the myelin disintegrates into droplets cellulifugally from the lesion, as far as the peripheral termination. By the fourth day a multiplication of the nuclei of the neurilemma can be made out. Liquefaction of the myelin begins by the sixth or seventh day and continues until the sixtieth or eightieth day, when all of it is dissolved and most of it has been absorbed. The absorption is complete by the end of three or four months. If the degeneration affect medullated nerve fibres inside the central nervous system, neuroglia cells can be seen undergoing proliferation after some forty-five or fifty days (Ceni). This proliferation ceases at the end of three months and sclerosis follows.

Marchi's method demonstrates the existence of degenerating fibres as early as eight or ten days after the lesion, and will continue to demonstrate their presence until all the myelin of the degenerating fibres has been absorbed, that is, until some three months have elapsed after the injury. At a later period we have to resort to Weigert's method; the areas which have degenerated show, of course, an absence of black fibres. Marchi's method is far more delicate than Weigert's; the former will reveal single degenerated fibres; the latter can be relied upon only when there is a considerable area of lightening in the region otherwise uniformly filled with black fibres. Anatomists have applied these methods most extensively in experimental work for the determination of the course followed by the medullated axones of the various groups of neurones of which the nervous system is made up. Pathologists utilize them to study the secondary degenerations which accompany various diseases of the nervous system in human beings.

For many years it was believed that the cellulifugal alteration, described by Waller, was the only one which occurred after axone lesion, but the introduction of more delicate methods still has revealed the fact that surprising changes occur in the neurones cellulipetal from the lesion, and particularly in the cell body or perikaryon itself. Nissl by the application of his methylene-blue-and-soap method has demonstrated definite alterations in the cell body as early as a few hours after axone lesion. The changes are most marked, however, when animals are killed from eight to fifteen days after the operation in which the axones have been cut. Nissl refers to this method of study as "the method of primary irritation." His results have been confirmed by Flatau, Marinesco, Lugaro, Van Gehuchten, Erlanger and myself, and many others.

The change which takes place in the cell bodies of the nucleus nervi facialis, for example, after section of the nerve trunk near the pes anserina, consist chiefly in alterations in the tigroid masses, in a moderate swelling of the perikaryon, and in a displacement of the nucleus toward the axone hillock. The change seems to affect the tigroid masses first. The spindles lose their typical stichochrome arrangement, break up into minute particles, become scattered diffusely throughout the cell, and finally undergo solution, the solvent process affecting the tigroid masses in the interior of the cell first, and extending gradually toward the periphery. This disintegration and solution of the tigroid has been variously designated. Marinesco calls it *chromatolysis;* van Gehuchten, *chromolysis;* Retterer, *chromophilysis;* Kohnstamm gives it the name *tigrolysis*, and the latter term is the one which I prefer.

Marinesco has described two distinct stages of the process: (1) A stage of *reaction*, in which the tigroid undergoes the changes above described; and (2) a phase of *repair*, during which the tigroid elements are restored to a more or less normal appearance. The first stage begins soon after section, and reaches its maximum in from fifteen to twenty days. The second stage lasts longer. It is essentially a phase of regeneration, and as in many cases of regeneration the elements regenerated are produced in excess; the individual tigroid masses are larger and more numerous than in the normal cell. During the first stage (that of reaction) the cell is swollen; during the second (that of repair) it gradually returns to its normal size. The nucleus, markedly displaced toward the axone hillock during the first stage, slowly reassumes its former position in the centre of the cell during the stage of repair. A few cells in motor nuclei, after section, fail to undergo this repair, and van Gehuchten assumes that in them the turgescence of the cell has taken place so suddenly during the first stage and the propulsion of the nucleus has been so violent that the latter has been completely expelled from the cell body. Such cells, deprived of their nuclei, necessarily undergo total degeneration. It was thought by Marinesco that the stage of repair was conditional upon regeneration of the distal end of the axone, but Nissl, van Gehuchten, and Foà have shown that this is an error, and that the altered cells return to their normal state entirely independently of the phenomena of regeneration at the point of section. At least this seems true of experiments upon animals, though there are some observations upon the spinal cord of human beings following upon amputation, which indicate that cells still tigrolytic may be observed in the cord for from three to seven months after the operation.

There would appear to be an intimate relation between the degree of injury to the axone and the changes which take place in the perikaryon, for when nerves are torn out, the effects are very different from those which follow simple section of a nerve. Thus Ballet and Marinesco showed that if a nerve be torn out, a large number of the cells undergo complete destruction and are absorbed. This may explain the cellulipetal secondary degenerations obtained by von Gudden's method (*vide infra*).

