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Pathogenesis of neurotrophic lesions

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THE PATHOGENESIS OF NEUROTROPHIC LESIONS

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INTRODUCTION

Certain lesions of questionable pathogenesis, characterized by trophic changes, and suggestively associated with pathology of the nervous system have been roughly classified as neurotrophic lesions.

To justify this classification, and in attempting to account for the pathogenesis of these lesions on a neurological basis, there has been assumed a function of the peripheral nerves which exerts some significant influence over the nutrition of the tissues. The mechanism of this action has long been a question, but rarely a debate, for there is little data upon which to base an opinion except an apparent cause-effect relationship of the nervous system and the lesions.

The classification of the fibers of the peripheral nervous system according to function has always been restricted to two fundamental groups, the receptors and the effectors. As the special actions of peripheral nerve fibers have been revealed, they have been delegated to one or the other of these two groups. The division is fundamental and characteristic of the nervous system throughout the phylogenetic series. The receptors are not considered to have a trophic effect, except reflexly, and the effectors in most instances, as far as is known, influence local nutrition only indirectly through vasomotor control, which control as described at present, is probably inadequate to cause the specific localized pathology characterizing trophic lesions.

However, there is no absolute indication that fibers of trophic function do not exist, and it is true that there are present those pathological states which may be best explained by some such action.

An attempt is made here to present the various conditions described as neurotrophic in origin together with the opinions of their etiology, and to discuss in general the subject of the relation of the nervous system to tissue nutrition.

The problem is largely unsolved. Neuroanatomical data is wanting, experimental evidence is rare and inconclusive, and opinions of the pathogenesis of these lesions, founded largely upon supposition, are many and varied. The commonly seen quotation marks about the term "neurotrophic", and the use of the term "so-called neurotrophic" seem to be well warranted.

Yet the significance of the problem is large. A proper understanding of the conditions now cited as neurotrophic, if established as such (together with the nature of their pathogenesis), or if found to be due to other factors, would allow proper advance in the prophylaxis and treatment of these lesions, which at present are without effective therapy and include many distressing, incapacitating, and serious ailments.

Recent advances in neurology and particularly in the physiology of the peripheral circulation suggest promising progress toward the solution of this problem, which be-

comes of considerable interest as a subject for investigation and research.

THE NEUROTROPHIC LESIONS

In a consideration of trophic disturbances, the meaning of the terms may be confusing. For the present discussion a tropic lesion is a gross pathological change caused by faulty local nutrition. The fault may be occasioned by any abnormality of local nutritional supply from the standpoint of the cell, thereby including arteriolar change, capillary change of caliber or permeability, local metabolic dysfunction, or obstruction of venous or lymphatic return. A neurotrophic lesion is one in which the faulty local nutrition is caused by changes in the innervation of the part involved.

The following pathological states are described as instances of probable neurotrophic lesions. Some conditions only obscurely construed as neurotrophic are omitted or given little mention. Certain conditions having obvious gross circulatory dysfunction as the primary etiological factor are omitted, although the nervous system may be responsible for the circulatory change, for example, Raynaud's disease and erythromelalgia.

Decubitus Ulcer:

Decubitus is an ulcerating lesion of the skin and underlying tissues, usually occurring in bedridden patients, resulting from prolonged irritation and pressure over bony prominences of the body, together with variable factors of debility, metabolic disease, poor nursing care, and nerve involvement. It is notably difficult to treat and re-

quires careful nursing care to prevent its occurrence.

The suggestion of neurologic etiology arises from the incidence and rapid development, sometimes despite the most arduous prophylactic care, in cases with neurologic disease accompanied by paralysis and anesthesiae. The factors involved are complex. The paralyzed patient is unable to move and thus relieve the pressure (and subsequent anemia and trauma) over the bony prominences. Particularly if the area is anesthetic does the protective mechanism fail to prevent the harmful pressure. Bed-ridden patients are most frequently in poor condition, and the general nutrition and circulation are impaired. This is usually the case when bed sores are formed in the absence of neurological disease. Stasis, marked in paralysis, further contributes to a sluggish blood flow and impaired nutrition. Minor lesions of the skin in anesthetic areas are unheeded and may initiate chronic ulcer. Irritants as urine, perspiration, and feces undoubtedly contribute to the severity and high incidence of bed sore in neurological patients when incontinence is present.

However, in cases with nerve involvement in which the ulcer develops characteristically over the involved area in healthy persons in spite of meticulous care, and heals with great difficulty if at all, at least a predisposing effect must be granted the neurologic lesion though the pathogenesis is still largely unexplained. In severe cases of myelitis, the prevention of decubitus is almost impos-

sible. Leloir (64) describes acute decubitus as frequently accompanied by bullae and may resemble herpes zoster or become associated with neuralgic pains.

Samuel (Leloir (64)) first drew attention to the condition described as acute decubitus, rapidly forming sloughs of considerable area and depth, appearing a short time, even hours after the onset of some acute neurological lesion, and in the area of nerve involvement. This was confirmed by Charcot (64) who emphasized the grave prognosis. Leloir also adds the significant observation that they may be occasionally found "on portions of the integument where there can be no question of pressure as the cause", viz. the anterior abdominal wall, dorsum of foot, etc.

Stewart (103) has noted the acute decubitus developing in a few hours or days after hemiplegia or paraplegia in spite of best nursing care.

Common sites for this lesion are over any bony prominence, particularly those subject to the greatest pressure in a bed-ridden patient. It does not necessarily follow that pressure primarily is the causative factor, for in a denervated limb any trophic lesion would naturally occur in the areas of trauma and pressure if the predisposing cause were due to nervous lesions. Also the occurrence in patients without neurological lesions is usually limited to the aged and debilitated and those whose general nutrition is greatly altered.

Charcot noted significantly that infantile paralysis

and acute spinal paralysis of adults is not usually accompanied by decubitus, although the factor of paralysis is present. He attributes the predisposing factor to "an irritation of the post-central portion of the grey matter". (Goodhart (40)) Goodhart (40) also cites Dejerine and Leloir and others, who showed that neuritic lesions are invariably present in decubitus. A trophic influence was thought to be interfered with, external pressure simply playing the part of an incidental determining cause.

The treatment of decubitus is essentially empirical and little has been achieved in attempting to reach the ultimate etiology. Latimer (62) reports in detail upon the local treatment and prophylaxis, emphasizing the tannic acid treatment. Pollack (83) further discusses the tannic acid treatment, which seems to rely upon the protective and hardening nature of its action. The rationale of the use of theocresol as described by Reiman (90) is based upon experiments indicating that the sulphydrl group is in greater concentration in cells undergoing mitosis, and is a characteristic chemical feature of these cells. The mechanism is described as a stimulation of the multiplication of cellular elements. Local applications of every sort have been described as of especial benefit.

Riehl (91) reports excellent results with continuous bath therapy. The patient is placed in the bath at the first sign of development of decubitus. The general and local stimulation combined with the absence of pressure and

irritating discharge causes the ulcers to heal rapidly. No comment was made upon any differences in those ulcers associated with nerve lesions.

