RECENT STUDIES ON THE FINER STRUCTURE OF THE NERVE CELL.

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The finer structure of the nerve cell remains the object of study for numerous investigators. Interest centers here from many points of view. From the physiological view-point there is sought the correct differentiation of the protoplasm from the metaplastm and the determination of the relation which each of these, in its various aspects, holds to the activities of the cell. The pathologist demands, further, the structural basis and explanation of the various morbid activities as distinguished from each other and from the normal. And for the morphologist the subject presents a variety of problems which may be approached by both comparative and embryological methods.

In a field of so varied interests and in which at the same time there is much diversity of opinion, the results from various sources must undergo frequent critical analysis and synthesis. In no other way can the general trend of facts be discovered and progress in the subject as a whole be measured and made useful. With this thought in mind I have undertaken to study such recent papers and monographs relating to the structure of the nerve cell as were available and to bring together synthetically the opinion of different authors under topics which appear to hold important place in the minds of investigators.

The discussion is arranged according to the following plan:

- Ground Substance and Neurofibrillae
- The Moniliform Condition of the Dendrites
- Golgi's Endocellular Net
- The Gemmules
- Golgi's Pericellular Net
- Intracellular Canaliculi
- The Nucleus
- The Nucleolus
- The Centrosome
- The Tigroid Substance and Chromatolysis

The Ground Substance and Neurofibrillae.

The challenge which came to the neurone theory through the works of APÁTHY and BETHE has awakened new interest in the finer structure of the cytoplasm of the nerve cell. That there are structures in the properly fixed and stained neurone, especially of invertebrates, which accord with the neurofibrillae of these authors can no longer be doubted. But the exact relation which these fibrillae hold to the protoplasm of the living cell, to the inter-relation of neurones, and, therefore, to the conduction paths of the nervous system, is not satisfactorily explained. Is the neurofibril a protoplasmic thread or is it a derived substance of the protoplasm as PUGNAT and others argue? If it is a derived substance, it may well pass beyond the limits of the cell and form extra-cellular nets in the neuropil, as BETHE and APÁTHY and their followers describe. But if the fibril is protoplasmic its nature excludes the possibility of such nets since the limits of the cell would coincide with the limits of the protoplasm. But if the fibril be protoplasmic, are there structural features of the cytoplasm by which the origin, development and final behavior of the fibril can be explained? Towards the answer of such leading questions, some of the following works contribute in a positive manner.

HOLMGREN ('99), in his monograph upon the spinal ganglion cells of *Lophius*, does not commit himself to a definite statement regarding the ultimate structure of the cytoplasm. He describes however, a certain radial appearance about the nucleolus in its migration from the nucleus into the cytoplasm which he considers suggestive of the alveolar structure. Yet his figures and descriptions in general do not seem to sustain this interpretation throughout. In his beautifully executed drawings (Taf. IX-X, Fig. 3) he represents the cone of origin as marked with stripes which are directed from the axone into the cell body. In the more distal part of the cone these stripes seem to form elongated and very narrow meshes. As the structure recedes into the cell body the meshes become shorter and broader, and especially is this true in the peripheral region of the cell where the meshes become very irregular in shape and size. Though HOLMGREN does not discuss this structure in detail as related to the structure of the cytoplasm his figures are strongly suggestive of the cytoplasmic reticulum as described by HATAI and others.

In a later work upon the structure of the nerve cell HOLMGREN ('00) finds more positive data on this feature of the neurone. He demonstrates a fibrillar structure which he considers identical with the fibrillar substance of FLEMMING. The fibrillae of the cytoplasm are

continuous with those of the axone, but none of them anastomose. They follow an undulating or somewhat spiral course through the cell body, with a tendency to be more nearly parallel in the peripheral zone. The interfibrillar substance is homogeneous.