One of the more recent developments of the study by Nissl's method indicates that tigrolysis occurs constantly after section of a cerebral nerve, but may or may not occur after section of a spinal nerve, though it inevitably follows the tearing out of the same spinal nerve (Van Gehuchten and de Neeff). The inference has been drawn that the lower motor neurones in the spinal cord of the rabbit and dog possess a greater resistance to experimental injury than do the lower motor neurones of the medulla, pons, and midbrain.

The method introduced by Nissl is of very great importance to anatomy, since by means of it the exact cell bodies which give off the motor axones to individual muscles can be easily localized in the central system.

It is now much easier to understand the early investigations bearing upon atrophy of the motor roots and gray matter of the spinal cord after amputation. The younger the individual at the time of amputation, and the longer the time elapsing between the operation and death, the more marked are the alterations. It would appear that if an amputation be done early in life, many of the neurones concerned in innervating the amputated limb undergo complete degeneration and disappear totally, that is to say, in addition to the Wallerian cellulifugal degeneration, which of course occurs in the amputated stump, there takes place in young individuals a slow atrophy or slow cellulipetal secondary degeneration of the whole neurone, notwithstanding the fact that the perikaryon with its nucleus is left in the mutilated neurone. This vulnerability of neurones in young animals is especially well illustrated by the long series of experiments which were made by von Gudden. The distinguished Bavarian investigator showed that after removal of an eye in a young rabbit, in the course of some months not only did a total degeneration of the optic nerve of the same side and partial degeneration of the optic tract of the other side take place, but also extensive degeneration occurred in the superior colliculus of the corpora quadrigemina and lateral geniculate body of the opposite side. This general observation showed immediately what regions of the gray matter are intimately related with the optic nerve. The study of the microscopic changes in these primary optic centres proved that this method permits one to draw also important conclusions concerning the finer histological connections of the axones of the optic nerve with their centres of origin and of termination. Thus while in the superior colliculus after the operation above mentioned entire rows of nerve cells had

disappeared from the superficial layer of gray matter, in the lateral geniculate body the ganglion cells were but very little altered; but between them, and especially in the gelatinous substance lying in the lateral part of this nucleus, there had been a very great loss by absorption of fine nerve fibres, the terminals of the optic nerve. It was easy to interpret these observations. Where as a result of the lesion there had occurred cellulifugal degeneration of the ground substance in direct continuation with cellulifugal degeneration of nerve fibres in the optic tract and optic nerve, we have to deal with the nucleus of termination of the axones of neurones, the cell bodies of which are situated in the retina. On the other hand, in the part of the colliculus superior where there had been a cellulipetal disappearance of ganglion cells, as a result of the removal of the eye, it was evident that we have to deal with a nucleus of origin of centrifugal axones which run out through the optic tract and optic nerve to the eye. That this conclusion is correct, the application of the methods of Golgi and of Flechsig to the problem have left no doubt.

Von Gudden and his pupils utilized this cellulipetal secondary degeneration in young animals in extending widely our knowledge of the anatomy of the brain. By it the nuclear origin of the various cerebral nerves were very exactly defined, and later, the connections of the lemniscus, the brachium conjunctivum, the cerebrocortical pontal paths, and various other tracts were determined and their centres of origin and of termination accurately established.

A study of a large series of pathological cases in human beings following upon hemorrhage, softening, or pressure from various causes in the brain has proven that in human beings also the cellulipetal degeneration (corresponding to the experiments of von Gudden) occurs as well as the typical cellulifugal secondary degeneration of Waller. What is more, a study of human cases reveals the fact that if a neurone of a high order fails to receive its normal impulses from a set of neurones of the next lower order, owing to degeneration of the latter, the former undergoes a slow diminution in size throughout its whole extent (diminution in size of lemniscus accompanying sclerosis of posterior funiculi of cord). Again, if a set of neurones in a neurone chain is unable, through degeneration of the next higher group of neurones in the chain, to pass on its impulses to the latter, it undergoes a slow atrophy, all the neurones of the set gradually diminishing in size. This is well shown when, for example, the somæsthetic area of the cortex is destroyed and secondary degeneration of the thalamocortical neurone system results; the lesion is followed in the course of years by marked diminution in the volume of the lemniscus medialis, of the stratum interolivare lemnisci, and of the nucleus funiculi gracilis and nucleus funiculi cuneati of the opposite side, the cell bodies of which give rise to the axones of the lemniscus.

