there are multiple references to studies of the nervous system in uræmia, cholæmia, coprostasis, adrenal cachexia, thyreoid cachexia, experimental glycosuria, insomnia, and the auto-intoxications following burns. Finally, the alterations in the neurones, occurring in a whole series of infectious diseases, have been examined and studied; tetanus, diphtheria, hydrophobia, bubonic plague, yellow fever, botulismus, septicæmia due to various micro-organisms, anthrax, infectious peritonitis are among the number. It would be beyond the scope of this article to discuss these in detail, and besides Barbacci has given an excellent epitome of the whole subject in his collective review, to which in this section reference has so frequently been made. Perhaps nothing better can be done, under the circumstances, than to quote Barbacci's summing up of the whole matter. It is his opinion that the alterations perceptible in the nerve cell under various conditions are best understood as follows: "When a harmful influence affects the nerve cell, two series of processes are possible: either the harmful influence is so intense that it quickly kills the cell, in which event the microscopic picture shows only the typical signs of cell necrosis; tigrolysis has neither time nor reason for appearance. The alterations of the protoplasmic masses, and especially those of the nucleus, are those which betray the effect of the morbid causative agent. If, on the other hand, the intensity is less, the cell reacts powerfully at first against the abnormal stimulus and uses up, in the exertion of the reaction, its reserve supply of nutriment more or less quickly. Herein we see the significance of tigrolysis; it is the expression, simply of a phenomenon of reaction. If during this first phase the total activity of the pathological stimulus becomes exhausted, the alterations in the cell progress no farther and the normal condition is quickly regained, the reserve supply of tigroid substance being quickly restored. In this phase of the reaction, the neurones retain their functional capacity unaltered—a fact which explains very well the striking contradictions between the anatomical findings and the clinical symptoms in many affections. During the development of a disease the nervous system may betray no symptoms which would indicate alterations taking place in it, and yet its elements, on microscopic examination, show that extensive tigrolytic processes have already occurred. This is seen especially frequently in infections and intoxications, and particularly in those which follow an acute course. But when the influence of the noxa continues to act upon the neurone after the latter has exhausted all its reactive powers, it becomes affected in its most vital parts and degeneration follows upon the reaction. The cell is irretrievably condemned to death, and the microscopic specimens show most often only the signs of a cell cadaver."

It would seem not unlikely that our knowledge of the general pathology of the neurone will be materially increased through the extension of experimental pharmacology, and of those modern researches which are attempting to explain the phenomena of immunity. A start has already been made in the investigations which bear upon the relations of the chemical constitution of bodies to their distribution in the organism and their pharmacological effects. Since Stahlschmidt, in 1859, proved that strychnine could be robbed of its tetanizing effect through the introduction into it of one methyl group, and so be transformed into a paralyzant, not unlike curare, interest in such problems has rapidly grown. It was soon shown by other investigators that other ammonium bases, derivable from various alkaloids, possess properties not unlike those of curare—a fact of the highest interest, since Böhm has since demonstrated that curarine itself is an ammonium base.

The work which has been done upon artificial antipyretics has furthered the ideas under consideration. The synthetic preparation of antipyrin and phenacetin may be mentioned as an illustration. It has been shown that the antipyretic effect of aniline derivatives and amidophenol derivatives like phenacetin, is proportional, within certain limits, to the amount of para-amido-phenol which is split off in the organism, and it has been demonstrated that the introduction of acid salt-forming residues (like $SO_3H$ and $CO_2H$) prevents the antipyretic power of such substances. Again the studies upon cocaine and allied bodies support the same principle. It has been shown that it is the benzoyl residue which in cocaine gives it its anæsthetic power. It was a knowledge of this fact which led to the synthetic manufacture of new anæsthetics which contain the anæsthesiophore benzoyl group as their active agents; thus eucaine, orthoform, and nirvanin have been made available. The somniferous effect of the introduction of ethyl groups into molecules has been adduced as further evidence along these lines. Sulfonal, amylene hydrate, alcohol, and dulcin all owe their specific properties largely to the ethyl groups contained in their molecules.

Ehrlich's studies upon the staining of the living nerve tissues by a certain small number of basic aniline dyes (methylene blue, Bismarck brown, chrysoidin, neutral red, etc.) is calculated to throw some light upon the subject. He has shown that these neurotropic dyes entirely lose this power if a sulpho-acid group be introduced into their molecules. The introduction of the acid group alters the distribution in the organism and completely destroys the neurotropic properties. Ehrlich has pointed out as specially significant the fact that the majority of basic dyes which stain the living brain substance have also an affinity for adipose tissue. In other words, neurotropy and lipotropy are intimately connected with one another. It is obvious, therefore, that when substances are ditropic or polytropic their distribution in the organism, and with it their pharmacological effect, will vary more or less with the quantitative relations of the tissues for which they have affinity. Thus the poisons which have at the same time neurotropic and lipotropic effects, if administered in equal amounts per kilogram of body weight, will have a much more marked influence upon the nervous system in an emaciated animal than in one which is very fat; for, according to the *loi de partage*, much more poison will be taken up by the brain.

