where the patch is anesthetic and the nerve supplying it is thickened, this explanation may look quite satisfactory. However, there are cases where the nerve may be thickened but the patch may be nonanesthetic (Text-fig. 5), although the same patch after subsidence in the natural course of events usually becomes anesthetic. We do not know the exact mechanism by which this change takes place. We also fail to explain the return of sensation, pigmentation and growth of hairs in a previously anesthetic, hypopigmented and depilated patch after intradermal injections of hydnocarpus oil although the nerve supplying the patch may remain as thick as before (Text-fig. 6). Other similar cases have also been seen in which the return of sensation did not follow the principles of regeneration of nerves. This will be discussed later.



TEXT-FIG. 5. Red, thick, nonanesthetic patch on left side of face and forehead, nonanesthetic although the corresponding great auricular and supraorbital nerves are considerably thickened. (Case No. 10,079.)

TEXT-FIG 6. A. Thick, red, anesthetic lesion on right forearm. Right medial antebrachial cutaneous nerve thickened. B. The skin lesion faded, sensation returned completely, and hairs grew, but the nerve remained as thick as before.

(b) Destruction of the terminals: Where the sensory nerve trunk supplying an anesthetic patch is not found thickened, the explanation given is that the terminal fibers within the skin lesion are pressed upon by the granuloma, this causing blocking of their function, and—if pressure is severe and prolonged—their destruction. This does not explain on the one hand the absence of anesthesia in cases like that shown in Text-fig. 5, in which the granuloma was fairly marked, nor on the other hand the presence of anesthesia in a hypopigmented patch with very slight cell infiltration. It is true that in histological sections of some anesthetic macules the nerve branches are found to be infiltrated and sometimes

degenerated, but this correlation is not always possible, and sometimes similar changes are found in nonanesthetic patches.

Secondary anesthesia, motor and trophic changes.—These changes are found in the polyneuritic cases. The mechanism of the affection of a mixed nerve was well described by Dehio (6), whose diagram is reproduced in Text-fig. 7. When degeneration occurs in a mixed nerve the signs and symptoms should follow certain anatomical principles. If, for example, the degeneration be in the ulnar above the elbow, one would expect to find anesthesia in the ulnar side of the hand and wasting of most of the muscles of the hand, producing claw hand. But these characteristic signs are not found in every case where the ulnar trunk is found thickened above the elbow (Text-figs. 1-3).



TEXT-FIG. 7. Mechanism of ascending nerve involvement, after Dehio. a = Leprous patch, anesthetic; e = affected sensory nerve whose end ramifications are destroyed. Ascending degeneration developed in all nerve fibers arising out of a and contained in e and which can be traced up to the mixed nerve stem l and upwards. i = Smaller mixed nerve; b = muscle, secondarily affected and atrophied because of the involvement of nerve i. c = Skin, secondarily affected and atrophied. c = Skin, and d = muscle, both secondarily affected because of the affection of the stem nerve. l.

Glove- and stocking-like anesthesias are said to be due to nerve trunk involvement. In order that there may be glove-like anesthesia (anesthesia of the hand and the lower half of the forearm) there should be thickening and degeneration of the ulnar, radial and median nerves and also of the antebrachial cutaneous nerves. But in cases with this form of anesthesia it is usual to find thickening of the ulnar, or of the ulnar and the radial but not of others. On the other hand, the three nerve trunks of the same arm may be thickened simultaneously but the anesthesia may not be of glove type (Text-fig. 4). Glove-and stocking-like anesthesias are said to appear in anatomical order, but that is not always true (Text-fig. 8).

Moreover, the restoration of sensation—when it occurs—is not in the order that would be expected if it were entirely due to regeneration of a degenerated nerve. After nerve injury and degeneration the regeneration takes place first in the proximal parts, and later in the distal parts within certain definite periods of time. In leprosy, the return of function is usually seen in patients having treatment. It is, however, slower, and sensation does not always return in anatomical order (Textfig. 9).



TEXT-FIG. 8. Demonstrating the irregular, nonanatomic development of anesthesia. It first appeared in right foot (A, April 1929), then in the right knee (B, March 1940), and finally it covered the whole of right foot, leg, knee, and thigh like a stocking (C, August 1943). (Case No. 1,751.)