Bethe also studied the degenerative changes in the axis cylinder after section of the nerve. He states that the first change is the disappearance from the fibrillæ of a substance which is primarily colored by basic dyes, and that with the disappearance of the primary colorability of the nerve there disappears its excitability. There follows a breaking up of the primitive fibrillæ into large and later into fine granules; at the same time a breaking up of the medullary sheath with ellipsoid formation. Degeneration is always apparent in the primitive fibrillæ before such is seen in the medullary sheath. This degeneration does not occur in the whole nerve at the same time, but is first apparent near the seat of the lesion from which it can be traced at later periods toward the periphery. Corresponding changes are found in the central stump, though here the degeneration is limited in extent, though certain fibres may be seen degenerating far toward the cord. He denies that in the central stump degeneration ends at the first nerve of Ranvier nearest to the point of lesion (traumatic degeneration). From his investigations he confirms the opinion that sensory fibres degenerate more quickly than motor, and he further states that thicker fibres, both motor and sensory, earlier show signs of degeneration than finer fibres.

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Regeneration of the Neurones.

The topic includes regeneration of the nervous system in whole or in part during embryonic periods, the regeneration of whole neurones in the adult condition, and the regeneration of portions of a neurone after injury.

In connection with regeneration of the nervous system in the embryo much work has been done. Recent studies have revealed a wholly unexpected capacity for regeneration in young phases of the embryo. The doubling of the whole nervous system, or of one end of it, is by no means uncommon. In later embryonic phases the capacity for regeneration becomes less; but until quite a late period, especially in low forms, very considerable regeneration is possible. Interesting as regards the regeneration of the nervous system are the researches of Harrison, who experimented upon the tails of tadpoles. After cutting off the tail, its peripheral nervous system was regenerated from the spinal cord. There first arose a single pair of nerves from cells lying within the cord. A part of these cells wandered into the nerve root and gave rise to a large spinal ganglion. Subsequently groups of cells wandered farther into the periphery along the newly formed nerves and gave rise to from one to three small ganglia to take the place of those ganglia which had been lost through the operation. The total number of ganglia, however, was never completely replaced.

As to the regeneration of whole neurones in adult vertebrates much doubt has been expressed. The prevailing opinion is that if an adult neurone be once entirely destroyed, it can never be regenerated from neighboring neurones. That karyokinetic figures can occur in nerve cells adjacent to an injury has been shown by Tedeschi and Vitzou. The exact histological details of karyokinesis in neurones have been studied in the cerebral cortex of guinea-pigs after introduction of a hot needle by Levi (*cf. Barbacci's Review, loc. cit.*, p. 785).

Most interesting are the various studies which have been made to explain the well-known fact that regeneration of peripheral nerves after lesion occurs. There has been much dispute as to whether the regeneration of nerve fibres is due to an outgrowth of the axone from

the central stump entirely or to a fusion of the axone of the central stump with a new axone developed in the periphery as a result of the activity of the neurilemma cells. In favor of the former view, the investigations of Waller, Ranvier, Vanlair, Barfurth, von Notthaft, Ströbe, and Koister are important; while in favor of the latter view the studies of Beneke, Neumann, von Büngner, Wieting, and Ballance and Stewart may be mentioned.

According to the Waller-Ranvier-Vanlair view there is a continuous regeneration of the nerve fibres in connection with the part of the old axone preserved in the central stump. These authors observed in the distal part of the nerve the proliferation of the cells of Schwann's sheath and the formation of bands of spindle cells therefrom, but they maintain that the new axone is regenerated independently thereof. After the lesion the end of the central part of the axone becomes swollen and subdivides into several fine fibrils. These fibrils grow out from the central axones and ultimately reach the periphery; as they grow out they gradually become surrounded with myelin sheaths. The delicate young fibrils penetrate the intermediate tissue at the site of the lesion and reach the peripheral segment of the nerve, the fibres of which have undergone complete degeneration followed by proliferation of the neurilemma cells. These investigators assert, however, that the altered fibres of this peripheral segment take no active part in the formation of new fibres, but simply act as easy paths along which the new axones from the central stump can grow. If the central and distal stumps of the divided nerve are too far apart, the regenerating axones of the central stump may be unable to bridge the gap, in which event there will be no return of function; hence the importance of the immediate coaptation of the two cut surfaces of a divided nerve. Even when the coaptation has been carefully made by a surgeon, many of the newly forming fibres fail to grow out to the periphery.