But the fibrils of this net, it is important to notice, are to HOLMGREN the neurofibrillae. In both vertebrates and invertebrates they may enter or leave the neurone at any point in the periphery of the perikaryon or of the processes. Furthermore, Holmgren says, "die wabige, pseudowabige oder spongioplasmatische Structur, wie man sie auch nennen will, die ich bei *Lophius*, die RAMÓN-Y-CAJAL, LENHOSSEK, VAN GEUCHTEN u. A. beschrieben haben, nur einem accidentellen Aussehen der resp. Zellen entspricht, im besten Falle durch einen gewissen physiologischen Zustand hervorgerufen." That is to say, the "filare Substanz" of FLEMMING is resolved by HOLMGREN into the neurofibrillae of APATHY and BETHE, and the structural parts of the ground substance, such as granules, trabeculae etc., of many authors are interpreted as functional or artificial modifications of FLEMMING's amorphous "interfilare Substanz."

KOLSTER's monograph upon the nerve cell of *Petromyzon* contains an interesting demonstration of certain features of the ground substance. KOLSTER has made an exhaustive study of unstained preparations of the nerve cell mounted in media of various refractive indices, and also of unstained osmic acid preparations. In none of his mounts made by these methods has he found anything akin to a fibrillar or reticular structure. But in cells preserved in FLEMMING's solution for several months or even for more than a year, and subsequently stained in saffranin and differentiated in a 20% tannin solution followed by absolute alcohol, he discovers very fine lines running through all the cytoplasm. These lines are made up of a single row of dark red granules which the author treats as microsomes. In some of his figures these lines seem to form a net with relatively large, irregularly shaped meshes, but the author believes that anastomoses between the lines are relatively rare. In thick sections these granules appear large, but thinner sections show that these relatively large granules are made up of short rows of exceedingly small granules running in all directions. The whole structure, then, is resolved into a network of microsomes in linear arrangement. Furthermore, KOLSTER demonstrates that this net is concentrated into a dense granular mass directly around the centrosphere, where a granular effect is given in unstained preparations. From this central mass rather thick rays extend in different directions, and these fray out into the fine lines of

microsomes. KOLSTER interprets this structure as different from anything that had been previously described, but it would seem to be indistinguishable from the neurosomic net met with by other authors.

According to BOCHENEK ('01) a fibrillar net may be beautifully demonstrated in the nerve cells of *Helix* by the gold chloride method. In the body of the cell the meshes of the net are triangular or polygonal but in the axone hillock they elongate. The fibrillae which course independently through the axone are continuous with the fibrillae of the net. The author finds it impossible, however, to distinguish between the motor and sensory fibrils. He finds, also, that the net in *Helix* is much more dense than it is in the nerve cells of *Lumbricus*. He interprets this as indicating a higher state of organization in *Helix*, which would be, in respect to the degree of differentiation of the intracellular net, intermediate between *Lumbricus* and the vertebrates. BOCHENEK treats this net as "un réseau protoplasmatique."

VAN GEHUCHTEN, in his earlier work ('97) upon the internal organization of the nerve cell, took the position that the ground substance of the cytoplasm consists of a fibrillar net suspended in an amorphous fundamental substance. This net extends into the process in the form of elongated meshes which superficially give the appearance of distinct fibrils. These two elements are considered by VAN GEHUCHTEN "le véritable protoplasme de la cellule nerveuse." The net or organized part he homologizes with the "masse filaire" of FLEMMING. In a later work ('98), published jointly with NELIS, VAN GEHUCHTEN quotes FLEMMING as coinciding perfectly with this interpretation as given in 1897. The authors, however, proceed at once to modify their interpretation in certain details. They found certain spinal ganglion cells of the rabbit which, because of the absence of chromatic substance in the peripheral region, gave excellent advantages for studying the achromatic structure. In these cells, by the use of toluidin blue and erythrosin, they found the net to be made up of granules united together by thin trabeculae of the same substance. But they add: "Le réseau protoplasmatique qui existe indubitablement dans toutes nos préparations diffère totalement des fibrilles courtes, flexueuses, irrégulières et indépendantes décrites et figurées par FLEMMING." He believes also that the net differs clearly from the net described by DOGIEL and that it is much more regular than that figured by MARINESCO.