Prophylaxis in the form of careful nursing to avoid trauma, irritation, and prolonged pressure is the most significant procedure.

Herpes Zoster:

Herpes zoster is an acute disease due to inflammation of the posterior root ganglia or the sensory ganglia of the cranial nerves, characterized by the development of groups of vesicles on an erythematous base, distributed in the area of distribution of a cutaneous nerve (usually the intercostals). The eruption, rapid in onset, is usually preceeded by severe neuralgic pain, which may persist with varying duration after the disappearance of the skin lesion.

Involvement of the Gasserian ganglion may evoke herpes zoster in the distributional area of the trigeminal nerve, characterized by burning and itching, followed shortly by the development of groups of small vesicles on a reddened base which later ulcerates. Marked pain and tingling is associated and may be followed by hypesthesia. Hunt (51) has described instances of inflammation of the geniculate ganglia analagous to that of the posterior root ganglia in herpes zoster. The symptoms are the eruption of herpetic vesicles in the external auditory canal and pain in the auricle. This condition is occasionally a symptom of

certain types of facial paralysis.

Originally supposed to be strictly a skin disease, herpes was shown in 1861 by von Baerensprung (Parker (80)) and Daneilson (Leloir (64)) to be an inflammation of the posterior root ganglia, hence its more modern name of acute posterior poliomyelitis. Charcot in 1865 noted herpes of the neck associated with carcinoma of the spine accompanied by lesions in the spinal ganglia and cervical nerves (Leloir (64)).

Leloir cites also many interesting examples of nervous system pathology in conjunction with herpes. Herpes following peripheral nerve and cord lesions and involvement of the motor fibers with paresis and muscular atrophy is mentioned.

The skin lesions are not dependent upon destruction of the sensory nerves, although degeneration of the ganglion cells and posterior root and peripheral nerve fibers may result. (Boyd (12))

The pathogenesis of the skin lesions is not described, except in general as "trophic efect", or by the postulation of antidromal impulses on a hypothetical trophic fiber.

The herpes simplex lesion, "fever blister" or "cold sore", is due also to an inflammation of a sensory nerve ganglion, but does not follow a definite area of distribution of a nerve, shows no change in the cerebrospinal fluid, nor does it convey immunity as does herpes zoster. (Boyd (12))

Cord Diseases:

Many changes in tabes dorsalis may be described as trophic and appear to be dependent upon disturbances in innervation. One of the most striking is the perforating ulcer, formerly seen very frequently, but now quite uncommon. It is usually found on the sole or dorsum of the foot or one of the toes, as a deep seated painless ulceration, very difficult to heal.

Duploy and Morat, according to Leloir (64), "proved conclusively the nervous origin of perforating ulcer". Atrophic degenerative neuritis and parenchematous neuritis of the nerves to the parts involved were described as "absolutely analogous to what we observe in the peripheral portion of a divided nerve."

Secondary factors of pressure, poor general nutrition, and loss of protective sensory function are hard to evaluate, but the depth and perforating nature of the lesion, and the resistance to treatment suggest at least an underlying contributory factor logically attributable to the nerve lesion.

The arthropathies of tabes and syringomyelia are difficult to explain by the mention of loss of sensory defense. mechanism, but this cause is the usual one cited. (Boyd (12)) However, Goodhart (40) cites the interpretation of these lesions by Turney, who describes them as true trophic lesions to be distinguished from those of disuse; that they are produced reflexly by irritation and are strictly anal-

ogous to arthritic atrophy of the muscles. Other authorities also attribute these changes to a disease of the peripheral nerves, particularly those supplying the bones.

Campbell (21) states "we are still ignorant of the pathology of these arthropathies. Injury owing to the absence of local defense mechanism is an undoubted factor, but this is not the whole story. We need to postulate a trophic mechanism in the shape of faulty innervation. This does not imply the existence of trophic nerves in the sense of nerves having as their essential function the control of metabolism of single cells. Disturbed vasomotor activity may account for much.....There seems to be a close connection between the neurones pertaining to pain sensibility and trophic lesions of the bones and joints."

The Charcot joint is characterized by thickening of the capsules and membranes, excess synovial fluid, ulcerations of the cartilages, and atrophy and fragmentation of the bones; changes which suggest the trophic nature of the lesion.

Leloir (64) describes other neurotrophic phenomena in tabes; herpes occasionally associated with the root pains; disturbances in the growth of the nails, which may fall off; ecchymoses of the skin, changes in the hair, and vitiligo. Rapid painless falling out of the teeth and absorption of the alveolus of the jaw is cited as a trophic change in tabes; also rarely, corneal ulcers and tabetic ulcer of the mouth, all associated with involvement of the

trigeminal nerve.

The muscular atrophy associated with lesions of the ventral horn cells is characteristic. Contrary to other trophic effects, the denervation atrophy here is constant and marked. Obviously the factors of disuse and impaired circulation have their effect, but the resultant degeneration atrophy demands a more potent influence. It is characterized by a rapid disappearance of the contractile elements and their replacement by a similarly rapid growth of fat and fibrous tissue. (Bing (9)) Langley and Kato (60) state that thirty percent of the weight of the muscle is lost in the first two weeks. The reaction of degeneration employed clinically as a distinction in differential diagnosis between this and other types of atrophy, is further significant of a profound change in the physiology of the muscle.

Bing (9) attributes to the anterior horn cells a trophic influence upon the bony skeleton. "When destroyed (the motor cell) in a growing subject, a more or less marked inhibition is noticed in the further growth of the bones in the region of the affected muscles. Abnormal brittleness of the bones may also result under like circumstances." Here again the effects of disuse and interference with a well regulated blood supply must be taken into account, for it is well known that with immobilization, marked decalcification of bone results.

The muscular atrophy occurring at a considerable in-

terval after destruction of the posterior roots is cited by Bing (9) as evidence that the trophic effect of the ventral horn cell is probably called into action reflexly by the posterior root system. This atrophy would seem to be explained more simply by the prolonged loss of reflex tone occasioned by the sensory lesion.

Campbell (21) speaks of muscular and glandular atrophy after motor denervation as trophic lesions "par excellence". "The nerves ending in muscle cells and gland cells are in the truest sense trophic nerves. Beyond these no true trophic nerves exist." But here again there is no mention of the nature nor mechanism of this "trophic influence". Glandular changes after denervation is illustrated by the atrophy of the testis subsequent to division of the spermatic nerve. (21) Parker (80) discusses the rapid degeneration of the taste bud, and of the lateral line organs in fishes after section of their afferent nerve supply. Regeneration of these structures follows when, and only when, the nerve regenerates.

Evidences of suggestive relationship between sensory nerve lesions and trophic changes were noted above in decubitus, herpes, and tabes dorsalis.