One of the most important questions which we meet with is that which deals with the reason why certain tissues are selected by certain chemical substances. That the reasons are chemical in nature seems very probable. It is well known, however, that certain indifferent substances possess neither basic nor acid characters; and when introduced into the organism, though they have no marked chemical affinities, they nevertheless often exercise extremely toxic effects. This is true, for example, of ether, alcohol, and various narcotics. In such cases it is thought that direct chemical affinities on the part of the organism are not concerned, but that we have to deal with a sort of contact effect, due to the influence of unaltered and chemically unbound molecules present among the constituents of the tissue. But if this is true, what is it that determines the typical localization of these compounds in certain tissues, such as those of the central nervous system? Ehrlich has compared this kind of localization with the principle of the Stas-Otto extraction procedure. Writing in 1887 he said: "The principle of the mode of extracting poisons introduced by Stas-Otto is based on the fact that in general basic bodies, like the alkaloids, enter into firm chemical combination in acid solutions, and hence can only with difficulty be extracted, while they can easily be shaken out of alkaline solutions. Acid compounds show, of course, the opposite behavior, since they are held firmly in alkaline media, but are easily given up by acid media. If we transfer these principles to the questions in which we are here interested we can easily understand why basic dyes, particularly those which are not retained in the blood by chemical affinities, are preferably taken up by the brain, while the acid dyes and sulpho-acids which are firmly held by the alkalies of the blood in the form of salt, and, as it were, are anchored there, show exactly the opposite behavior." Ehrlich's observations that adipose tissue takes up many substances which are also taken up by the brain is significant when added to the finding of Pohl in 1891, that the





receptivity of the red blood corpuscles for chloroform depends upon the presence in the corpuscles of cholesterin and lecithin, and to his conclusion that the relation of the chloroform to the nerve tissues of the brain is dependent upon the existence of substances of a fatty nature in the brain. These studies afforded the basis for more accurate examinations of the cerebral effects of those substances which are easily soluble in fats and fat-like compounds. That these examinations have been fruitful will be clearly seen from the work of Hans Meyer on alcohol narcosis, and that of H. Overton on the causal relations existing between solubility in fat and narcotic effects.

But this loose contact effect of poison upon the brain and spinal cord will not explain another series of intoxications due to bodies like the antipyretics, various substances of a basic nature (alkaloids and phenols) which are not chemically indifferent, but, on the contrary, may be capable of entering into actual synthetic relations with the tissue cells. Loew suggested some years ago the existence in protoplasm of definite atomic groups endowed with powerful affinities; to these atomic complexes he ascribes an important rôle in the phenomena of intoxication. It was his opinion that atomic groups, on the one hand, perhaps, of the nature of aldehyde groups, on the other hand, the labile amido groups, were active in the protoplasm proper in catching hold of chemical substances circulating near them, and for which they had an affinity. Any compound, he thought, which could combine with either of these atomic groups could act as a protoplasmic poison; and the greater its affinity for these groups the stronger its toxic effect. But Ehrlich's experiments with aniline dyes speak against such a substitutive action of poisons, at least of poisons like the alkaloids; for most of them can be extracted from the tissues by indifferent solvents, and this would scarcely be the case if chemical combination with the protoplasm took place. Ehrlich assumes, on the other hand, that only two modes of explanation are possible, and that in one case one may be true, in another case the other. The one explanation is based upon Knecht's theory of the action of dyes depending upon the formation of insoluble salt-like compounds. Pfeffer, in studying the vital staining of plant cells, has convinced himself that the staining is due to the precipitation of granules of the difficultly soluble tannate of methylene blue. In animal cells the affinity of the tissue for an alkaloid might be due to the formation of a salt with nucleinic acid, or with various products of secretion present in the cell; that is to say, with substances in the protoplasm rather than with the protoplasm proper. The second possibility which Ehrlich sees lies in the probability of the formation under certain circumstances of so-called "solid solutions" (*feste Lösungen* of van't Hoff), a view which Witt has advanced in dye chemistry. Possibly, as he suggests, the distribution of an alkaloid in the organism sometimes depends upon both causes, the selection being due to a combination of "salt formation" and of "solid solution."

