we know must be the origin of the myelin sheath. Those histologists who assume that the myelin sheath is a product of the metabolic activity of the neurilemma cells seem always to forget that in the central nervous system we have innumerable myelin sheaths with entire absence of the neurilemma covering. That the axone builds the myelin sheath there can scarcely longer be doubt.

Ballance and Stewart have recently made an extensive publication attempting to revive the old doctrine of the discontinuous formation through fusion of rows of single cells. I cannot help but feel that they are falling into the error of a now large group of predecessors.

The bibliography of the subject must be read with great caution Many of the statements are obvious misinterpretations Such a finding as that of Korolow, who sees genuine ganglion cells in the central cut end, and that of Garrés, who describes regeneration of branches of the trigeminus after extirpation of the Gasserian ganglion, are based upon mistakes. What Korolow's mistake was, it is difficult to say. Garrés doubtless had to deal with partial instead of complete extirpation of the ganglion.

Regeneration of nerve fibres which have undergone solution of continuity inside the central nervous system is so imperfect that many have questioned whether it takes place at all. The physiological studies of Baer, Dawson, and Marshall, and the pathological researches of Worcester, make it seem probable that at least some regeneration takes place. The evidence in general has been sifted by Ströbe (*loc. cit.*).

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Intoxications of the Neurone.

The best review of the literature of nerve-cell intoxication up to 1899 is that given by Barbacci. He has collected with great assiduity almost the entire literature of the subject and arranged the results systematically. He distinguishes sharply between the toxic influences which are the result of the introduction of substances into the normal organism from the outside world—intoxication in the narrower sense—and those intoxications which are the effect of poisons developed in the organism itself through a disturbance of metabolism—auto-intoxications. The former, in turn, can be further subdivided according to the chemical nature of the poisons, whether they be mineral or organic; and in the latter case, whether we are concerned with a so-called organic poison proper or a vegetable alkaloid or a poison of animal origin. Finally the effects of intoxication are considered by themselves, according to the special nature of the intoxication to which the alterations met with in the nerve elements are to be referred.

In his review of the general pathology of the nerve cell Barbacci refers to a series of special modifications which the nerve-cell protoplasm undergoes in various intoxications and infections. Most of these have been dealt with above under the caption, "Degenerations of the Neurone." A few additional ones, however, deserve especial mention.

Golgi's method has been utilized by a number of investigators for the study of pathological alterations in nerve cells, though it has been, of course, of far greater service in revealing the normal anatomical relations inside the central nervous system. One is always more or less in doubt in studying pathological tissues with Golgi's method as to how many of the appearances met with are artefacts. One of the commonest findings in pathological tissues is the so-called *varicose atrophy of the dendrites.* Instead of the normal dendrite, one sees a process studded by rows of round or oval swellings connected by thinner or thicker threads, reminding one of a chain of beads. This change is preceded, as a rule, by a falling of the "gemmules" or lateral thorns from the dendrites. The alteration affects the finest branches of the dendrites first and extends to the thicker trunks, until, finally, all of the protoplasmic process of the cell may be involved. Occasionally, however, the change is limited to a single dendrite or even to a single branch. The changes in the larger protoplasmic trunks of the dendrites, however, are not, as a rule, so typically beadlike. Instead, one sees an irregularity of contour, nodules, indentations, erosions, roughenings, wrinkles, etc., in the Golgi pictures. Any of the appearances described may be met with in normal tissues, but the change may be regarded as pathological when it is extensively distributed. For a list of conditions in which these changes have been noted, Barbacci's article may be consulted (*loc. cit.*, S. 798).