Trophic changes seemingly dependent upon sensory nerve lesions in syringomyelia, in newgrowths involving the cord, and in cord injury are occasionally noted. Guillin and Thevenard (43) cite an instance of "familial perforating ulcer of the foot", associated with syringomyelia in the

lumbo-sacral part of the cord, occurring in two brothers. Faisons (Leloir (64)) has seen purpuric hemorrhages associated with nerve lesions in transverse myelitis and secondary carcinoma of the spine, as well as in tabes. These are associated with the "severe crises of fulgerating pain, and their appearance usually coincides with the abatement of the pain".

According to Leloir, (64) "the posterior central grey substance of the cord seems, as regards the skin, to play a role analogous to that of the anterior cornua for the muscles". Goodhart (40) speaks of vasomotor and trophic centers in the cord, but with no direct evidence of the existence of the latter.

Lesions of the Peripheral Nerves:

The atrophic changes in the muscles due to motor denervation in peripheral nerve injuries are similar to those observed in disease of the ventral horn cells of the spinal cord, with this additional feature; that in the case of peripheral regeneration of the nerve axon, the muscle may resume its former structure and function, as has already been noted to be the case in experimental denervation of taste buds. There are numerous instances of pathology, particularly in the skin and joints, which appear to be related to a trophic effect of the sensory nerve lesions. Many may be at least partially explained upon the basis of interference with a properly regulated blood supply through the

disturbances in the vasomotor control subsequent to injury of the nerves, and perhaps the vessels themselves. But the nature and severity of others again suggests an effect not so simply explained.

Weir Mitchell (75) described the trophic changes of the skin and its appendages in the case of nerve injury, particularly when associated with causalgia, which is characterized by nerve irritation and follows trauma or incomplete severance of the nerve. Thickening and drying of the skin, atrophy of the skin, hair and nail growth changes, and "glossy skin" were noted. Leloir (64) describes glossy skin as "a classic type of trophoneurotic erythematous dermatitis". The skin is smooth, shining, and tense, devoid of hair, with a diffuse or mottled pink or red color. Later develop changes in the nails, which may fall off; generalized atrophy of the skin and its appendages may follow. Violent neuralgic pains are often associated with causalgia (eight in thirty-eight cases of Benisty's--Pollack and Davis (85)). Benisty believed that glossy skin resulted from vascular lesions, but in forty cases these lesions were rarely demonstrable. Riddoch (90-A) considers all of the trophic disorders associated with nerve injuries as "paralytic phenomena resulting from destruction of the vasoconstrictors of the nerve....Massage, warmth, and protection of the part causes many of them to disappear." He also mentions another factor, "certain other nutritional changes of common occurrence are due not to the nerve

lesion but to immobilization of the limb."

Pollack and Davis (85) emphasize the probability of a vascular lesion in addition to the nerve injury, and quotes Meige and Benisty, who pointed out the necessity of suspecting a concomitant injury to a large vessel supplying the part involved, especially when vasomotor changes seem apparent.

The changes in the hair and nails are usually alloted to the abnormality of the circulation.

The subcutaneous tissue may show "hard elastic infiltration quite unlike edema". (85) The hair grows more slowly and perspiration is absent. Ulcerations are frequent, and are suggestively limited to the area of nerve involvement. They have a red floor with thick indurated edges and heal poorly with marked scarring. Pollack (85) describes the cause of these ulcers as primarily the loss of defensive sensory mechanism and possibly a decreased resistance of the tissue due to interference with vasomotor regulation. "Healing is very slow because of repeated injury and concomitant vasomotor changes, but otherwise the process of healing resembles similar pathology in normal tissues." Yet he states further of the ulcers that "at times they occur without cause", and that "these ulcerations differ materially from those seen in vascular lesions where areas in which sensation is preserved are involved, and massive ulceration and gangrene occur."

"The changes in the subcutaneous tissues are attrib-

uted rightly by Benisty to vascular or perhaps perivascular lymphatic changes. Similarly, vascular lesions may preceed fibrous degeneration of fibrosclerotic changes in the flexor muscles of the fingers with retraction of their tendons (similar to Volkman's contracture)". Steward and Evans (104) present a similar opinion, but mention at the same time three functions of the nerves; motor, sensory, and "trophic".

Edema of the leg and foot are common in sciatic nerve lesions according to Pollack and Davis (85), and brawny infiltration of the calf is often associated. They noted decalcification of the bones in ulnar nerve paralysis, and describe stiff, fibrotic, and ankylosed joints as the rule following peripheral nerve injuries, and rare in anterior poliomyelitis, yet cite immobility as the probable cause. The pronounced pathological changes are infiltration and fibrotic contraction of the capsules and ligaments, and sometimes synovial adhesions. "Little is known at present concerning the effect of nerve lesions upon joint capsules, ligaments, or aponeuroses." Riddoch (90-A) claims that in nerve injuries, "adhesions in joints, between tendons and their sheaths, and fibrous contractions of muscles are complications which can be entirely avoided by the adoption of adequate and regular treatment".

According to Campbell, (21) nerve injury may lead to massive atrophy of skin, muscles, and bone. He cites ulnar nerve injury with atrophy of a large part of the hand in-

cluding the muscles innervated by the nerve, and atrophy of the foot from injury of the posterior tibial nerve. The varying effects of apparently similar lesions is striking. "The writings of Haller and Quesnay in the eighteenth century stated that section of the nerves of a limb might cause gangrene of the part. This opinion held until 1817, when Hebreard and Wolf demonstrated by experiments on a dog that sections of the nerves, made after the method followed by Haller and Quesnay did not give the results claimed. We find in the literature however, a number of cases of gangrene following peripheral nerve lesions." (Leloir (64)) Leloir (64) further describes a case of cutaneous gangrene of the face following a trigeminal neuritis, and multiple areas of gangrene of the skin due to lesions of the peripheral nerves and mentions cases of gangrene secondary to peripheral neuritis described by Pitres and Vaillard in 1883 and Dejerine, 1882.

Campbell (21) cites Packard's description of trophic changes in joints of the knee and foot following compression of the sciatic nerve by tumor; and Chipault's case with trophic changes in the elbow after compression of the brachial plexus by the callus from a fractured clavicle.

An interesting phenomena of obscure etiology associated with nerve lesions is the condition of "congealed hand", first described by Meige, and characterized by paralysis with contractures of hypotonic flaccid paralysis without a corresponding lesion of the nerve trunk. Bab-

inski and Froment (3) emphasized the sympathetic system in view of vasomotor and thermal disturbances which influences the muscles, due to vasoconstrictor spasm by reflex irritation originating in the peripheral lesion. Leri and Roger, admitting a functional element, called attention to similar contractures in organic cases, occurring in muscles which are antagonistic to the paralyzed groups. (85) Ischemia and prolonged immobilization of the part are cited as etiological factors. Benisty (6) summarizes the apparent pathogenic factors as a painful neuritis after a slight wound, accompanied by voluntary prolonged immobilization of the extremity, resulting in generalized atrophy, periarticular fibrosis, and contractures of muscle and fibrous tissue. (Summarized by Pollack and Davis (85))

An apparent relationship to Volkman's contracture is suggested, but the latter is quite generally considered as a result of disturbance of the circulatory system primarily, and not associated with nervous lesions. (Bertoncelj (7))

Evidences indicating the vascular origin of the trophic disturbances in peripheral nerve injury is offered by Stopford (105). In a case of causalgia with trophic disturbances in which the sciatic nerve had been injured, he made a histological examination of the peripheral arteries and found great thickening of the intima and other pathological changes characteristic of endarteritis obliterans. Todd (107) published similar clinical and histological

findings in a case of injury of the brachial plexus by a cervical rib.