TEXT-FIG. 9. Demonstrating the irregular return of sensation. From the maximum extent of anesthesia (A, May 1938), sensation returned first in the distal part (B, August 1940) and later in the proximal part (C, July 1943). (Case No. 5,955.)

Because these explanations are not satisfactory, further investigations were considered necessary.

PRESENT STUDY

This study was based on the possibility that changes of circulation and of local temperature may have something to do with functional changes of the kind under consideration. This possibility was suggested by observations like the one mentioned at the beginning, of return of sensation in an anesthetic macule when the area becomes thick and red. One thing definitely associated with this development is increase of temperature of the part, which of course is related to the blood circulation. It is not impossible that the latter is concerned with the return of sensation. Our investigation of this possibility was clinical, therapeutic and experimental.

Clinical.—The temperatures of the skin lesions of different types were recorded in 36 neural cases, together with those of corresponding normal parts. Lacking an electric thermometer the temperatures were taken with a clinical one, and this work was done in summer months. The bulb of the thermometer was placed on the part to be tested, the skin from either side was folded over the bulb, and it was kept there for five minutes. It was found that the temperature of active, red, thick patches was about $1^{\circ}F$ above normal; the temperature of chronic, slightly red and slightly thickened patches and of hypopigmented patches was about $0.5^{\circ}F$ above normal; and the temperature of anesthetic wasted and deformed limbs was about $1^{\circ}F$ below normal. This is in agreement with the findings of Stein (20).

We also observed the bleeding which took place after the intradermal injections of oil in different types of lesions. It was maximum from erythematous patches, and minimum from hypopigmented patches. This was very well seen in zone-type patches, where the centers were flat and hypopigmented and the margins were thick and red. From limbs with acroteric neural changes there was practically no bleeding, unless some large vein was punctured. These differences were found not only in different cases, but also in different types of lesions in the same person. They were clearly due to differences in vascularity.

Corresponding macroscopic and microscopic differences in the vascular condition of the different types of lesions were seen when biopsy specimens were removed, and in the histological examination of the sections.

Therapeutic.—While treating cases I noticed return of pigment in hypopigmented patches after painting with trichloracetic acid solution, or after intradermal injections of oil, measures which cause hyperemia of the upper levels of the skin. With improvement of the patches there is gradually more and more bleeding after the intradermal injections. In some cases, due to the oil injections, the lesions faded, hairs grew, and patches began to sweat again.

Hyperpigmentation is frequently seen even in normal persons as a result of repeated applications of hot compresses to painful parts. Dermatologists (18) have also observed excessive growth of hair on parts treated by the Finsen light, or resulting from frequent repetition of fomentations for ulcerations of the limbs, and it is regarded as a natural response to increase of temperature and vascularity.

Experimental.—The effect on the so-called permanent lesions, of procedures leading to improved circulation of the affected parts was studied. These lesions were the muscular wastings, paralyses, trophic ulcers, and anesthesias that persist after subsidence of skin lesions. The general impression is that in these cases the residual abnormalities are due to fibrosis inside the nerve, and that they are therefore not likely to improve with any treatment.

Several cases having such permanent lesions were selected, and injections of hydnocarpus oil were given in the affected parts and alongside the nerves supplying these parts. In all these cases the treatment had to be continued for years, and was combined with massage, exercise, etc.

The following results were obtained.

Drop-foot: In the majority of cases with this condition there was

some return of strength in the affected legs, and less difficulty in walking. In some instances, in fact, the correction was complete. There was considerable return of sensation in most of the cases.

Weakness and deformity of hand: Correction was complete in some cases (Text-fig. 10), and in others there was considerable improvement. Sensation returned to a great extent (4).

Lagophthalmos: Some of the patients recovered completely, while in others the correction was partial. Lacrymation stopped in all cases.

Tropic ulcers: These cases responded very well. Most of them healed satisfactorily and have remained so for years (17).

Residual anesthesia in macules: My principal experimentation with oil has been with this condition. The following observation led to this work.

One patient with a hypopigmented anesthetic lesion (Text-fig. 11) had received injections of oil for 10 months. The lesions faded completely and treatment was stopped, but the anesthesia persisted. The lesion remained inactive for five years, during which time there was no return of sensation. Treatment was then started again, local injections of oil being given. Sensation gradually returned, recovering completely after 3 years.

Similar improvements were seen in some other cases.