A somewhat similar atrophy affects the axones as seen in Golgi preparations, under certain conditions. What appears to be the same or a similar condition has been described by Golgi as *varicose hypertrophy.*

Of the changes met with in intoxications in tissues studied by Nissl's method, that of *chromatolysis* or *tigrolysis* has already been referred to (*vide supra*). The process has been carefully described by Ewing, Marinesco, and others. It begins, as a rule, with a swelling of the tigroid masses, though this is not always demonstrable. Once begun, the process involves a gradual vanishing of the tigroid from the cell protoplasm. The tigroid masses may disappear in various ways. In the first place, it is not uncommon to see an irregularity of arrangement appear. In the cells of the anterior horn, for example, instead of the typical stichochrome arrangement, one may meet with great irregularity and disorder. Again, instead of sharply isolated tigroid units, these elements may lose their individuality and be connected with others in the cell protoplasm in the form of a network. Instead of sharp, clean-cut pictures of the individual tigroid mass, one frequently sees ragged edges and indefiniteness of outline.

Ewing has described a fine subdivision of the tigroid masses occurring when the tigrolytic process goes on slowly. In other cases, in which the process is more rapid, the tigroid elements are broken up quickly into very fine granules and become evenly distributed throughout the cytoplasm, giving it a very characteristic "dust-like" appearance. This is the change designated by Ewing as "*granular subdivision*" and by the Germans as "staubiger Zerfall." In the final stages all the stainable substance of Nissl has disappeared from the cell (stage of *achromatosis*, described by Marinesco).

The tigrolysis may be total, or it may be limited to smaller or larger portions of the cell, in which case we speak of *partial tigrolysis.* If it involves the region immediately adjacent to the nucleus, the condition is spoken of as *central* or *perinuclear tigrolysis;* when, on the other hand, it is the periphery of the cell which is affected, the central portion remaining almost intact, it is spoken of as *peripheral* or *marginal tigrolysis* (Fig. 3587). By *intermediate* or *concentric tigrolysis* is understood the involvement of the middle zone between the nucleus and the periphery—a very rare condition. Finally the tigrolytic process may involve some particular segment of the

cytoplasm, in which event it is spoken of as *segmental* or *circumscribed tigrolysis.*

The tigrolysis which follows section of the axone has been referred to as *degeneratio axonalis* (Fig. 3588); it is of the central variety as a rule. It was supposed by many that, on the other hand, when a toxic agent acted upon the cell from without, the change nearly always consisted in peripheral or marginal tigrolysis. A review of the extensive bibliography, however, teaches that no hard-and-fast rule can be laid down.

The changes demonstrable by

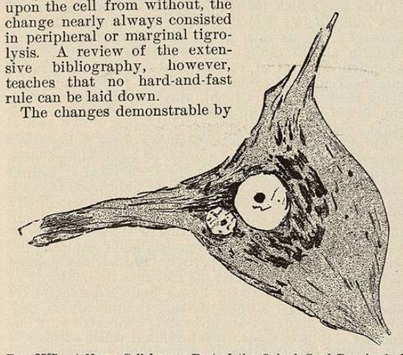

Fig. 3587.—A Nerve Cell from a Part of the Spinal Cord Deprived of Blood for Six Hours Through Ligature of the Abdominal Aorta. (After G. Marinesco, *Presse méd.*, Par., 1897, pl. v., p. 45). The peripheral portion of the cytoplasm contains only a few tigroid masses, although the latter are still numerous near the nucleus. Typical *peripheral tigrolysis.*

Nissl's method in the nucleus in various intoxications include (1) swelling of the nucleus, (2) diminution in the size of the nucleus, (3) alterations in the form of the nucleus, and (4) alterations in the contents of the nucleus.

Swelling of the nucleus may vary in degree. In extreme cases actual dropsy of the nucleus has been met with. Such swelling has been described in a whole series of conditions, including faradic excitation of the cell, commotio, uræmia, cholæmia, tetanus, rabies, and acute delirium.

A diminution in the size of the nucleus may or may not be accompanied by alterations in its nucleolus. As a rule the form of the nucleus is also somewhat altered. The contour is irregular, the nucleus looking as though shrunken. When the contents are altered, they may be homogeneous and stain diffusely and evenly. Sometimes this homogeneity is associated with shrinking—so-called "acute homogenization with atrophy" (Sarbo). Sometimes the contents of the nucleus stain evenly, but take a different tint from other constituents of the cell, especially a shade different from that taken by the nucleolus and the tigroid mass. This "metachromatic" staining has been met with by Barbacci in various pathological conditions, but especially in experimental cholæmia. He points out, however, that metachromatic staining frequently occurs in tissues which have undergone post mortem change, and that therefore great care should be exercised in reporting instances of the alteration.