In regard to the cone of origin, also, the authors have changed their views slightly. Instead of the comparatively thick and regular

fibrillae which most authors describe, VAN GEHUCHTEN and NELIS find a delicate, granular striation which they fail to connect certainly with the cytoplasmic net. The granules of the striae are so arranged as to give in some cases a cross-striated effect.

PATON ('00), in his studies of the neurofibrils of the cerebral cortex of the pig, finds that the fibrillae of the axone run independently of each other into the cell body, where they enter into a most intricate net-work. He holds that the fibrillae of this net are continuous with those of a pericellular reticulum, which he interprets as identical with GOLGI's pericellular net.

PATON believes that the fibrils are very quickly affected by post-mortem granular disintegration which begins at the center of the cell. He believes this fact may account for the view of certain authors that fibrils exist only in the apical process of the cell.

PRENTISS has recently published in this Journal his latest results upon the neurofibrillar structures in *Hirudo* and *Asticus*. As to the general arrangement of the fibrils in the cell body he confirms APÁTHY's position. He concludes, however, that "Neither in vertebrates nor in crustacea do the neurofibrillae of the nerve cells show any marked correlation in size and function." He believes that the differences in size which APÁTHY observed are due to incomplete impregnation of the fibrillae and perhaps to the cleaving together of smaller fibrillae in the cell process. As to the relation of the fibril to the cell and its processes PRENTISS supports BETHE's view that fibrils may enter one process and leave by another or by a collateral without coming into relation with the perikaryon itself. In *Hirudo* he finds a very limited fibrillar network in the neuropil. Such nets are more extensive in *Astacus* but they are not diffuse in their relation. They put relatively few fibrillae into communication with each other. PRENTISS considers that his preparations tend to confirm BETHE's theory that the cells are not the centers of nervous activity, and that the fibrillae are continuous from cell to cell.

PUGNAT, in his recent review on the finer structure of the nerve cells, comes to the conclusion that the formed substance of the cytoplasm is a net, in some cases of fibrillae, in others of trabeculae, and that this net is continuous with the fibrillae of the processes of the cell. The relation which this net holds to the life and function of the cell, he thinks, can best be explained upon BARD's theory of "derived substance." Although PUGNAT does not accept the sharp chemical and physical distinction between the protoplasm and the derived substance as BARD proposed, he believes that fibrillae are a product of the

protoplasm, that they are the conducting element and are therefore the seat of katabolic processes, while the protoplasm and nucleus are the seat of the anabolic process. How the fibrillae are repaired by the protoplasm, PUGNAT says, we are absolutely ignorant. Through this theory of derived substance PUGNAT attempts to bring the neurone theory into harmony with the results of APÁTHY and BETHE and their followers. He thinks that whether the fibrillae as derived products of the cell are continuous or not from cell to cell, the nerve cell itself may be considered as an anatomically distinct unit. He would, in other words, place the neurofibrillae in the same category with the fibrillae of the muscle or connective tissue cell. However, before such a compromise of the neurone theory is conceded HATAI's methods, by which he has received such brilliant pictures of the finer structures of the nerve cells and of the axone terminals, must be given a thorough test. The results which he has recently published are remarkably convincing.

In the afferent neurones of the electric lobe of *Torpedo* HATAI ('01) demonstrates fine fibrillae in enormous numbers, crowding the cell processes and the perikaryon. By serial sections through one of these large cells he shows the behavior of the fibrillae within the cell body. Upon emerging from the process into the cell body they diverge in clusters. Some sweep around the nucleus to form here a dense net, others pass to various processes of the cell in such a manner that there is direct fibrillar connection established between each dendrite and every other dendrite and between the axone and all the dendrites. By this coursing of the fibrillae from the dendrites into the axone there is a beautiful spiral configuration given to the ground substance of the cone of origin. Superficially HATAI's figures in this case have a striking resemblance to the familiar drawing of the fibrillar elements in the nerve cell by MAX SHULTZE.