TEXT-FIG. 10. Correction of claw hand after local injections of hydnocarpus oil. From the condition indicated by the reversed-S symbols in (A, January 1935), there was gradual clearing (B, September 1940) and finally complete clearing (C, May 1943).

TEXT-FIG. 11. Showing residual anesthesia that had persisted for 5 years (A, January 1934), with complete return of sensation (B, April 1942) after local injection of hydnocarpus oil for 3 years. (Case No. 4,298.)

To determine whether or not these results were due to any specific action of hydnocarpus oil, or only to vascular dilation produced by local injections, I gave intravenous injections of saline to some patients. It is said (19) that the immediate effect of intravenous injection of saline or blood is to raise the venous pressure, and that the peripheral and pulmonary capillaries and veins dilate to accommodate increased blood volume.

For this experiment I selected patients with deformities, paralyses, trophic ulcers, etc., and normal saline was used for the treatment. As all were outpatients, the usual procedure was modified. Smaller quantities of saline than usual were used,

and an attempt was made to increase the venous pressure of only the affected parts by applying a rubber binder tightly around the affected limb proximal to the lesion; i.e., if the lesion was on the foot, the binder was applied on the leg or the thigh. Slightly warm saline was then injected into a distended vein below the binder, which was kept in position for another five minutes. Injections were usually given once a week, the quantity varying from 50 to 100 cc. according to the tolerance of the patient; some patients felt uneasy after a large dose. In some cases these injections were continued for about one year; other patients discontinued treatment after a few months.

Of the 32 cases selected for this experiment, 5 were new and untreated; the 27 old cases had had injections of oil and, after some improvement, their condition had remained stationary. Injection of oil was stopped in these cases, and saline was used as described to see whether or not further improvement was possible.

The immediate effect of the injection was that the patient usually felt the affected part to be lighter than before, but that was only temporary. Later, most of the patients showed definite signs of improvement in further return of sensation or increased muscular strength.

In one case there was complete correction of drop-foot. In other cases the strength of the leg increased, and the patients could walk better and even run short distances and carry weights on their heads, which they could not do before. In one case muscular development was noticed in the outer side of the leg, and it assumed more or less normal shape.



TEXT-FIG. 12. A. Before treatment: red, thick, anesthetic patch covering lower part of left thigh and the knee, leg and foot, with foot drop. B. After treatment with hydnocarpus oil for 6 years the lesions had faded, leaving extensive anesthesia; foot drop still present. Oil injections were then stopped, and injections of saline were started. C. After six months of the saline treatment there was some return of sensation; the foot drop persisted, but there was some strength in left leg. D. After $7\frac{1}{2}$ months' on saline injections there was further return of sensation, with strength in left leg. E. After $14\frac{1}{2}$ months' treatment with saline; considerable return of sensation, more growth of hairs on leg and thigh, and less difficulty in walking although the foot drop persisted. (Case No. 5,456.)

Reduction in the size of perforating plantar ulcers was another effect observed.

Deformity of hands was not completely corrected in any case, but in some of them it became less. There was a gain in strength so that the patients could do manual work better than before. In one of them a chronic, persisting ulcer on the right middle finger, which had baffled all other treatment, healed completely after injections of saline. In some instances there was increased growth of hairs.

In other cases there was no improvement in touch sensation or in deformities. But the affected limb, which was lifeless and insensitive, like a piece of wood, regained deep pressure sensation.

ILLUSTRATIVE CASES

CASE No. 5,456 (Text-fig. 12). An erythematous, thickened lesion covered the left foot, leg and part of the thigh, with drop-foot. Anesthesia was present on the knee and leg, and partly on the foot, but not on the thigh. Patient received injections of hydnocarpus oil for 6 years. The lesions subsided, but the anesthesia became more extensive; the drop-foot persisted. The oil treatment was stopped, and injections of saline were started. After 6 months of that treatment there was return of sensation in the upper part of the leg and part of the foot. Improvement increased, and after another 7 months or so anesthesia remained only on part of the knee and slightly on the inner side of the leg and foot; sensation had returned completely in other parts. There was some return of strength of the left leg and less difficulty in walking, and growth of hairs on the leg and thigh.

CASE No. 7,749 (Text-fig. 13.) There was anesthesia on the left finger and ulnar side of left hand. The left little and ring fingers were bent. Injections of saline were given, and after about 25 days improvement was noticed. There was some return of sensation on the ulnar side of left hand and on the dorsal surface of little finger, and the fingers were less bent than before.