Pollack and Davis (85) summarize their opinion of the status of trophic changes in peripheral nerve injury as follows, "Too little is known of the nature of trophic disturbances to enable us to employ them profitably in interpreting the severity of the lesion. When protopathic sensibility was lost, trophic ulcers were likely to occur. When an extremity was immobilized, growth of nails ceased. When an extremity was protected by dressings, hypertrichosis was at times observed. Generalized atrophy of the bones indicated only disuse."

Inflammations of the Peripheral Nerves:

Trophic symptoms in multiple neuritis are discussed by Fieling (37) as follows; "In the majority of cases... trophic changes are an inconspicuous feature. It is rare to see the extreme changes which occur after division or severe injury to the peripheral nervous system. The more severe trophic lesions such as bedsore and trophic ulcers are seldom found." Mild dermatological changes and edema are described. "Other vasomotor changes are not uncommon. Occasionally changes in the joints are found, and have been considered as trophic lesions, dependent upon the disease in the nerves. Charcot joints are not found."

Leloir (64) describes the nails in multiple neuritis as brittle, lustreless, and presenting riffles and in-

equalities, and that in chronic neuritis, fantastic shapes occur. Bielschowsky reports "leucopathia unguinum" following multiple neuritis. Boeck has seen a case of multiple neuritis begin with an eruption of purpura which he attributed to the nervous changes. (Leloir (64))

Skin changes in neuritis and neuralgia are not uncommonly observed. Leloir cites numerous instances; pigmented spots over the area involved in neuralgia, rare cutaneous hemorrhages in the course of certain neuralgias, and cites three cases of ecchymoses during neuralgia of the sciatic nerve, in the region controlled by the inflamed nerve.

Weir Mitchell (75) noticed petechiae in the course of neuralgic attacks in anemic women. Caradec (Leloir (64)) reports a case of secondary syphilis in which thirty minute neuromata developed on the short saphenous nerve; some days later a pigmented line appeared corresponding exactly to the course of this nerve. "In this line the hairs were more numerous, shorter, more friable, and whiter; and the local temperature was two degrees (centigrade) lower than on other parts of the integument.

In two cases of serpentine ichthyosis Leloir (64) demonstrated marked lesions of the peripheral nerves and posterior spinal roots. He states that lesions of the peripheral nerves of obscure etiology may be followed by an appearance of the skin suggestive of ichthyosis. Numerous cases of vitiligo are mentioned, limited to specified areas of the skin, following the distribution of a certain

nerve, found to be diseased.

Brier (14) reports an interesting case of gangrene of the face and ear, associated with diabetes and nerve lesion. The patient experienced the rapid development of a painful lesion and subsequent (four days) development of gangrene of the skin in front of the right ear. Changes in the seventh nerve were noted in twenty days, but fifth nerve changes may have been primary, and resulted in anesthesia of the right face, tongue, and cheek, accompanied by burning and redness of the right eye with total anesthesia of the conjunctiva. A corneal ulcer followed. Nine months later the patient showed anesthesia of the right tongue and cheek, residual muscular involvement, the gums of the right jaw were unhealthy, and there was no sweating on the right side, even in hot weather beneath the goggles worn to protect the right eye.

The lesions of leprosy are widely considered to be trophic. (Mason (68)) This is true in the nodular type as well as the typical nervous variety. In the latter type, the nerve trunks are thickened, and it is here that the bacilli are characteristically found. Leucodermic areas and hyperpigmentation are common over the involved areas. Sensory changes, anesthesiae, and paresthesiae are typical and there may be severe neuralgic pains. The "perforating" ulcers of the palms and soles are very similar to those of the same name in tabes and syringomyelia.

The nodular areas are often the seat of an ulcerative

process which may start spontaneously or from slight traumatism. The large trophic necroses are usually free from organisms. (McCoy (73))

Boyd (12) states that, "The lesions of the nerve trunks are peculiar to leprosy. They occur in the nodular as well as the anesthetic form. There is a perineuritis, and the thickened nerves can be felt as cords under the skin of the arm and leg. The nerve fibers are destroyed, so that anesthetic areas are produced, followed later by motor and trophic disorders. The destructive lesions already mentioned may be partly trophic, but in part they are due to loss of sensation with subsequent injury.

Cruz, Abnel, and Samson (36) report the results of periarterial sympathectomy in trophic ulcers of leprosy. Thirteen lepers presenting eighteen trophic plantar ulcers of from two to twenty years duration, in which no other treatment benefitted, were subject to the operation. In all cases the ulcers dried up and healed in from ten to thirty days, but in 61.5% reocurrence occurred within ten days to four months after healing. Others did not recurr in five months. This report suggests a vascular basis for the trophic disturbance, but on the other hand, the change in the blood supply after operation may consist of merely a superimposed aid to substitute for a time the absence of the theoretical specific trophic influence.

The neuritis in pellagra has been associated with trophic disturbances. Sullivan (106) reported a case of fulminating pellagra of four months duration, apparently

cured; three months later bilateral symmetrical ulcers appeared on the feet, and healed in eight weeks. Two weeks later a second set of ulcers, more severe and diffuse, also symetrical, appeared on new sites on the feet and legs. Energetic dietary and local treatment for six weeks found the ulcers enlarging. On the basis of the success in bed sores with insulin treatment of non-diabetic patients, (Partrier (81)) insulin therapy was inaugurated and in two weeks the ulcers healed.

The dermatological lesions of pellagra are considered by some as trophic manifestations of the neurological lesions. (68)

Dermatological Lesions:

The manifestations of trophic change occur predominantly in the skin; many of the above-noted conditions are dermatological, but in which the nerve lesion is primary. Prominent among these is herpes zoster, in which the dermatological lesion is marked, and seems quite definitely proven to result directly from a lesion of the nerves supplying the area. Unfortunately no such direct and proven relationship is found in a great many of the trophic skin lesions. A perversion of a trophic function of the nervous system may occur without demonstrable lesion of the nervous system, as in the marked skin manifestations of hysteria and mental shock.

In regard to the neurodermatoses, the following clin-

ical observations are suggestive of their nervous origin.

1. Limitation of the lesion to the distributional area of a nerve trunk or segment, sometimes symmetrically placed.

2. Rapid onset of well developed lesions with external cause absent or inadequate.

3. Presence of various neurological manifestations such as pruritis, neuralgia, paresthesias, hyperesthesias, pareses, and paralyses; either before, during, or after the appearance of the lesion.