According to the opposite view there is a *discontinuous* regeneration of the nerve fibres taking place independently of any connection with the central stump, the new fibres becoming connected with the latter only secondarily. The majority of those who support the view attribute the discontinuous regeneration of the fibres of the distal stump to the development of single segments from elongating cells; these single segments then fuse to form a continuous fibre, which later becomes attached to the end of an old nerve fibre in the central stump. There is thus a series of fusions of single cells to make the new nerve fibre and subsequently a fusion of the new fibre with the end of the old one. The same investigators believe that the cells which are concerned in building the new nerve fibres are derived by karyokinesis from the cells of Schwann's sheath (neurilemma); a few observers in the group, however, deny this, maintaining that the new fibre is derived from the connective-tissue cells of the endoneurium or even from leucocytes.

Neumann's ideas concerning regeneration resemble closely those just described, though they differ somewhat in details. He states that the myelin sheath and axone of the old fibre do not undergo complete degeneration and absorption, but, contemporaneously with the proliferation of the neurilemma nuclei, mix with one another, becoming transformed to a common protoplasmic mass, which possesses the chemical properties of both axone and myelin sheath. This mass, filling up the old nerve tube, gradually gives rise to the new fibre by again becoming differentiated into myelin sheath and axone. This differentiation is not, however, a *continuous* process but takes place in segments, and its origin and progress are, he thought, dependent upon and under the control of the axis cylinder of the nerve of the central stump, for the segmental differentiation begins at the lesion in contact with the old nerve fibre and gradually extends toward the periphery. The segment first differentiated fuses with the extremity of an old fibre of the central stump, and gradually the more peripherally situated segments fuse to form finally a continuous fibre.

Von Büngner undertook the study in 1891 with new methods. He decided that the peripheral portion of the nerve undergoes complete degeneration after section, and that therefore "healing by the first intention," postulated by some surgeons, does not occur. From the third day on, the neurilemma cells proliferate, the nuclei dividing by karyokinesis, and the protoplasm of these cells rapidly increases in amount. These cells fill up the interspaces between the balls of degenerating myelin and probably participate actively in the destruction and absorption of the old myelin sheath and disintegrated axone, since leucocytes are not present. No better illustrations of degenerating nerve fibres are to be found anywhere than those which accompany von Büngner's article. The neurilemma cells next line up in one, two, or more longitudinal rows and soon a slight fibrillation appears near the elongated nuclei until finally the nuclei of the row appear to be connected by bands of fibrils. Herein von Büngner saw the earliest indications of the newly forming axone. Through fusion of the rows of proliferated neurilemma cells and fusion of the segmental bands of fibrils, continuous fibril bands are formed, at the sides of which the nuclei, leaving their former central position, now arrange themselves, so that the fibres go past them in a slight curve. The process is always most advanced near the side of the lesion, the regeneration being slowest at the peripheral extremity of the nerve. Von Büngner believes that the neurilemma cells, and they alone, give rise to the new fibres; he does not hesitate to designate them "neuroblasts," and believes that they are truly "nervous" in nature and origin.

From the beginning of the third week on, new myelin sheaths begin to appear about the newly formed fibres, and a little later the new neurilemma and the new sheath of Henle appear, being derived, von Büngner believes, from the connective-tissue cells of the endoneurium. The nodes of Ranvier can be seen as early as the fourth week.

As to the mode of union of the axone of the central stump with the newly formed fibres in the peripheral nerve, von Büngner asserts that traumatic degeneration occurs in the central end up to the first or second node of Ranvier. Here the end of the old axone undergoes bulbous enlargement and fuses with new segmentally regenerated fibres derived from neurilemma cells of the central stump; the latter fuse with new segments in the space between the two ends of the divided nerve, and they with the newly formed fibre of the peripheral portion of the nerve. He denies anything like an outgrowth of the old axone to the periphery, and even an outgrowth across the space between the two cut ends of the nerve.

Neumann, more recently, states his position as follows: "At present no one doubts that a very important factor in the re-establishment of conduction in an interrupted nerve lies in the outgrowth of young fibres from its central stump; the only dispute possible concerns the extent to which this process takes place. While those who hold the Waller-Ranvier doctrine assume that the young fibres grow out into the peripheral degenerated part as far as its termination, according to the view which I have founded and which has later been supported by von Büngner and Wieting, the outgrowth from the central stump is limited, occurring only in sufficient degree to bridge over the gap in the nerve, whereupon new fibres are formed autochthonously out of the protoplasmic material supplied by the degeneration process."