TEXT-FIG. 13. A. Anesthesia and deformity of the left hand, in a patient who had not received injections of oil. B. After only 25 days of saline injections there was some return of sensation on the dorsum of the hand, and slightly on the little finger. The ring finger was less deformed than before.

DISCUSSION

From the observations here recorded the conclusion is irresistible that the neural signs and symptoms of leprosy have a close relationship with

the blood circulation of the affected parts. Previous workers, from their extensive clinical and histological observations, concluded that the various symptoms—sensory, motor, and trophic—could be explained by ascending degeneration of nerves, the nerves supplying the skin being the first to suffer, those to the muscles becoming involved later (7, 12). While I agree that involvement of the nerves leads to their thickening, I do not believe that thickened nerves are necessarily always degenerated. In some cases there may be degeneration, but in other cases there is no degeneration although they are put out of commission by other causes (e.g., malnutrition caused by vasoconstriction) and this may produce signs and symptoms akin to those of degeneration.

Of the two different types of lesions under consideration the first is the *hypopigmented macule*, the so-called simple macular lesions. Hypopigmentation, anesthesia, depilation, anidrosis and keratosis of these lesions are variable. If all these signs and symptoms were due to nerve degeneration they should not be variable, but all of them should be present to the same extent. As far as our knowledge goes, degeneration of sensory nerves can cause anesthesia, degeneration of motor nerves can cause muscular paralysis, deformity, etc., and degeneration of the sympathetic nerves can cause anidrosis and nonerection of hairs. But the cause of hypopigmentation, keratosis and depilation remains unexplained.

If it be assumed that all these changes are due to nerve degeneration, we must admit that we not know the actual process of regeneration and the time required for it in these cases. After injury of a normal nerve, regeneration takes place in a definite anatomical order and at a definite rate (3 to 4 mm. per day), but this differs from our usual clinical findings in leprosy.

In tuberculoid reactional conditions, sensation may return very quickly in a previously anesthetic part. Furthermore, pigmentation and sensation may return after a few weeks or months of intradermal injections into a hypopigmented anesthetic patch. These facts indicate that, in cases of that kind, the nerves do not actually undergo degeneration but are somehow inactivated. The only visible change taking place under the conditions mentioned is hyperemia of the part, due to vasodilatation. Vasodilatation, therefore, is instrumental in bringing back sensation in the one case and pigmentation and sensation in the other case. Sometimes the return of function is complete.³

That vasodilatation, or return of normal blood supply, whether due to injections or reaction or some other factor, may be responsible for return of normal function in the neural patches will be evident from the fact that in normal persons increased supply of blood to the sweat and

³ In the case shown in Text-fig. 7 there was complete return of sensation and pigmentation, growth of hairs, and return of functions of sweat and sebaceous glands after local injections of hydnocarpus oil, although the nerve supplying the part remained as thick as before. Similar observations have been made in other cases.

sebaceous glands increases their secretion, and also that increased growth of hairs is seen after application of Finsen's rays and that increased pigmentation is seen in a part if hot compresses are applied repeatedly.

If increased blood supply can cause these changes, it is only reasonable to suppose that decrease of the supply of blood may have the opposite effects. If that is correct, it follows that in cases like those discussed a diminution of supply to the nerves and to the skin and its appendages may cause different degrees of the changes under consideration, according to the involvement of the blood vessels— mainly the capillaries—supplying different parts of the skin and nerves, and also the degree of diminution of blood supply.

Whether the dilatation and constriction of capillaries take place independently or through the sympathetic nerve is a matter for consideration. The balance of evidence appears to be against nervous regulation (1). It has been shown (13, 15) that capillaries can contract independently of one another, and that those of the human skin can contract and dilate independently of the arterioles. Thus they are capable of influencing the nutrition of the tissue elements they directly supply. That may explain the fact that some of the signs of leprosy may be present in a patch, while others are absent. For example, a patch may be hypopigmented due to capillary contraction and diminished nutrition of the basal cell layer, but the capillaries supplying the sensory nerves may be unaffected and the patch therefore nonanesthetic. Similarly, a patch may be red, thick and hot to touch, due to capillary and arteriolar dilatation, but the vessels supplying the sensory nerves may be contracted and the patch therefore anesthetic.