HATAI, however, makes an important step in advance by demonstrating that these same fibrillae in the electric neurones of *Torpedo* can be resolved into rows of neurosomes. Furthermore, he asserts that these neurosomic fibrils in reality are a modified reticulum. It is only in thicker sections and under lower magnification that the structure gives the fibrillar appearance.

HATAI has demonstrated the reticular structure more exhaustively in the nerve cells of the white rat. He has studied these cells ('03) by the methods of BETHE and DOGIEL, but finds no such fibrillar structures as they describe. On the other hand, he demonstrates by other methods a neurosomic reticulum which is modified into a pseudo-

fibrillar structure. The fibrillae are made up of rows of neurosomes connected by slender protoplasmic filaments. Generally, around the periphery of the cell body the meshes are larger than in other regions. Around the nucleus and in the cone of origin they become more narrow and very much elongated. A more pronounced modification of this character is found in the axone so that the reticular condition is difficult to see. In the axone, however, the neurosomes stain brighter than elsewhere. Especially is this true of the neurosomes of the axone terminals, where they are also larger than in other parts of the cell. The dendrites contain a relatively small amount of the ground substance and the neurosomes stain more faintly than in the axone. This fact enables HATAI to differentiate the finest dendritic branches from the contiguous terminals of the axone. Even in the gemmules he demonstrates the neurosomic reticulum as continuous with that of the rest of the cell, but he finds that its neurosomes differ both in size and staining reaction from those of the axone terminals. He concludes that there is no continuity of the so-called fibrillar structures between the nerve cells.

Now HATAI finds that a number of these neurosomic filaments may mat together into thicker strands and that several of these strands in some cases form a complicated network around the nucleus. Such a network does not appear in the cone of origin or in the periphery of the cell body. He homologizes this network with the intracellular anastomosing fibrils of APÁTHY and also with the endocellular network of GOLGI. Thus HATAI resolves the neurofibrils of APÁTHY into the protoplasmic elements of the cell and denies that they pass continuously from cell to cell. The diffuse nets in the neuropil and pericellular nets also may be resolved into the reticulum of axone terminals which would be strictly protoplasmic and not extra-cellular, derived substance.

Moniliform Condition of the Dendrites.

Since DOGIEL's discovery of the dendritic varicosities in the cells of the retina this feature of the nerve cell has held an important place in neuro-cytology. Among the most comprehensive contributions upon the subject are those of SOUKHANOFF. This author made four experiments by ligature of the abdominal aorta, three upon guinea pigs which died from the experiment in from one-half to twenty-four hours, and one upon a rabbit which was killed after twenty-four hours. In these experiments he found that the diminished blood supply had produced a very rapid modification in the nerve cell, varying directly in

intensity with the duration of the anemia. The modifications of least intensity consisted in the appearance of swellings along the dendrite which made its contour irregular. As this condition became more intensified the swollen regions of the dendrites became fusiform and then spherical. During this process the connecting regions between the enlargements of the dendrites became more attenuated till a final beaded or moniliform condition resulted. This modification he considered pathological.

In another article ('98) upon the modification of the dendrites under the influence of narcotics SOUKHANOFF reports in considerable detail the results of nine experiments upon mice, rabbits and guinea pigs. These animals had been subjected to the vapor of ether, chloroform or alcohol for various periods of time. Two of the experiments were made by injection of trional. As a result of these experiments and of a critical review of the work of other investigators, SOUKHANOFF draws the following conclusions: (1) The moniliform condition may occur in certain dendrites under normal conditions, a conclusion reached by practically all authors; (2) under the influence of ether, chloroform or alcohol there is not a very appreciable increase in the moniliform condition; (3) injection of trional causes a moniliform condition of nearly all the dendrites of the cerebral cortex; (4) this change is accompanied by a more or less complete loss of the gemmules; (5) a loss in weight in guinea pigs subjected to trional injections can be attributed only to profound nutritive derangement. This suggests that the moniliform condition of dendrites may be "une degenerescence sui generis" manifested whenever nutrition is severely affected.