Wieting agrees with von Büngner in ascribing the regenerative process in the first stages entirely to the nuclei of the neurilemma cells. He believes that the neurilemma cells give rise to a large amount of protoplasm throughout the whole extent of the degenerating nerve, and that it is through further differentiation of this protoplasm that the new structures are formed. As early as the fourth day extremely fine fibrils appear in the protoplasmic contents of the old neurilemma sheath. These fibrils are always continuous with the central axone. About the fifth day, advancing from the central stump toward the periphery, there is a sharper arrangement of

the protoplasmic masses and fibrils with formation of fine fibrillary strips, stained of a pale rose color and otherwise homogeneous. Later, the cell boundaries disappear, the protoplasm is drawn out lengthwise, and is deposited as a finely granular covering upon the strips. The strips represent young axones. The gray covering is the beginning of the new myelin sheath, and is also to be looked upon as an excretory product of the cell, the excretion taking place first from the central stump and advancing toward the periphery. While Wieting emphasizes that the fibril formation takes place in direct connection with the old axones, and that the process advances evenly toward the periphery, he maintains that we do not have to deal with the simple outgrowth of the old fibre for which the neurilemma cells merely point the way, but have in reality to do with a fibrillary transformation of the protoplasm yielded by the nuclei of Schwann's sheath or with a fibril formation in the protoplasm in connection with the fibrils of the old axone.

A somewhat intermediate position is taken by Howell and Huber, though they incline to the view that the young axone grows out of the old one in the central stump; it grows into the young "embryonic fibre" born from the proliferating cells of Schwann's sheath. They think that when the new axone grows into the young "embryonic fibre" the formation of the myelin sheath has already begun in the latter. Their paper is readily accessible to readers of English, and need not, therefore, be further reviewed here. Their work was done independently of von Büngner's, and it is interesting to note the nearness of von Büngner's description of his fibril bands to that of Howell and Huber of their "embryonic fibre."

The whole subject was taken up again by von Notthaft in 1892, his research winning the prize offered by the medical faculty of Würzburg. His studies of degeneration of the nerve, the proliferation of the neurilemma cells, and the formation of fibrils in the protoplasm inside the old sheath confirm very closely the observations of von Büngner; but he differs entirely when he comes to describe further stages of the process of regeneration. He asserts that the neurilemma cells do not build the young nerve fibres at all. Instead, the young nerve fibres all grow out from the axones of the central stump, and all pass, without exception, into the interior of old sheaths of Schwann. The young fibres pass by nucleus after nucleus of the proliferated neurilemma cells, but any such thing as discontinuous regeneration of nerve fibres from the spindle cells is, he maintains, impossible. The microscopic pictures do not even yield a remote suggestion of such a probability. Von Notthaft cannot conceive how von Büngner came to the idea that the fibrillary construction of the protoplasm of the proliferated neurilemma cells could be the *Anlage* of the new axones. He seems, however, to have neglected a careful study and description of the finer histological relations occurring in the spaces intermediate between the two cut ends of the nerve.