Hypopigmentation and hyperpigmentation can be explained on the same grounds. Any change in the vascularity in the papillae is likely to influence the activity of the basal cells. If, for example, there be hyperemia due to some cause, as painting with trichloracetic acid, there may be increased transfer of nutrients from the papillary blood vessels and increased formation of pigment. If this be so, then the corollary should also be true, i.e., that contraction of blood vessels in the papillary layer and consequent diminished supply of nutrient to the basal cell layer may result in decreased pigment formation.

The other type of lesion to be considered is secondary anesthesias, muscular wastings, deformities, and trophic ulcers. The same phenomenon of capillary contraction is possibly responsible for the production of these changes. When hydnocarpus oil is injected subcutaneously around trophic ulcers there is inflammation of the part with vascular dilatation, and the ulcers gradually become smaller and ultimately heal. That this result is due to vasodilatation is confirmed by the findings of Cruz *et al.* (5) and of Goheen (8). Cruz and associates tried periarterial sympathectomy for trophic ulcers, the idea being to remove the vasoconstrictor action from fairly normal vessels; they found that all of them healed, but the results

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were temporary. Goheen tried sympathetic ganglionectomy; the ulcers healed and remained so for nearly a year, but after that they relapsed. Vascular dilatation is better maintained by periodical injections of hydnocarpus oil around trophic ulcers.

Vascular changes in a mixed nerve may produce signs and symptoms of various kinds, sometimes diametrically opposite in nature. For example, if there be acute dilatation of the capillaries in the nerve trunk it may cause neuritis, and the nerve trunk will be hypersensitive. This is usually relieved by vasoconstrictors like adrenalin or ephedrine. Sudden swelling in the epineurium and perineurium due to reaction may press on the blood vessels supplying the sensory and motor fibers and may cause temporary paralysis or deformity like drop-foot or claw hand; these conditions may be rectified with the subsidence of reaction and restoration of normal blood supply to the nerves (Text-fig. 14).





That the temporary suspension of the blood supply to a limb can produce sensory and motor symptoms is supported by the observation of the effect of cold upon the skin (16). A fall of temperature to 10° C or more benumbs the skin after a time, so that perception of fine touch and pain is lost; it also weakens the muscles of the limbs, particularly those of the hands. Similarly, if the blood circulation of a limb is temporarily suspended by using a binder, numbness and tingling is felt within a short time. If the binder is on the arm, a glove-like anesthesia appears, and if it be on the leg or thigh the anesthesia will be of the stocking type. Ultimately there will be inability to move the fingers or toes.

It would appear therefore that circulatory changes inside the nerve trunk may lead to sensory, motor or trophic changes in the parts supplied by the nerves. When contraction of vessels starts inside the nerve it may not be uniform all over; in consequence, it may affect different nerve fibers differently, with the result that there may be atypical distribution of anesthesia and deformity, or anesthesia without any deformity, or paralysis without anesthesia, etc., although the nerve trunk may be equally thickened in each case. This would explain the disproportion sometimes seen in the thickening of the nerve and the symptoms produced.

In chronic cases there is gradual contraction of the blood vessels of nerves and tissues, causing gradual wasting of muscles, paralysis, etc. Usually not all of the muscles are affected at the same time, as they are in degeneration of a nerve after injury. That there are vascular contractions in these chronic lesions (claw hand, drop-foot, etc.) is also known by the fact that the affected extremities are cold to touch, and the thermometer shows that the temperature is reduced. It is also supported by the fact that with the gradual improvement of the deformity the affected part becomes warmer, and there is increased bleeding after local injections of oil.

If these so-called permanent lesions were due to degeneration of the sensory and motor nerves involved then this degeneration must have been irreversible, as there was no sign of regeneration for many years, until the local injections of oil were started. If we assume that the nerves were degenerated, we have also to assume that injections of hydnocarpus oil produced a change in this irreversible condition and stimulated the nerves to regenerate, which is absurd. It would appear therefore that the improvement seen in the so-called permanent lesions after injection of the oil into the affected parts and around the thickened nerves was caused by improved blood supply in these parts. In cases where the damage to nerves or other tissues is not irreversible, beyond repair, the return of function may be complete (Text-figs. 7 and 11). That these improvements are caused by vasodilatation and are not due to any specific action of hydnocarpus oil is evident from the fact that similar results can be obtained with intravenous injections of saline.