A third contribution by SOUKHANOFF ('98) deals with the varicose atrophy of the dendrites in the cerebral cortex under pathological conditions. His pathological studies were checked by examination of a normal specimen. From an exhaustive study of the latter case he concluded that the moniliform condition of the dendrites is occasionally found under normal conditions, but that it is very slight and not to be compared with that found in cases of poisoning. From nine experiments upon guinea pigs which had been subjected to arsenic poison in varying degrees for periods of from six to thirty-three days, he concludes that in acute and subacute poisoning by arsenic there occurs a moniliform degeneration of the dendrites of the cerebral cortex. This is very slight in some cases, but very marked in others. This difference cannot be accounted for by difference in the duration of the poisoning. Its cause is more likely to be found in individual differences in the specimens as regards resistive power and general health.

SOUKHANOFF's experiments include also poisoning by rabies and tuberculin and a case of thyroidectomy. In a rabbit infected with rabies during eighteen days and fatally, the varicose degeneration of the dendrites was slight. The experiment upon the influence of tuberculin was performed upon a dog that had some time previously been inoculated with tuberculin for immunization. It was then inoculated with an emulsion of the *Bacillus of KOCH*. From his study of this case SOUKHANOFF concludes that the varicose condition occurs in many dendrites of the cerebral cortex but that this is due to derangement in nutrition. In the case of thyroidectomy, upon a dog which lived a week after extirpation of the thyroid gland, profound changes were observed in both large and small dendrites of the cerebral cortex. This also SOUKHANOFF attributes to nutritive derangements which are known to follow thyroidectomy.

In general SOUKHANOFF concludes that although some dendrites in the normal nervous system are found in the varicose condition, the large numbers found changed under certain conditions are indicative of a morbid process; and that all poisonings which cause profound derangement in general nutrition cause a pronounced varicose degeneration of the dendrites.

The condition of the dendrites in the spinal cord of the rabbit has been studied by SOUKHANOFF and CZARNIECKI ('02). The spinal cord of two specimens, which were killed quickly with chloroform were treated by the GOLGI method. To bring about quicker penetration of the fluid incisions were made along the cord. The authors find that the cells of the cord show very pronounced differences in the form of the dendrites. The cells of the anterior horns differ strikingly in this respect from all other cells in the cord. Some of the dendrites of the anterior horn cells have comparatively regular contour, others are in a distinct varicose condition while the majority are in a condition intermediate between the two extremes. On the other hand, the dendrites of many of the small cells of the cord were found in a very marked varicose condition.

GEIER ('01) reports a series of experiments which are especially noteworthy for their thoroughness. They were made upon mammals and birds killed with chloroform or ether, and involved an examination of at least an entire cerebral hemisphere in each case. He describes each case in detail and draws the general conclusion that anesthesia by chloroform or ether does not of itself cause a moniliform condition of the dendrites, but that such a condition must be considered as the expression of a morbid or fatigued state of the cell. He holds also that the

moniliform condition is not an expression of the plasticity of the cell as certain authors have claimed.