There is a class of poisons, however, quite different from all these thus far mentioned, poisons which like foodstuffs may actually enter into the molecules of the protoplasm proper and be *fixed* in the protoplasm and become non-extractable by indifferent solvents; for such poisons a view like that advanced by Lœw would be more applicable. Sugar residues, for example, cannot be withdrawn from the cells by simple solvents; they must first be split off by acids in order that they may be obtained in a free condition. For such chemical anchorage, as in all syntheses, two combining groups of maximal chemical affinity must be assumed to exist, one in the cells designated by Ehrlich as a "side chain" or "receptor," the other in the food-stuff molecule and called by him a "haptophore" group. Ehrlich assumes that living protoplasm is supplied with a large series of such "side chains" (*Seitenketten*), which by virtue of their chemical constitution have the power to anchor the various kinds of food-stuffs; in other words, the activities of such side chains underlie the phenomena of cellular metabolism. It is this "side-chain theory" also which forms the basis of Ehrlich's doctrine regarding the action of bacterial toxins and the production of antibodies. He believes that the toxins, like the food-stuffs, possess definite haptophore groups which, uniting with corresponding receptors in the protoplasm-molecules of the cells, permit the toxic effect. As a result of the throwing out of function of these receptors the cells "regenerate" new receptors of the same kind in excess, many of them being thrown off into the blood to form "antitoxins." Only such poisons as possess haptophore groups can give rise to the formation of antibodies; against alkaloids, glucosides, or the antipyretic substances, no true immunity can be produced.

In tetanus, to take a concrete example, the symptoms all point to an intoxication of the central nervous system. According to Ehrlich's side-chain theory, the poison acts on the nerve cells because its haptophore group combines with corresponding receptors in the nerve cells. Tetanus antitoxin consists of such receptors regenerated in excess and thrown off into the circulating blood. When tetanus poison enters the blood of an immunized animal it is bound by these receptors and the side chains in the nerve cells themselves are protected. Wassermann has shown that the normal tissue of the central nervous system of most animals that are susceptible to tetanus is capable of entering *in vitro* into firm combination with tetanus poison, and that a mixture of normal nerve tissue and tetanus poison is harmless when introduced into animals, because the haptophore groups of the poison are saturated with receptors, and so cannot combine with the living nerve tissues of the animal under experiment. Other organs of the body do not combine with the tetanus poison *in vitro*.

Interesting, too, in connection with the pathology of the neurone is another series of facts—those bearing upon specific cytotoxins. It is now known that the injection of the red blood corpuscles of a species *a* into a species *b* leads to the development in the blood serum of species *b* of specific products of reaction which are highly toxic to the corpuscles of species *a*. These toxic substances are the so-called specific hæmolysins. Delzenne and Madame Metchnikoff, by treating animals with the central nerve tissues of other species, have been able to prepare a specific highly neurotoxic serum. Small amounts of this serum injected into the cerebrum of species *a* caused paralysis and epileptiform convulsions. Experiments made with other cells give similar results; thus specific leucotoxins (for the white blood corpuscles) and specific spermotoxins (for spermatozoa) have been produced. The fact that anti-hæmolysins and anti-leucotoxins can be made experimentally is very hopeful for the future of therapy.

Along the pathways just indicated the hope of the experimental pathologist and therapeutist would seem to lie. But an immense amount of work must yet be done before extensive practical application of these ideas in clinical neurology may be expected.

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REFERENCES BEARING UPON INTOXICATIONS OF THE NEURONE.

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**NEUROSES, PROFESSIONAL.** See *Hands and Fingers, etc.*

**NEUROSES, TRAUMATIC.** See *Nervous System. Traumatic Affections of.*

**NEUROSES, TROPHIC.** — DEFINITION. — Derangements of nutrition determined by variations in the supply of nervous energy, without observable change in the nerve tissues.

The study of the diseases usually included under this head is in large part a matter of the last few years. Several members have been added to the group, and those known for a longer time have been more closely scrutinized and their phenomena described. In spite of this fact considerable doubt exists as to what particular diseases belong in this category. Authorities differ a good deal in regard to the nature of some of the diseases and their ultimate causes. In order to obtain an adequate conception of the general features of trophic disorders it is necessary to consider with them some of the vaso-motor diseases. Nourishment and decay are closely and necessarily linked with the blood supply; this latter is varied, at least in quantity, by a special nervous mechanism constituting the cardio-vaso-motor system, so that the action of the nervous system on nutrition must be divided into its direct action, and the one exerted through the vaso-motors.

It is obviously impracticable to include in the group all neuroses associated with trophic change. Nutrition is profoundly affected in many, somewhat affected in most of the neuroses, including such widely varying diseases as chorea, epilepsy, and various neuralgias. Overgrowth or decay should be the predominant and essential feature of the process, and should affect specific structures. The results of ordinary vaso-motor action and mere connective-tissue hyperplasias should not be classed as trophic disorders.

It is first to be noted that a neurosis is properly a nervous disease without observable organic basis in the nerve tissues. It will not be here used in its broader sense of nervous disease, whether organic or functional, as the trophoneuroses would then of necessity include diseases (syringomyelia, poliomyelitis, neuritis, and many others) which, although accompanied by trophic changes in various tissues, are evidently not contemplated in the present classification.