Even more convincing than von Notthaft's confirmation of the Waller-Ranvier theory is that which we owe to the still later researches of Ströbe. Instead of being satisfied with the indirect proof of the view which is embodied in this theory, he determined to make a wholly clear series of observations (so controlled that they should be free from objection) of the phenomena which occur during the earliest period of formation of the new fibres and their connection with the old. He admits that he was influenced by the promulgation of the neurone doctrine, which has emphasized the importance of the nerve fibre as a process of the ganglion cell, but did not permit this to prevent him from studying the actual process in detail. He was helped very much in his investigations by the invention of a special staining method for the axis cylinders. Preparations hardened in Müller's fluid were stained in concentrated aqueous solution of aniline blue (Gruebler), after which they were differentiated in a slightly alkaline alcohol. This gives a deep blue stain to even the finest young axones, while the cell protoplasm in general stains of a very pale blue tint, or by counterstaining in safranin it stains light red in contrast to the deep red stain taken by the nuclei. After studying all stages of the degeneration itself, and confirming again the fact that it is complete for both myelin sheath and axone to the very periphery, he took up the study of the changes of a progressive nature, finding, as had previous investigators, that the degenerative and the regenerative processes in the injured nerve accompany one another in time and place. He separates sharply the progressive phenomena which concern the cellular elements of the old nerve fibre, that is, the cells of Schwann's sheath, and the progressive phenomena of true nervous origin, namely, the new formation of the axone and the myelin sheath. The latter alone have the significance of the true regeneration of the nerves. The phagocytic activities of proliferated neurilemma cells were carefully studied. Ströbe also describes how these cells become transformed into long spindle-shaped elements with longitudinal oval nuclei filling up the old sheath of Schwann. These unite to form spindle-cell rows as the degeneration products disappear; portions of nerve fibres filled up by such rows of spindle cells may alternate with other portions of the same fibre consisting of entirely empty and collapsed Schwann's sheaths. An especial study at the site of lesion showed that the proliferating cells of Schwann's sheath enter into this region from both ends of the divided nerve; but here, instead of forming rows, the cells are prone to be irregularly mixed up and interwoven with proliferating connective-tissue cells of the endo-, peri-, and epineurium. This proved that the neurilemma cells possess no inherent tendency to the formation of longitudinal rows, but do so in the peripheral portion of the divided nerve simply on account of the adaptation of the cells to the special relations of the old nerve tube in which they arise.

True regeneration, according to Ströbe, has nothing to do with this proliferation of the neurilemma cells and the bands of spindle cells resulting therefrom, but depends entirely upon the outgrowth and splitting up of the old fibrillary axis cylinders directed peripheralward from the central nerve stump. These young fibres, by the method of staining employed, appear as sharp microscopic pictures; so sharp, indeed, that there can be no excuse longer for confusing them with the fibril-like structures in the protoplasmic bands described by von Büngner. The impression is never obtained of a new axis cylinder becoming differentiated out of the protoplasm of the rows of neurilemma cells. From the very beginning the young axones are continuous with the old axone, and show on their first appearance a very delicate but distinctly developed continuous myelin sheath. The illustrations which accompany Ströbe's article are very convincing. The new fibres gradually lengthen and grow out farther and farther distalward. The formation is continuous, not discontinuous. Passing from the central nerve stump into the tissue intermediate between the two ends of the divided nerve, the new axones pass between the rows of spindle cells, when such exist, and between the fibroblasts which have not been arranged into rows of spindle cells. Having passed through the site of lesion, the new fibres enter the old peripheral nerve, sometimes entering into the interior of old nerve tubes still open; at other times passing between the bands of spindle cells formed from the degenerated nerve fibres. The course is tortuous and the fibres frequently cross one another. The young fibres frequently possess a knobbed terminal swelling.

The young nerve fibres, delicate at first, gradually increase in thickness, the degeneration products of the old fibres gradually diminish in amount through absorption, and the normal condition is slowly restored. The cells of Schwann's sheath are not nervous elements at all, and the designation of "neuroblast" is wrongly applied to them. They are secondary connective-tissue ensheathing cells, corresponding to their mesoblastic origin in the embryo. Ströbe's work is in complete accord with the neurone doctrine, and furthermore is compatible with what

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

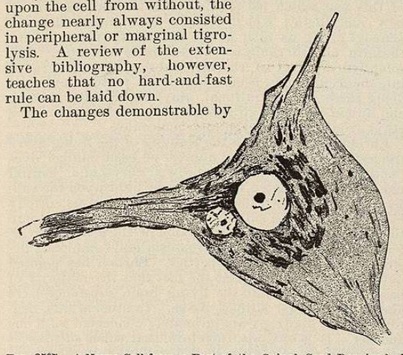

Fig. 3587.—A Nerve Cell from a Part of the Spinal Cord Deprived of Blood for Six Hours Through Ligature of the Abdominal Aorta. (After G. Marinesco, *Presse méd.*, Par., 1897, pl. v., p. 45). The peripheral portion of the cytoplasm contains only a few tigroid masses, although the latter are still numerous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

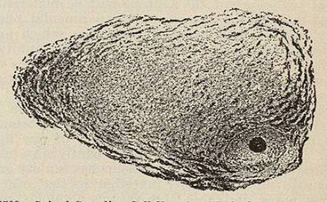

Fig. 3588.—Spinal Ganglion Cell Showing Marked Alterations Following Section of the Sciatic Nerve. Sublimate fixation; thionine staining. (After Lugaro.) Typical *central tigrolysis* with eccentric position of nucleus: *degeneratio axonalis.*

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