In a later contribution GEIER ('02) presents important data upon the development of the protoplasmic processes as well as upon their form in the adult. He has studied by the GOLGI method the cells of the spinal cord of rabbits of different ages; one day, two weeks and one month; and of kittens at birth and at three days, seven days, one month and two months old. The two series of experiments lead to the same conclusions: the protoplasmic processes of the anterior horn cells are less regular in outline in the new-born than in the adult. As the animal grows the outline of the processes become more regular and the process straightens. In the new-born the dendrites have a more regular contour in the region of the cell body than in the distal region, and the process of straightening progresses from the cell body outward. As for the dendrites of the posterior horn, GEIER finds it difficult to determine whether there is any such change accompanying growth as he describes for the anterior horn cell. This difficulty arises from the fact which he demonstrated in his earlier work and which his present investigation confirms, that the dendrites of the posterior horn of the adult are normally very irregular in outline as compared with the dendrites of the anterior horn cells. He finds, however, that there are certain cells in the anterior horn which have very irregular dendrites. He considers them commissural cells. In his youngest specimens he found the varicose condition of the dendrites very conspicuous, but less marked in the older specimens. The condition tends to disappear as the animal grows.

Golgi's Endocellular Net.

SOUKHANOFF ('02) has made a specific study of GOLGI's endocellular net in the cells of the cerebral cortex of mammals by modifications of the GOLGI method. He finds this net only in a zone around the nucleus, although it does not lie directly upon the nucleus. Surrounding the net is a zone of protoplasm which is noticeably clearer than the rest. Some of the filaments of the net are fine, others are coarse, still others are ribbon-like. Often they are of irregular contour. In some small cells the net consists of only a few curls of the filaments, and it is a much simpler structure in the cortical cells than it is in the cells of the cord and spinal ganglia. In general form the net conforms rather closely to the shape of the cell. Sometimes one branch of the net, sometimes two or three, pass out into the process.

In the interpretation of the endocellular net SOUKHANOFF speaks

positively on three points: it is a strictly endocellular structure; it has nothing to do with the neurofibrils of APÁTHY and BETHE; it is not identical with the canaliculus HOLMGREN. Regarding its relation to "l'état spiremateau" of NELIS, he could not at the time of writing offer a positive opinion.

As already stated in the discussion of the structure of the ground substance, HATAI ('03) resolves the net in question into a modified protoplasmic reticulum. His position upon this point is strongly supported by almost every feature of the net which SOUKHANOFF emphasizes,—the lack of uniformity in size and the irregularity in contour of the fibrils, the restricted perinuclear position of the net, its conformity in shape to the shape of the cell and its relation to the processes of the cell. In all of these features the net has a striking resemblance to the filaments which HATAI describes as formed by the matting together of numerous fibrillae of the neurosomic net. But it will be remembered that HATAI considers that the neurofibrils of APÁTHY are identical with this modified reticulum. The interpretation would place him in direct opposition to SOUKHANOFF when the latter says that the GOLGI endocellular net has nothing to do with the neurofibrils of APATHY and BETHE.

By HATAI's work, therefore, another of the manifold structural elements of the nerve cell is explained upon the basis of the fundamental structure of the protoplasm.

The Gemmules.

The structures which BERKELEY called "gemmules" have received various names by other investigators: "épines" by RAMÓN-Y-CAJAL; "appendices piriformes" by MLLE. STEFANOWSKA; and "appendices collatereaux" by others. As treated by many authors they may vary in form from short club-shaped to spindle-shaped or even filamentous structures. In his study of the cellular changes in the cerebral cortex under experimental anemia, SOUKHANOFF ('98) finds that as the symptoms become more acute the gemmules become modified and ultimately disappear. In another work of the same year, he discovered similar changes in the gemmules in animals which have been subjected to the vapors of ether, chloroform and alcohol. In other animals treated with injections of trional the pronounced modifications in the gemmules, as well as other changes in the central system, were attributed to the derangement of general nutrition and not to the specific action of the drug.

In further pathological studies with the GOLGI method, SOUKHAN

OFF ('98) observes that the gemmules are lost in varying degrees in the nerve cells of animals subjected to poisoning by arsenic, rabies, tuberculin and also of animals suffering from thyroidectomy. These studies were checked by preparations of nerve cells from a normal guinea pig killed by decapitation. The nervous tissue was quickly placed in the fixing reagents and received like treatments with the abnormal tissues. The preparations showed gemmules present almost universally upon the dendrites.