Granted that the changes in these diseases may occur under the immediate influence of the nervous system, whether by so-called trophic nerves or otherwise, there still remains the question whether the nerve changes are determined by the action of poisons or take place as a result of inherited or acquired tendency or from other causes. Nutritional and degenerative abnormalities are usually the result of poisons taken into the body from without, or formed in the body by bacterial or glandular action. The idea that there are purely functional disorders without organic change is being much modified, and is giving place to the conception of function as varied by changes of structure or of environment, and especially by variations of the blood supply and blood content. Especially in the group of diseases known as the trophoneuroses the symptoms from which the patient suffers are almost exclusively those of obvious organic change in the most various tissues. To suppose a functional basis for such changes is a theory to be adopted, if at all, after a careful scrutiny of the facts.

The idea of trophoneuroses is suggested by analogy from the muscular atrophy that supervenes on destruction of the fibres of motor nerves or of motor ganglion cells in the cord. While trophic changes in such diseases as tabes and syringomyelia suggest the possibility of tissue death from deficient innervation alone, facts are rapidly accumulating which tend to show that some trophic diseases formerly classed as neuroses are in reality vaso-motor and trophic disorders determined by lack or superabundance of secretion of some of the ductless glands. The discovery of the importance of the secretion of the thyroid gland in myxœdema, cretinism, and possibly scleroderma, and the close relationship of the latter in its varied forms with the atrophies and hypertrophies, facial hemiatrophy, acromegaly, and other diseases has thrown much light on nutritional variations.

With these facts in view it will be well critically to examine the diseases sometimes classed as trophoneuroses, so as to find out which, if any, of them are entitled to a place in this category.

Acroparæsthesia affects mainly women who are much exposed to cold, and especially those who have their hands much in cold water. The symptoms are numbness and tingling of the extremities, especially of the hands, sometimes increasing to burning or tearing pains. There may be either hyperæsthesia or anæsthesia, and analgesia, usually of moderate degree. The symptoms do not follow the distribution of any nerve or nerves. The sensory symptoms constitute the essential elements of the disease. Vaso-motor phenomena are sometimes added, and consist of either redness or blanching of the hands. Nutritional changes are slight and unessential.

The fact that vaso-motor symptoms are variable and sometimes absent indicates that the disease is an affection of the sensory nerves, possibly a hyperæmia or low grade of inflammation. The efficiency of ergot in controlling the symptoms makes this view probable. The disease usually runs a long but mild course.

Angioneurotic œdema is the name given to œdematous swellings which occur suddenly in various parts of the body, sometimes without apparent cause, sometimes on exposure to cold. The swellings do not pit on pressure; they may be white or pink in color; they disappear completely. The neurotic nature of the disease is sufficiently indicated by the skipping of the œdematous spots from one place to another, sometimes with a rapidity quite remarkable. It is not in any sense trophic, but is purely vaso-motor; sometimes, possibly always, on a toxic basis.

In many people of low vitality one or more fingers become white, cold, and corpse-like on plunging them into cold water in the morning, especially in winter. These are the so-called "dead fingers." The blanching in severe cases may involve the hands and extend to the elbows, or even to the shoulders. Numbness and tingling are present but moderate. The phenomena soon pass off when the hands are warmed by the fire. The disease is not dangerous, nor even threatening except in some cases in which vascular spasm may be so great as to induce faintness. The condition is related on the one side to acroparæsthesia; on the other to Raynaud's disease, the first stage of which it may simulate. Trophic features are absent. A more profound affection of the vaso-motors is seen in Raynaud's disease, one essentially of vascular spasm of extreme degree. The stages of blanching, of local asphyxia with blackish discoloration and of gangrene, are those of tissue death rather than of retrogressive metamorphosis. These phenomena are vaso-motor. There are, to be sure, trophic symptoms in many cases, amounting to marked scleroderma. The fact that scleroderma may exist without perceptible vaso-motor change, that in Raynaud's disease blanching and local asphyxia may go on indefinitely without atrophy, and the lack of proof that there is any necessary connection between the two sets of phenomena, show the non-identity of the two diseases in spite of the existence of mixed forms. Vascular spasm of known origin is usually toxic. An extreme instance of this kind is seen in the gangrene of ergot poisoning. Organic lesion of the vaso-motor centres is also capable of setting up vascular spasm and gangrene. No poisons have been found to account for Raynaud's disease, and organic nerve lesions have not been discovered.

It is hardly necessary to discuss the question whether the foregoing diseases are essentially trophic. The symptoms are those of derangement of the vaso-motor system; variations of nutrition are not prominent and are absent in many cases. The ultimate cause of these diseases is an interesting problem, but is not germane to the present inquiry.

The general diseases connected with abnormalities of the thyroid gland are interesting instances along the boundary between the vaso-motor and the trophic. They have so lately been assigned to their proper place that they still often figure as trophic neuroses, and they are so closely related with the other diseases under discussion that they deserve a brief mention.