4. Resistance to treatment ordinarily successful

5. Similarity to trophic skin lesions directly associated with known nerve lesions.

6. Association with vasomotor changes suggestively limited to areas of nerve distribution; cyanosis, erythema, temperature variations, edema, and purpura.

Leloir (64) emphasizes the relation between nervous disease and skin diseases, even citing their common embryological derivation from the ectoderm as a basis of fundamental mutual relationship. "The predisposition to certain skin diseases seems to go hand in hand with a predisposition to nervous affections.....We know that nervous afflictions may often imprint their seal upon the cutaneous surface, and that in certain cases the skin may be regarded as the mirror of the nervous system." Probably included in this generalization were the observed relationship between functional diseases ("nervous instability") and con-

ditions now described as allergic. However, much of the recent work (Walzer (113)) indicates that some allergic and neurological phenomena are quite intimately related in the consideration of their ultimate manifestations in the tissues and capillaries; and in the familial relationship of the functional nervous disorders, certain types of epilepsy and migraine with the allergic manifestations of hay fever, asthma, and allergic dermatitis.

In this connection, many refernces may be found as to the influence of functional nervous diseases in the production of urticaria, purpura, herpes, pigmentary disturbance, psoriasis, and bullous eruptions of the skin, in addition to the varied vasomotor phenomena of cyanosis, anemia, and hyperemia of psychogenic origin. These may be characteristically accompanied by pruritis, hyperesthesia, neuralgia, anesthesia, and paresthesia.

Many types of trophic lesions are rare, and most nerve lesions are not accompanied by marked dermatological manifestations; also similar nerve lesions may have extremely varied effects. Neither does the extent of the vascular change parallel the incidence or severity of the trophic lesion. Likewise, external conditions of immobilization and trauma have variable effects when considered as causes or precipitating factors in these lesions.

Irritant lesions of the sensory nerves seem to be accompanied by a greater incidence of severe trophic changes. Lesions destroying the afferent nerves are productive of

chronic trophic changes of slow development. Many seem to be largely accounted for by the neuro-vascular changes.

Scleroderma:

Goodhart (40) states that "The various manifestations of scleroderma point unequivocally to the nervous system as the seat of this disease." Others take an opposing view, many favoring particularly the endocrine theories. Laignel-Lavastine (58) state "There are cases which confirm all the pathogenic theories, the trophoneurotic, the angio-trophoneurotic, the sympathetic, the vascular, the pituitary, the thyroidal, and the pluriglandular. However, none of these can be applied to these cases as a whole."

Marinesco and Goldstein (58) are of the opinion that the condition is due to a change in the sympathetic nervous system induced by disturbance in function of the thyroid gland.

Besnier and others noted the many points of similarity between scleroderma and localized cutaneous atrophy, and considered the nervous origin of the latter as very probable.

Scleroderma is sometimes associated with progressive facial hemiatrophy, Raynaud's disease, erythromelalgia, and other trophoneuroses. Lesions in the sympathetic ganglia have been noted, as well as pigmentary changes. Resection of the sympathetic ganglia and trunks (Brown (16) and Mayo (70)) have been performed upon selected cases with

variable success.

Pigmentary Changes:

The role of the nervous system in the production of pigmentary change is very uncertain (Saunders (96)). Ellerman and others (36) state that pigmentary anomalies, both an increase and a decrease, may be due to nervous disease. A "viscero-cutaneous reflex" is cited as the cause.

Nehl (Goodhart (40)), writing on the influence of the nervous system on the pigment contents of the skin, mentions the pigments of scleroderma and facial hemiatrophy as referable to irritative conditions of the sympathetic fibers of the peripheral nerve. "Interruption of these fibers in lesions of the cervical sympathetic causes unilateral canities: resection of the uppermost cervical sympathetic ganglion may be followed by a loss of pigment in the iris. One occasionally sees a patch of grey hair on the side of the head of patients affected with migraine, hemicrania, and trifacial neuralgia."

Numerous cases of vitiligo following the distribution of a certain nerve found to be diseased are mentioned. (64) Joseph in 1886 produced baldness in the ears of cats and rabbits by excision of the second cervical ganglion; and mastoidectomy may be followed by alopecia areata. (Ormsby (78))

The nervous origin of naevus was proved by Masson (69)

who describes this condition as a proliferation of the entire end-apparatus of the sensory nerves of the skin, in particular the cells of the Meissner's corpuscles in the dermis. Medullated and non-medullated fibers may be demonstrated among the tumor cells. "The neurogenic origin of the pigmented tumors is of interest in view of the frequent occurrence of patches of pigmentation in multiple neurofibromatosis." (Boyd (12))

The relation of the nervous system to the chromatophore mechanism of fishes and amphibians (Parker (80)) and the newer work on the melanophores (76) indicate an intimate interrelationship between the peripheral nervous system, the pigments, and the hormonal system of the body.

Edema:

Many observations of edema suggesting nervous origin are found. Vulpian (64) says, "it is not uncommon to see an edema develop....in consequence of an injury of the nerves." Longet (64) described a case in which a lesion of the trigeminal nerve produced marked edema of the corresponding half of the face and anesthesia of the region and ulceration of the cornea on the same side. "Ranvier has shown that ligature of the vena cava is not followed by edema of the lower limbs if the nerve filaments which surround it are respected. And edema is not produced by ligature of the sciatic vein unless the sciatic nerve is also divided." (64)

J. Roux (64) describes injury to the radial nerve, with severe pain in its distribution, followed shortly by edema of just that area. Edemas otherwise unexplained are described in a great variety of organic nervous diseases. (123) This concept is also applied to angioneurotic edema and hereditary edema, but with little evidence of the pathogenic process involved. Boyd (12) says of angioneurotic edema that "the nervous impulses may lead to vascular hyperemia or to metabolic disturbances in the tissues resulting in increased osmotic pressure, possibly both." Certain phenomena of allergy are apparently closely allied, particularly the urticarial wheals. Osler (79) finds in these cases a predisposition to nervous influences evidenced by the appearance of migraine, neuralgia, exophthalmic goitre, and melancholic tendencies. A relation to urticaria is also mentioned, and a suggestive relationship to purpuras and erythemas.

Experimentally, stimulation of the cut dorsal nerve roots in animals may cause capillary dilatation with increased transudation into the tissues. (123)

The association of Milroy's disease with "neurotic stigmata", vasomotor instability, spina bifida (rarely), and the segmental distribution have suggested a nervous origin. (123)

Krogh (56) in discussing the physiology of the capillaries, is convinced that the capillary endothelium may become permeable to protein from nerve stimulation, but

experimental production of edema by this means has not been accomplished. (123)

Erythredema is cited by Ormsby (78) as "definitely a nervous system disease. This condition occurs in children, and is associated with restlessness, depression, and drowsiness; and a characteristic eruption of the hands and feet ("raw-beef hands and feet"), which are cold, cyanotic, erythematous, and swollen.

Acromegaly is cited by Ormsby (78) as "preceeded by transitory swellings and vasomotor change", and accompanied by pigmentation, hyperidrosis, and hypertrichosis.