It may be concluded therefore that circulatory changes in the skin and nerves play an important part in the production of symptoms that are generally considered to be caused by degeneration of the nerves. Symptoms like hypopigmentation, anidrosis, keratosis and depilitation in the patches are probably caused mainly by diminished blood supply to the skin and its appendages. Sensory, motor and trophic symptoms are no doubt related to changes in the nerves, but in the majority of cases the change is not of the nature of degeneration of nerve fibers, but is dependent on diminuation of blood supply to the nerves, resulting in their dysfunction. Except in cases of actual degeneration and irreparable damage, the function can be restored, completely or partially, with restoration of normal blood supply.

Although the work reported here does not bear on the subject, it is believed that the diminished blood supply in the nerves may be caused by any or all of the following three factors: (1) pressure of a thickened nerve sheath on the vasa nervorum; (2) pressure from cellular infiltration

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between the nerve fibers on the vasa nervorum; (3) pathological changes in the blood vessels of the nerve.

SUMMARY

1. The signs and symptoms in leprosy such as hypopigmentation, anidrosis, keratosis, depilation, loss of sensation, paralysis, and trophic ulceration are often explained as due to degeneration of nerves, sensory, motor and sympathetic.

2. While recognizing that nerves are involved in leprosy, and that this involvement gives rise to various symptoms, the author does not agree that degeneration of the nerves is always the cause of the conditions mentioned. The reasons for this belief are enumerated.

3. The clinical, therapeutic, and experimental work done to investigate this problem is described.

4. The results of the investigation indicate that the various signs and symptoms under discussion are due mainly to diminution of the blood circulation in the capillaries of the skin, its appendages, the nerves, and the muscles affected by the disease.

5. It is concluded that, although these symptoms of leprosy are beyond doubt related to changes in the nerves, in a majority of cases the changes are not of the nature of degeneration of the nerve fibers. In most cases it is diminution of blood supply to the nerves that results in their dysfunction, and with the restoration of normal blood supply the function can be restored. Restoration of function is complete in some cases, but in other cases there may be actual degeneration of nerves or irreparable damage of the skin and other structures supplied by the nerve, and as a result the normal function cannot be restored or can be restored only partially.

6. The symptoms like hypopigmentation, anidrosis, keratosis, and depilation in patches probably do not depend on nerve involvement but are caused by diminished blood supply to the skin and its various appendages, and the disappearance of these symptoms and return of normal functions of the skin depend on the return of normal blood circulation to different parts of the skin.

SUMARIO

1. Los signos y síntomas observados en la lepra, tales como hipopigmentación, anhidrosis, queratosis, depilación, anestesia, parálisis y ulceración trófica, se explican a menudo a base de degeneración de los nervios sensoríales motores y simpáticos.

2. Aunque reconociendo que los nervios son atacados en la lepra, y que esta invasión da origen a varios síntomas, no conviene el A. en que la degeneración de los nervios sea siempre la causa de los fenómenos mencionados, enumerando las razones en que se funda su creencia.

3. Descríbese la labor clínica, terapéutica y experimental llevada a cabo para investigar este problema.

4. Los resultados de la investigación indican que los varios signos y síntomas aqui discutidos se deben principalmente a disminución de la circulación sanguínea en los

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capilares de la piel, los anexos de ésta, los nervios y los músculos afectados por la dolencia.

5. Dedúcese que, aunque esos síntomas de la lepra se relacionan indudablemente con alteraciones en los nervios, en la mayoría de los casos, las alteraciones no son de la naturaleza de degeneración de las fibras nerviosas. En la mayor parte de los casos, es la disminución del riego sanguíneo de los nervios lo que ocasiona su disfunción, y al restablecerse el riego sanguíneo normal, puede restituirse la función. En algunos casos, esta restitución es total, pero en otros tal vez haya degeneración real de los nervios o lesión irreparable de la piel y otros tejidos servidos por el nervio, y a consecuencia de ello, no puede restablecerse, o sólo puede restablecerse parcialmente, la función normal.

6. Los síntomas del género de hipopigmentación, anhidrosis, queratosis y depilación en placas, no dependen de la invasión, nerviosa, sino que son motivados por la disminución de la circulación sanguínea a la piel y sus varios anexos, y la desaparición de dichos síntomas y el retorno de las funciones normales de la piel dependen del retorno de la circulación sanguínea normal a las diversas partes de la piel.

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