Exophthalmic goitre is characterized by vaso-motor phenomena with some secondary nervous manifestations. The rapid heart action, vascular enlargement of the thyroid gland, and bulging of the eyeballs point to an involvement of the sympathetic system, and tremor, nervousness, and vomiting make up the usual picture of the disease. There seems little doubt that the symptoms are caused by increased functional activity of the thyroid gland. The cause of this increase is not known, but there is no ground for thinking it a pure neurosis; and exophthalmic goitre now finds its place among the glandular affections. Changes of nutrition of the body tissues are great but not specific.





It is otherwise with myxœdema, a disease now known to be due to lowered function of the thyroid gland. The deposit of mucinous material in the skin, giving the characteristic œdematous appearance, is not a condition of overgrowth, and the changes in the kidneys, blood-vessels, and nerve tissues are degenerative, not trophic. The disease makes good its title to a place among trophic disorders chiefly by arrest of development in patients in whom the disease begins in childhood. To this condition the name of cretinoid idiocy is given. Its dependence on lack of secretion of a ductless gland (the thyroid), its improvement by administration of thyroid extract, and its close relationship with myxœdema are pregnant with suggestions in regard to trophic variations and many so-called trophic diseases. Meanwhile, in spite of the fact that trophic conditions are so largely present in cretinism, and are so closely simulated in myxœdema, neither of them is a neurosis, and neither of them is properly a trophic disease.

So far we have considered diseases that vary by more or less perceptible degrees from sensory into vaso-motor, and from vaso-motor into trophic phenomena. In few of them is trophic change entirely absent; and while sensory symptoms do not increase in proportion with the severity of the remaining symptoms, they are still present throughout the entire series. We now come to a disease in which sensory and vaso-motor symptoms play an entirely minor part, and in which changes mysterious in origin are apparently essentially trophic.

Scleroderma is a disease not, as its name implies, of the skin alone, but in its well-developed form is a wasting of the tissues in general, including skin, bones, muscles, mucous membranes. Clinically the present tendency of authorities is to include in the same category all cases, whether of atrophy limited to a small portion of the skin or of wasting of almost all of the tissues of the body, as in the terrible but happily rare instances of diffuse scleroderma. These cases have the one symptom of skin wasting in common, but it is improbable that they depend upon the same cause. In fact the partial cases, the so-called morphœa, have in some instances been shown to be due to organic changes in the nerve tissues, which is not the case with general scleroderma. The striking features of this disease are the atrophy without sensory disturbance, whether anæsthesia, hyperæsthesia, or pains other than the discomfort due to the shrinking tissues; and the absence of vaso-motor changes as an essential part of the phenomena. The latter is limited to a hyperæmia of moderate degree, shown in the lilac border about the patches of morphœa. Pathologically the tissues show a change into connective tissue and a disappearance of the normal elements.

That so profound and widespread changes as occur in well-marked scleroderma should be brought about by changes in the structure or functions of the nerve tissues without direct involvement of their more familiar functions, those connected with motion and sensation, is sufficiently improbable. We may leave out of account organic change in the nerve tissues. If such were present and could be shown with a fair degree of probability to be in causal relation to the symptoms, the disease would be assigned to the organic nerve diseases. Let us examine in brief the reasons usually urged for considering any disease neurotic in origin.

Symmetry of the lesions or of the symptoms is often supposed to indicate their nervous origin. It is sufficient to observe on this head that although the nervous system is symmetric, so are the other organs of the body. In especial the blood-vessels are in the main symmetrically disposed. Accordingly vascular disturbances, whether conditioned by blood supply or by blood content, are usually symmetric, except when determined by local causes, as heat, cold, violence, pressure. It is to be noted that of the two ways in which these agencies have their effect, one is by mechanical change, and the other is change of tissue through the action of the vaso-motors, so that asymmetry itself is in many cases the result of nerve action. While vascular action is usually symmetric, nerve action is not usually so. Walking is alternate, not symmetric action; the hands are sometimes moved together, usually separately; the finer motor acts, as of speech and writing are functions of one side of the brain; the possession of special sense organs in pairs is an instance of redundance for safety in case of accident rather than a necessary symmetric arrangement.

General sensibility is only symmetric in the sense that the whole of the skin and the other tissues is supplied; the very point and essential feature of the whole mechanism is the distinguishing of one side from the other and of one spot from another. In some special instances, as with contraction of both pupils from the impact of light on one retina, a bilateral result follows from a unilateral cause. Dilatation of the pupils, however, from an injection of atropine is not an instance of the same kind, but is determined by distribution of the poison to the sympathetic on both sides; excitation of the sympathetic in the neck on one side, by galvanism, and the action of atropine on the nerve filaments of one side, by instillation into the eye itself, are followed by dilatation of the pupil of the corresponding eye alone. These and other considerations of a like kind tend to show that symmetry of nerve action is usually the result of causes acting bilaterally.

The proposition that most nervous symptoms are not symmetric, and most symmetric symptoms are not nervous, is susceptible of easy proof, and lends little support to the inference often made that symmetric lesions are of nervous origin if not proved otherwise.