Vacuolization of the nucleus has been referred to above in connection with vacuolar degenerations in general.

Eccentricity of the nucleus or peripheral disposition of that structure is one of the typical changes in the nerve-cell body following upon lesion to its axone. That it may occur under still other conditions has been manifoldly stated. Thus it has been described after ligature of the aorta, in embolism, and in various intoxications. In some of these instances, however, the eccentricity may depend not upon the direct action of the harmful agent upon the cell body and nucleus, but rather upon a simultaneous injury to the nerve fibre, in which event the change in the nerve cell would correspond to the ordinary axonal degeneration.

Various alterations in the nucleolus, under pathological conditions, have been described. All degrees of pallor of the nucleus have been observed in stained preparations, the pallor occurring most frequently when the volume of the nucleolus is increased. Swelling of the nucleolus is met with under many conditions, but particularly after tetanus or strychnine poisoning. Occasionally the nucleolus is diminished in size (Ewing). Uneven staining of the nucleolus with actual vacuole formation has been emphasized by Lugaro as a common appearance after arsenic poisoning Similar phenomena have been described by Ewing in hydrophobia.

The shape of the nucleolus is often altered; instead of being round with regular margin, it may become polygonal. In extreme cases it may be fragmented, a condition not to be confounded with the existence of the so-called secondary nucleoli.

When one approaches the subject of special intoxications he is almost overwhelmed with the immense number of researches which have been undertaken in connection with them. The great vulnerability of the Nissl bodies and the observations of marked alterations in them in various intoxications led Nissl and others to hope that we might find in the study of the stainable substance safe criteria for the histological diagnosis of the action of specific poisons. Much disappointment has, however, been met with as the investigations have proceeded. The lesions in the majority of instances are not pathognomonic for the special poisons. If specific alterations are some day to be found, they will probably be in the ground substance of the nerve cell or unstainable substance of Nissl rather than in the tigroid masses. That specific poisons have specific effects is indubitable from the physiological and pathological results of their action. That specific physical and chemical alterations take place in certain groups of nerve cells under such circumstances we cannot doubt, but we are far from having found anything like histological changes corresponding to these specific effects. In all probability we must wait until our technique has become much more refined before we can hope for histological demonstration. It may be that the alterations concern portions of the nerve-cell protoplasm measuring less than the wave length of light, in which event microscopic demonstration would be impossible.

Of the mineral poisons, the effects of which have been studied, may be mentioned arsenic, lead, antimony, mercury, phosphorus, silver, and aluminum. Of the organic poisons proper the effects of alcohol, chloroform, antipyrin, trional, acetone, and malonnitril have been studied. The effects of powerful alkaloids have formed the basis for a large series of histological investigations. Strychnine, morphine, quinine, ergotine, atropine, muscarine, nicotine, cocaine, and veratrine are among those which

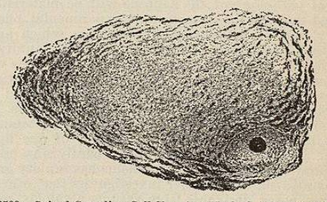

Fig. 3588.—Spinal Ganglion Cell Showing Marked Alterations Following Section of the Sciatic Nerve. Sublimate fixation; thionine staining. (After Lugaro.) Typical *central tigrolysis* with eccentric position of nucleus: *degeneratio axonalis.*

have been used. Of the poisons of animal origin blood serum of animals of the same and of other species, urine, thyreoiodine, neurine, and snake poison may be mentioned as those whose effects have been particularly investigated. Special interest has attached to the examination of the changes in the nerve cells which occur in the so-called auto-intoxications. Thus in the bibliography

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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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.