Miscellaneous Observations and Experimental Evidence:

A number of unusual and uncommon syndromes of obscure pathogenesis seem to present evidence of neurotrophic influence.

In facial hemiatrophy, all of the tissues of one side of the face are affected by a slowly progressive atrophy. Anhidrosis and alopecia are usually present. Certain autopsy findings suggested a neuritis of the trigeminal nerve with involvement of the descending intracranial roots; and "vasomotor disturbances and inequalities of blood supply on the two sides of the face are almost invariably present in cases with peripheral localization in the superior cervical ganglion." (40) Langelaan (40) noted associated neurological findings which caused him to assume a "lesion of the red nucleus where the oculomotor nuclei come in contact with the peri-ependymal grey matter of the Sylvian aqueduct."

Krueger (40) cites a case of facial hemiatrophy with sensory disturbances and homolateral tonic and clonic spasms of the masseter muscle. "the irritative motor phenomena are most readily accounted for by a lesion of the trigeminal nucleus." (40)

Schlittler (97) reports a case of "Trophic postencephalitic ulceration of the external nose and cheek, in which other possible factors of etiology were proven wanting."

An interesting observation in regard to rodent ulcers, especially those of the face, is reported by Cheattle.(24) It was shown that the commonest points of occurrence are at the positions where the various branches of the trigeminal nerve become cutaneous. Also that these spots are the favorite points of incidence of leucoderma and scleroderma; and that rodent ulcers are frequently limited to the distribution of normal nerve areas; that the spread of the ulcer ceases abruptly when it reaches a cutaneous area which has become denervated by division of its sensory nerves.

River (92) discusses perverted trophism as a probable cause of carcinoma.

Leloir (64) states that "In acrodynia, nervous symptoms are remarkable for their constancy and multiplicity of manifestations; paresthesias, hyperesthesias, algesias, thermesthesias, anesthesias, spasms, and contractures." He also states that changes in the spinal cord are noted.

Boas (10) in a discussion of the capillaries of the extremities in acrocyanosis concludes that "the innervation

is evidently interfered with, resulting in a change of elasticity, contractility, and finally also of configuration."

Muscular atrophy associated with lesions of the joints has been commonly noticed and usually ascribed to immobilization and disease. But Charcot is cited (3) as repeatedly insisting upon the impossibility of explaining the atrophy of articular origin on this basis. He mentions cases of rapid onset of atrophy as a result of articular infection, which could not be attributed to an extension of the inflammatory process, as the latter was minimal. Vulpian's theory (3) is that afferent articular impulses transmit the irritation to the spinal grey substance, where it is relayed to the muscles involved. Other theories have regarded the reflex effect on vasomotor functions as important. Occasionally this atrophy is followed later by a similar reaction of the opposite limb.

Dejerine (6) reports two cases of deformities of joints due to nervous causes. One resulting from an irritative lesion of the median nerve was "exactly limited to the area of this nerve". "In the other case the joint lesions, which resembles those of chronic rheumatism, were bilateral, and appeared to be the result of an elongation of the roots of the brachial plexus", and was associated with a traumatic spinal injury. (Benisty (6))

Goodhart (40) states that trophic and vasomotor changes were demonstrable in nearly all of the dystrophy cases in

a series of Goodhart, Isaccson and others. Weiss and Kennedy (114) believe myotonia to be due to an increased activity of the autonomic nervous system. According to Boyd (12) the trophic changes in the skin and bones in the muscular dystrophies suggest that the disorder is not a primary muscular one, but possibly an endocrine or an autonomic nervous system disease.

Kuntz (57) discusses peptic ulcer associated with parasympathetic hypertonus, either as a local or general autonomic dysfunction, and observed changes in the autonomic ganglion cells.

Cushing's (32) lecture, "Peptic ulcers and the Interbrain", presents a number of very interesting observations, and indicates significant unexplained influences of the nervous system upon the tissues innervated. Gastric ulcerations, erosions, and perforations occurred as sequelae to intracranial operations, were associated with intracranial tumor, and in infants with birth injuries, and were experimentally produced by lesions of the vagus and of the brain. The influence of drugs acting upon the autonomic nervous system were noted. A parasympathetic center in the diencephalon is postulated.

An interesting theory of trophic effect in tuberculosis is presented by Ponomorew (Kuntz (57)). The toxin produced in a tuberculous lesion poisons the nerve cells, resulting in trophic disturbances at the periphery, and reduction in the capacity of the lungs to resist the in-

fection. Trophic disturbances at the periphery in tuberculosis patients also have been emphasized by Pottenger (Kuntz (57)), who described a large number of trophic reflexes arising in the pulmonary area and pointed out the significance of certain trophic disturbances in localizing tuberculous lesions in the lungs.

Goodhart (40) was led to believe arthritis deformans due to changes in the nervous system, "by observation of extensive material."

Corneal ulcers after destruction of the sensory nerve to that area are of possible neurotrophic etiology, (Verboeff (111)) and the lesion is called "neuro-paralytic keratitis" by Hartman. They may follow operations upon the Gasserian ganglion, as may herpetic eruptions over the distribution of the fifth nerve.

Experimental data concerning a possible neurotrophic action of the nervous system, and the mechanism of this action, is inconclusive and incomplete. A few instances have already been mentioned.

The effect of experimental nerve injuries in the production of alopecia areata was investigated by Wright (121) with the following conclusions:

1. Cutting sensory nerves supplying the scalp in human subjects is without effect on the growth of the hair.

2. Cutting the posterior root of the second cervical nerve in man is without influence on the hair although Joseph claimed to have produced alopecia in cats and rab-

bits by this procedure.

3. Cutting the entire supply of sympathetic nervous system to the scalp is without influence on the hair.

4. Correlation of these facts indicates that alopecia areata is not a trophoneurosis.

"One is led to suspect that the patchy fall of hair is due to interference with the vascular supply, which in turn would result from vasoconstriction of a vessel or vessels supplying the scalp." In the discussion of this paper, Dr. F. D. Weidman says, "There are many reports in the veterinary literature showing that pressure on the nerves does cause total alopecia." Dr. Wright (122) suggested that hair continues to grow in Thiersch grafts.

It is of interest to note that the tissues of the embryo are probably not dependent upon the nervous system for a trophic influence. Wound healing is the same in embryos of different ages, and whether the peripheral nervous system has developed or not. (Poynter (87)) Sherrington (99) describes a full grown amyelous fetus; the cord and brain were entirely absent and the only representatives of the central nervous system were the dorsal ganglion cells and their processes, which formed an almost normal appearing peripheral nerve pattern. Yet the skeletal muscles and their fibers revealed no obvious departure from the normal. Destruction of the ventral horn cells after birth results in rapid degeneration of the fibers of skeletal muscle, and a trophic effect of the anter-

ior horn cells is thereby postulated. Here the muscles developed and were in a normal state without having ever had an efferent innervation. The bones, skin, and other tissues of the body were all well developed, and the microscopical pictures were normal. "The trophic influence of the motor nerve cells must therefore lie still in abeyance during the period of foetal life. Perhaps the muscular degeneration of later periods is more rightly apprehended as a result of forced inactivity in paralysed muscles accustomed to be active, and not strictly of loss of a pure trophic influence exerted on them by nerve cells."