Another usual reason for considering a manifestation of any kind as of nervous origin is its association with so-called neurotic or hysteric symptoms, such as causeless laughing and crying, wandering anæsthesia, clavus, and the like. Leaving aside the inherent improbability that grave organic changes depend on vague and so-called nervous conditions, or that they have no better excuse for being than is implied by the insufficient and unnecessary word hysteria, we may at any rate leave this factor out of account in considering scleroderma, sufferers from which disease are singularly unemotional considering the hideous and destructive changes which they are undergoing.

Acromegaly is characterized by increase of size of the extremities, the hands, feet, and head; and this fact gives the name to the disease. The name, however, is a misnomer, for the enlargements are true hypertrophies affecting almost every organ in the body. The muscles are large, and in the early stages of the disease they are powerful. The bones are thickened and the subcutaneous tissues form great pads in the palms and soles. The lips protrude, there is an undershot lower jaw, the nose is big and bulbous. This is, however, only a superficial view, for the heart, the liver, the kidneys, and the spleen are also enlarged. The brain is increased in size, the skin is thick and coarse, and the voice is heavy from roughening of the vocal cords. When the disease begins in early life the general increase in size produces true gigantism. Marie's saying that "acromegaly is gigantism in the adult, gigantism is acromegaly in the adolescent," while only partly true, is accurate as regards many cases. One feature of the disease, the enlargement of the pituitary gland, early attracted Marie's attention. He considered this the cause of the disease. Further study brings to light the following difficulties in the way of this theory. First, not all cases show enlargement of the pituitary gland. In one case the gland was entirely absent. Second, the changes in the gland are not uniform but of the greatest possible variety. Third, many cases

of disease of the gland are reported in which no symptoms of acromegaly were present. Fourth, pituitary extract administered to patients does not control the disease as does thyroid extract in myxœdema. Last, and possibly most important of all, experimental removal of the hypophysis does not produce the symptoms of the disease in animals.

Disregarding for a moment the evidences in regard to the pituitary gland as the cause of the disease, let us consider the theory that acromegaly is primarily the result of disordered nerve action. The only alternative theory worth considering is that it is due to alterations in the blood supply, either quantitative or qualitative. In estimating comparatively the trophic influence on the tissues of nerve and blood supply, the balance is largely in favor of the blood in regard to the importance of its action. That nervous influences do affect nutrition is undoubted, especially in the case of the muscles and of the skin. It is to be observed, however, that even in these instances the muscles increase in size under stimulation, apparently as a result of the increased action of the muscle fibres and their increased vascularity, rather than as a result of any inherent trophic activity of the nerves supplying them. The muscle fibres disappear after the nerves are cut, not directly as a part of the degeneration of the nerve fibres, but as an indirect and remote result of their loss of function. Atrophies of the skin sometimes occur as the apparent result of nerve lesion, but usually there is only a limited amount of change, such as is seen in the glossy skin of neuritis and hemiplegia; ulcerative processes are in such cases probably the result of germ action from lowered resisting power rather than destructive processes the direct result of nerve lesion. But many of the tissues have a much less rich nerve supply than have the muscles and the skin. The widespread hypertrophies of acromegaly would, if of nervous origin, require for their explanation a trophic influence out of all proportion with the comparatively scanty facts at our disposal in regard to the trophic influence of the nervous system on the organs in general.

The blood supply we know, on the other hand, to be everywhere and always of vital importance in nutritional processes. To say that nutrition is always carried on by the blood supply is a platitude, but in this connection it needs statement. The nervous system, when it affects nutrition through the blood-vessels, does so by changing their calibre. In acromegaly congestions play no part in the clinical phenomena. We are driven to the conclusion that, so far as we know, the hypertrophies in acromegaly are due to qualitative changes in the blood; whether these changes consist in an increased or deficient secretion from the ductless glands, the pituitary or the thyroid or both, it remains for the future to determine.

Facial hemiatrophy is characterized by a wasting of all the tissues of one side of the face. The disease occurs at all ages. Various causes have been assigned, especially injury at the time of birth, blows, abscesses, infectious diseases, and cases have been reported in which it has followed division of the fifth nerve. The mechanism of its production is not apparent, as division of the nerve is usually not followed by it. On the other hand, although undoubted changes have been found in the fifth nerve in cases of apparently spontaneous development, the nerve has in these cases seemed to share in the general progress of the disease rather than to be primarily affected.

Severe neuralgic pains may usher in the disease, or it may begin quite painlessly as a small atrophic spot on the skin of the cheek, much like a sclerodermatous patch. The atrophy gradually involves more of the skin and the other tissues, especially the subcutaneous tissue and the bones. One-half of the tongue and the mucous membranes and other structures of the mouth of the affected side share in the process. The cranial bones are thinned and wasted, the forehead is furrowed, and the whole side of the face hollowed and much smaller than the other side. The hair and beard are thinner than normal.

The changes in the skin may be accompanied by anæsthesia, especially in cases in which the nerve trunks are much affected. Sensibility to tactile and painful impressions and the temperature sense may be retained, however, even when the skin and the other tissues are markedly atrophic. The muscles often show less change than do any of the other tissues. They may retain voluntary power and electric excitability, or may share in the general atrophy. Tears, saliva, and perspiration may be secreted normally on the affected side. The pupil remains normal and there is no change in the fundus of the eye.

The changes are progressive, but may come to a standstill at any time. The disease is not dangerous to life and the changes do not extend beyond the face, which it disfigures in a way very distressing to the patient. All known methods of treatment are quite ineffective. Electricity, massage, and cod-liver oil have been tried without much apparent effect. The relation of the nervous system to the disease is not definitely known.

*Hyperostosis cranii*, otherwise known as *leontiasis ossea*, is an enlargement of the bones of the head. The rest of the body tissues are not affected. The fact that the bones alone are enlarged brings the disease into interesting relation with the so-called progressive pulmonary osteo-arthropathy. The latter disease consists in an enlargement of the bones of the extremities, so that patients present a superficial resemblance with those afflicted with acromegaly. These patients, however, show no involvement of the head and no thickening of the soft parts; they lack the pads in the palms and soles, the roughening of the voice, the bulbous nose and thick lips of acromegaly, and simply show enlargement of the bones of the arms and legs, and chronic joint affection with creaking, pains, and resulting disability. While there is not always lung disease, as was at first thought, there is always toxæmia from some cause, tuberculosis, syphilis, gastrectasis among others. The changes in both these diseases are inflammatory, the osteitis in the one disease affecting not only the long bones but the joints as well, in the other the change being curiously limited to the bones of the head. Such peculiarities of distribution do not, in the writer's opinion, show that the poisons work primarily on the nervous system. A similar selective action is exercised by rheumatic poisons on certain joints, on the pericardium, the endocardium, at times the skin and meninges in different patients, and in the same patient at different times. The selective action of poisons is sometimes on the nervous system, at other times through the nervous system; but in these diseases there is nothing to show that the action is not on the affected tissues direct. The organs most richly supplied with nerves are not the ones affected, the nervous system shows no special sign of involvement, and osteitis, even though chronic and proliferating, is not a usual accompaniment of any known nerve change.

Two diseases which may be grouped together are *adiposis dolorosa* and *symmetrical lipomatosis*. Both are characterized by enormous deposits of fat; the essential difference is that in one the fat deposits are the seat of severe pains, in the other the nutritional changes are painless. The symmetry of the lesions, and in adiposis dolorosa the occurrence of pains, have been supposed to indicate a neurotic basis for the overgrowth of tissue. These diseases are certainly essentially trophic. They are both, however, to be traced to either syphilis or overindulgence in alcohol; that is, in either case to poisons which are necessarily symmetrically distributed by the blood stream, apart from any intervention of the nervous system. In the case of adiposis dolorosa it is still somewhat doubtful whether the symptoms are the expression of a separate disease process or are simply an extreme accumulation of fat and a low grade of neuritis, both common results of chronic alcohol poisoning. Symmetrical lipomatosis is a curious symptom of toxic origin.

Localized hypertrophies of varied distribution have been described. Facial hemihypertrophy is the analogue and opposite of facial hemiatrophy. It is much more rare. It is sometimes acquired, but may be congenital.





Hypertrophy of one-half the body has been described, and so also have hypertrophies of single limbs. One finger may be involved alone. These hypertrophies usually involve all the tissues. Nothing is known of their causation. The affected part may be unduly large at birth and may continue to grow or increase in size, or the enlargement may begin in later life. No cause has been traced for these strange variations from the normal, and in the absence of evidence to the contrary they must be regarded as the result of an innate tendency, possibly but not surely of an atavistic character.

Returning now to the criteria to be applied in distinguishing toxic from functional nervous diseases, we may observe that functional diseases are properly vicious habits set up in the nervous system by irritants or poisons, and are to be distinguished from symptoms due to their direct and continuing action. The poisons of most of the infectious diseases, as well as alcohol and other volatile poisons taken into the body from without, are apparently capable of leaving their impress on the nervous system, causing symptoms which long outlive their exciting cause. The action of toxins on the affected tissues themselves, and their action by indirection through the nervous system, are not always easy to distinguish. The symmetry of the lesions, as already pointed out, usually means simply bilateral diffusion through the blood stream; in the one case to symmetrically disposed nerve structures, in the other to the affected tissues direct. In especial when inflammatory lesions are the result, the chances are much in favor of direct toxic action and against intervening nerve action.

The above considerations warrant the following conclusions in regard to the diseases under discussion, which permit, however, the elements of a provisional classification only.