Wischnewsky (118) produced a chronic trophic ulcer in a dog by irritation of the central end of a divided nerve. If neurotomy is performed, healing results in most cases. This phenomena was confirmed clinically in forty-five cases, of which twenty-five chronic ulcers due to irritation of a nerve were healed by neurotomy in two years, seven recurred, and thirteen were considered failures or partial results.

Stephani (Goodhart (40)) investigated the trophic action of the nervous system upon body metabolism on the basis of animal experiments, and concluded a "direct regulatory influence on general metabolism".

Completely desympathectomized cats (Kuntz (57)) lived successfully under the protection of laboratory life, bearing and nursing their young, and otherwise living a normal life. They were unable to withstand changes in temperature

or activity, however, and failed in adjusting to a variable environment.

Mott and Sherrington (21) found that section of the dorsal roots in monkeys causes ulceration of the feet, not of the hands, "due doubtless to the removal of the defensive mechanism afforded by sensitivity, and to infections of the injured skin."

Head and Sherren (46) have shown that diminution in the growth of the fingernails occurs as readily when the hands and fingers are immobilized by splinting as when they are paralyzed by a lesion of the median and ulnar nerves. Also that in the case of the latter, they will grow with normal speed when massage is practiced daily.

Muscular Atrophy:

A great many reports of the muscular atrophy following degeneration may be found, and the histological picture has been studied in detail at various stages of degeneration, but no explanation of the mechanism of the action of the nerve is found.

It has been determined that the muscle spindles are preserved for considerable periods after the muscular atrophy resulting from denervation, although the sensory nerve terminal begins to degenerate twenty-four to forty-eight hours before any definite changes are observed in the myelinated part of the nerve fiber. (Horsley (50)) Batten (5), Feldburg (38), and Tower (109) have made at-

tempts to determine the trophic influence of the sympathetic nervous system upon skeletal muscles. Many investigations have been made of the effect of the sympathetic innervation of muscle upon muscle tonus, fatiguability, and power. (Coman (28)) Yet the existence of the sympathetic innervation of muscle, and its nature are still in debate. (11, 49, 59, 89, 116, 120)

As early as 1876 is was found that the taste buds degenerated after section of their sensory nerve. These observations have been confirmed and supplemented repeatedly, and similar observations were made upon the lateral line organs of fishes. Regeneration of these organs follows regeneration of the nerve and only at that time.

According to Benisty (6) the Paccinian corpuscles and Meissner's corpuscles have a double innervation; a large myelinated fiber, and a small, often unmyelinated fiber. "We are therefore inclined to think that an irritation of the nerve trunk in the wound (in causalgia) is transmitted by centrifugal fibers to the sensory corpuscles causing intense pain spontaneously as well as by an external irritant." These fibers are described as affecting especially the small capillaries about the nerve endings. A difference between this trophic effect and that of simple vascular dysfunction is emphasized. (6) These trophic impulses coursing peripherally along sensory nerves are described by some as antidromal inpulses of the sensory nerves. Others postulate an autonomic fiber coursing with, or within, the

sensory nerve.

Meyer and Bruce regard antidromic phenomenon as being in the nature of an axone reflex. (102) The following experiment serves to illustrate the axone reflex and its importance in the health of tissue locally. If a sensory nerve is cut, cutaneous irritation still produces redness and inflammation. But if time is allowed for degeneration of the nerve, the reaction does not occur. (102)

However certain vasomotor responses, particularly the histamine wheal reaction, will occur in a completely denervated area. The local hormonal vasomotor control is quite significant. It was found that animals continue to live and maintain normal vascular tone after the posterior pituitary, adrenal medulla, and the entire sympathetic nervous system were removed.

DISCUSSION

A Classification of Lesions According to Degree of Neurotrophic Influence:

In general, the trophic lesions may be divided into groups according to the apparent significance of the nervous lesion.

Group I: Those of questionable neurotrophic effect, which are associated with other etiological factors adequate to account for the lesion.

Group II: Those associated with disturbances of innervation which may consist only of absence of nerve impulses other than "trophic". In these, the absence of sensory defense mechanism, and the circulatory abnormality due to interference with the nervous vasomotor reflexes may cause a diminution of vitality and resistance to otherwise innocuous trauma. Examples of this type are corneal ulcers developing rapidly after denervation, "acute" decubitus, perforating ulcers of tabes and syringomyelia, and the Charcot joint. The characteristic feature is a failure of the normal defense reaction of tissue to ordinary trauma.

Group III: The third type of lesion is most characteristic of a definite neurotrophic effect, occurring irrespective of external influence, often unaccompanied by marked vasomotor change, and directly associated with a nerve lesion. Examples of this type are herpes zoster, the denervation atrophy of taste-buds, muscles, and glands, acute decubitus appearing in areas protected from pressure and irritation, gastric erosions following nerve injury, and certain derm-

atological lesions accompanying nerve injuries and not explained by vasomotor change.

Classification According to Type of Nerve Involvement:

Some characteristic differences in the trophic effect seem to be characteristic of the type of nerve lesion; whether motor or sensory; irritative or paralytic.

1. The interruption of motor nerve impulses has the most characteristic influence upon muscles and glands, and assuming this effect to be trophic, it may be said that all effectors are subject to trophic disturbances when denervated. It does not seem plausible to account for this effect by only the absence of normal stimulus to activity provided by the nerve. Neither is it satisfactory to postulate on theory alone the loss of a specific trophic nerve impulse.

Tissue changes following involvement of the autonomic efferent neurones are usually accompanied by vasomotor changes, which complicate the consideration of any purely neurotrophic autonomic impulse. Vasomotor changes also accompany lesions of somatic motor nerves, and may be a factor in the atrophy of muscles. The sympathetic innervation of muscles, if established, may prove to exert a trophic effect.

2. An irritative lesion of the motor nerves may influence nutrition of tissue by vasomotor activity or by hyperfunction of the supposed trophic fibers. Hypertrophy

of muscles and glands due to excessive stimulation and use are generally considered to be due to increased metabolism and a response to increased activity. But this does not really explain the hypertrophy, which may be due to over-stimulation of trophic fibers.

3. The interruption of afferent impulses may affect the innervated tissue in a number of ways, so that an appreciation of a possible trophic effect is difficult. There is a loss of a protective mechanism, exposing the tissue to unappreciated trauma and neglect. There is a loss of autonomic reflexes which normally adjust the vascular supply to variable environmental factors of stress. The responses dependent upon the axone reflex are lost if the peripheral nerve degenerated. And finally, a trophic effect of the sensory nerve may be lost, whether due to an antidromal impulse, or a trophic efferent neurone accompanying the sensory neurone, or a trophic effect sustained by the presence of the sensory innervation. The degeneration of the taste-buds is the most striking example of this type of nerve involvement.