Acroparæsthesia is a sensory neurosis. Angioneurotic œdema is a sensori-vaso-motor and Raynaud's disease a vaso-motor neurosis. Exophthalmic goitre and myxœdema, including cretinism, are diseases of the thyroid gland; the first is characterized mainly by vaso-motor symptoms, the second with special trophic features when occurring in adolescence. *Hyperostosis cranii* and progressive osteoarthropathy are inflammatory diseases, the first probably, the second undoubtedly on a toxic basis. Acromegaly and scleroderma are trophic diseases, probably of toxic origin; the same may be said of *adiposis dolorosa* and symmetrical lipomatosis, but the poison in these diseases is usually if not always alcohol or the toxins of syphilis. Facial hemiatrophy and the localized hypertrophies are trophic diseases of unknown origin, possibly neurotic. *Henry S. Upson.*

**NEW-BORN, PATHOLOGY OF.**—The pathological conditions which may be present in the new-born at the time of birth, or which may develop during the first days of extra-uterine life are very numerous and of the greatest variety. These conditions are of great importance, not only from a scientific standpoint, but also from the fact that they may hinder or render impossible the normal delivery of the child, or cause its death either before, during, or following birth; or finally they may affect its after-development, either by giving rise to pathological states persisting throughout life, or by the establishment of such changes that death, though deferred to a later period, ultimately results.

The conditions known as congenital, further those pathological states acquired from the parents, the causes of still-birth, the disease processes incidental to delivery, the pathological conditions and diseases peculiar to the first days of life, are all to be considered in this connection. For convenience these conditions may be divided into the following groups: *Intrinsic*, inheritable conditions, arising either in the individual sexual cells or through germ variation; *anomalies of development*, due to extrinsic causes affecting the mother, abnormal conditions of the fœtal membranes, etc.; *infections* transmitted from the parents, particularly from the mother, acquired either during intra-uterine life, or during delivery, or after birth; *intoxications*, either acquired through the maternal blood, or auto-intoxications developing in intra- or extra-uterine life; *diseases of individual tissues, organs, or systems*, peculiar to the new born, idiopathic, or produced by infection, intoxication, etc.; *new-growths*, developing in intra-uterine life or immediately after birth.

The Autopsy of the New-born.—The methods employed in the autopsy of the new-born differ in a number of details from the ordinary autopsy technique. These differences are dependent partly upon different anatomical conditions, and partly upon certain procedures which are of great importance in the determination of certain pathological or medico-legal questions. In other respects the autopsy methods are the same as those given under the head of "Autopsy" (Vol. I., page 649). The chief points of difference are as follows:

1. *Section of Spinal Cord.*—The spinal canal is opened by cutting through the laminæ with the curved bone shears.

2. *Section of Cranium.*—After the removal of the scalp the skull cap is opened in the median line, in the posterior angle of the great fontanel. By means of the curved bone scissors the longitudinal sinus is then opened both anteriorly and posteriorly by cutting through the bone in the line of the sagittal suture. The sutures between the frontal and parietal bones and between the parietal and occipital are then cut through from above, downward to the sides of the cranium, far enough to expose the brain sufficiently for its safe removal. The dura being adherent to the inner surface of the skull cap is cut through and turned back with the bones. The two halves of the frontal bone, the parietal and occipital, are pressed back from the brain at the level of greatest circumference. If the head is to be restored the bones are held back by an assistant while the brain is removed, otherwise the bones and dura are cut through at the level of greatest circumference and removed. The anterior falx is then cut and the brain removed, as in the adult.

3. *Section of Thorax, Neck, and Abdomen.*—A small block of wood is placed beneath the lumbar vertebræ. The main incision is then made in the median line, downward from the thyroid cartilage, dividing just above the umbilicus into two diverging cuts, extending on each side of the umbilicus to the pubis. The abdominal cavity is then opened just below the ensiform cartilage, and the opening extended in the line of the skin incision, passing to the left of the umbilicus. The right flap of the abdominal wall is then lifted and turned over to the right, while the umbilical vessels are dissected from their peritoneal covering and slit open toward the liver and toward the umbilicus. The skin incision passing to the right of the umbilicus is now extended downward through the abdominal wall, severing the umbilical vessels. The flap of abdominal wall between the two diverging incisions is now turned back over the symphysis and the two diverging umbilical arteries are exposed, the urachus and bladder lying between them. The arteries are now exposed by careful dissection, cut through at the umbilicus, and slit open.

The thorax is opened by cutting through the ribs instead of the cartilages in order to obtain more room. This may be done with the bone shears or a dull knife. The thymus gland is first examined and then removed. After the opening of the four heart chambers the ductus Botalli is carefully examined. This is done by extending the incision through the conus of the pulmonary artery and through the wall of the artery. The ductus Botalli is then found and probed. When the thoracic organs are removed with the neck organs, the aorta may be opened and the ductus Botalli opened by means of a probe passed from the aorta into the pulmonary artery. The heart is now removed and examined, the foramen ovale receiving careful inspection.

In many cases it is better to take out the neck and thoracic organs together. When the question is raised as to the child's having breathed after birth, the section should be conducted as follows: After the abdominal cavity is opened the height of the diaphragm is taken.