4. The irritative lesions are more apt to produce trophic changes than any other type of sensory nerve lesion. (c. f. herpes zoster, causalgia) Here the antidromal effect of an efferent impulse passing outward along the sensory nerve seems significant. A pathological reflex may be in fault, exerting its effect by way of the motor nerves.

5. Disturbances of the nerve impulse in which there

is no demonstrable organic lesion may cause tissue changes, as evidenced by the trophic lesions accompanying psychic disorders.

Consideration of the Etiological Factors:

1. External factors of pressure, stasis, minor injury, infection, and irritation have been discussed. In group I these factors are primary; in group II they are significant only because the tissue has lost its normal resistance to them, and they become precipitating causes; in group III they are at a minimum, and obviously other causes must be present to account for the lesions.

2. Circulatory change.

The trophic effect of circulatory abnormality, per se, is often marked, and is probably a contributory factor in most of the trophic lesions, but it is difficult to account for all of the neurotrophic lesions on this basis alone.

Circulatory changes due to non-nervous causes may result from stasis, pressure, arteriosclerosis, varicose veins, endarteritis, thrombosis, and embolism. Generalized circulatory impairment may result from old age, debility, and heart disease. These may cause ulcers, atrophy, and gangrene, but not the characteristic lesions accompanying nerve involvement.

Neurocirculatory changes are marked in some trophic conditions, and the mechanism of their action is quite well

established in some instances. Thus the nervous system may produce trophic changes through the circulatory system without exerting a direct neurotrophic influence on the tissues themselves. Raynaud's disease, erythromelalgia, and the vasomotor changes in various nerve lesions are examples. But unless severe, or accompanied by definite external factors, these circulatory disturbances do not usually provoke definite trophic lesions spontaneously. In addition, these lesions do not parallel the ones associated with involvement of the nerves to the tissues themselves.

However, the mechanism of control of the circulatory system is still largely unknown, in spite of the recent advances in the understanding of the physiology of the peripheral vessels. This is particularly true of the regulation of the local vascular supply of the tissues. Recent investigation reveals an inherent mechanism of vascular control not entirely under nervous influence, maintained by a hormonal mechanism of the tissues, and of great significance in the adjustment of normal local nutrition. Histamine, acetyl choline, adenocine, and kallikrine are the best known of these hormones. They are present in the tissues, are liberated or formed there, and produce their action locally. They are active in very small amounts, and have definite pharmacological effects on arteriolar constriction and dilitation, and capillary size and permeability. Their relation to the nervous system and other hormones and enzymes in the body is complex and not well known. It

may be found, when these substances are well understood, that the influence of the nervous system upon nutrition is accomplished not only by direct innervation of the peripheral vessels but also by an influence upon the formation and liberation of these hormones, which in turn affect the nutrition of tissues locally by an action on the peripheral vessels more significant in the production of neurotrophic lesions than the present concept of neurocirculatory control can explain. (Morgulis)

3. The Neurotrophic Factor

When all of the above factors are considered, the pathological process in the trophic lesions is still not adequately explained. Why does a "pressure sore" in an area of nerve involvement continue to progress long after the original slough has fallen away, and pressure is no longer present? Why do certain lesions associated with nerve involvement, but explained by the loss of sensory defense mechanism, also occur similarly where anesthesia is not a feature? Neurocirculatory change of itself produces none of the marked lesions seen in some trophic lesions. Simple hyperemia of arteriolar dilitation causes hypertrophy; protracted arteriolar constriction causes overgrowth of connective tissue elements at the expense of the more specialized structures, and occasionally necrosis and gangrene. But typical "neurotrophic" lesions occur spontaneously and rapidly following the nerve lesion, are limited to the area of nerve involvement (not the area of vascular change), and

do not progress by stages as do the lesions in which circulatory dysfunction and external influence are factors. The many theories of this apparently "true trophic" action are open to criticism.

An interesting suggestion of the probable source of future significant information is presented by Parker (80) in his discussion of the neurohumoral theory. An intimate inter-relation between nervous activity and humoral control is evidenced by the autonomic nervous system and its relation to the endocrine glands and pharmacological actions. Progress in "auto-pharmacology" indicates that the hormonal mechanism is to replace the nervous system as the principal regulator and co-ordinator of all types of bodily reactions.

Parker reviews the studies of the neurohumoral relationship in the control of the chromatophores in fishes and amphibians. It was found that even when the cells were specifically innervated by nerve fibers, that the mechanism of their contraction and expansion depended upon the local formation of hormonal substances; and these chromatophores responded similarly to local injection or blood stream distribution of these hormones after extraction, as well as responding to certain drugs of hormonal nature.

No such conclusive experimental evidence indicates definitely that other motor nerves or sensory or intermediate neurones produce their characteristic actions by this same mechanism. But the evidence at hand indicates that this will probably be found to be the case. Recent work

on the physiology of smooth muscle stimulation indicates a neuro-humoral mechanism. The nervous regulation of heart action is accomplished by a pharmacological action. There is even suggestive evidence that the nerves to skeletal muscles secrete a substance at the nerve terminal upon which the subsequent contraction depends. There is also some evidence that end-organs stimulate the peripheral filaments of sensory nerves in this manner. Experimental work on the staining reactions of the opposing poles of the macrosynapse of the giant fibers of the earthworm strongly suggests that the synapses within the central nervous system function by means of a neuro-humoral substance.

In discussing the degeneration of lateral line organs and taste-buds following denervation, Parker says, "In both these instances the influence of the nervous part of the mechanism on the secondary cell is obviously trophic,.... a strictly neuro-humoral relationship. ...Both these examples are good instances of the independence of the normal nerve impulse and the trophic influence that passes over a nerve fiber to keep its sense cells intact..... If sensory nerve fibers are continually transmitting trophic impulses peripherally and thereby controlling the life of distally situated groups of sensory cells, may it not be possible that to some extent at least, the common cutaneous sensory nerves play a somewhat similar part in maintaining a normal state in the epidermal layers of the skin?" He then discusses herpes zoster. "Since this disease is a disturbance in the

sensory fibers..... is it not possible that its obvious external symptom is due to abnormal secretions from the integumentary nerve terminals induced by the deeper nerve disturbance? Such an interpretation, though purely hypothetical, shows a possible application of the neuro-humoral principle already advanced.....From the standpoint of the trophic activities of receptor neurones, there is already much recorded that indicates, without being finally conclusive, that neuro-humoral activities pervade the receptor portion of the nervous system... and there is no obstacle to the application of this hypothesis."

He concludes with the statement that there is much uncertainty, due to the novelty of the concept, but that the little that is known is in favor of neuro-humoralism.

Conclusion:

The opinions of the pathogenesis of neurotrophic lesions are largely conjectures, and are open to criticism.

The problem is significant from the standpoint of the fundamental neurological principles involved, as well as the clinical application.

Many inviting problems for investigation are suggested, and it is upon the solution of these that an understanding of these neurotrophic phenomena depend.

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