In collaboration with CZARNIECKI, SOUKHANOFF ('02) has studied the dendrites of the ventral horn cells of the rabbit with the GOLGI method. By killing the animals quickly with chloroform the authors considered that the tissue was found in the normal condition.

Upon the dendrites of certain cells very few gemmules were found; in others they were numerous, beginning to appear on the dendrites nearer the cell body and becoming more numerous as the distance from the perikaryon increased till in the distal region they almost covered the process. In another type of cell, which lay with the protoplasmic processes partly within the white substance, that part of the dendrite which lay within the white substance bore no gemmules, while the part lying within the grey substance was abundantly supplied with them. And even when the dendrite lay in the border line between the grey and the white substance the side of the dendrite which faced the grey bore more gemmules than did the side facing the white. The authors conclude that the gemmules are much less numerous upon the ventral horn cells than upon the cells of the cerebral cortex, but that they are much more variable in size and shape. They may be pyriform, filamentous, club-shaped, tubercular, or finely branched. Certain of these forms which the authors call "rejitons," which are very irregularly fibrillar and club-shaped, are not found in the cells of the cerebral cortex.

GEIER ('01) has studied with the GOLGI method the cerebral cortex of mammals and birds which have been subjected to the vapors of ether and chloroform for from five to ten minutes. In some of the experiments the gemmules showed a tendency to disappear, while in others the cells appeared perfectly normal. The disappearance of the gemmules was found to be concomitant with the moniliform condition of the dendrites. As GEIER considers the moniliform condition of the dendrites as morbid, due probably to exhaustion or want of nutrition, he would also interpret the disappearance of the gemmules as indicative of morbid processes in the cell.

In a later work GEIER ('02) described the development of the pro-

toplasmic processes of the cells of the spinal cord of the rabbit and cat. Besides the ordinary club-shaped gemmules there are others, in the animal just born, in the form of fine filaments or spines which often arise from a small conical projection of the dendrite. In the middle of this filament may sometimes occur a small thickening. The processes of the posterior horn cells have the same type of gemmules but have them in much larger numbers.

In a rabbit two weeks old the processes have become more regular in outline. This change appears only in the basal part of the dendrites and advances with age towards the periphery. The filamentous gemmules do not appear at this stage all along the dendrites as they did in the rabbit one day old, but occur only in the more distal, irregular part of the process. In a rabbit one month old they are found only on the extreme terminal branches of the dendrite. In cats from birth to one month old the same mode of development is followed. But in kittens two months old GEIER found no typical filamentous gemmules upon the anterior horn cells. In place of them were similar processes of much larger size. This, together with the fact that in an animal three days old the filamentous gemmules are two or three times larger than they are at birth, indicates that some at least of these gemmules grow into dendritic branches. GEIER believes that all such gemmules of the young cells are dendrites in the process of development.

This peculiar type of gemmule is not found upon the posterior horn cells, but the more complex forms are very abundant on the dendrites and occur also on the cell body. GEIER concludes that the gemmules are relatively rare upon the anterior horn cells and of a constant form while they are exceedingly numerous and variable in form upon the cells of the posterior horn. Their absence in any case is associated with the moniliform condition of the dendrites.

PATON ('00) interprets the gemmules as artifacts which mark the points at which the fibrillae of the pericellular net enter the cell or come in contact with it. He asserts that the appearance of the gemmules upon the cortical cells of the embryo is synchronous with the appearance of neurofibrils.

That the gemmules mark the point of continuity between the intracellular and the pericellular fibrils is denied by HATAI. He demonstrates the neurosomic net within the gemmule and the neurosomic nature of the axone terminals which compose this pericellular net. But, while the two fibril systems come into intimate touch with each other, especially at the gemmules, they differ sufficiently in structure

and reaction to enable one to determine a boundary line between them.

As to the physiological significance of the gemmules, their finer structure and their reaction to anesthesia as well as the features of their distribution as noted above, would seem to justify us in according to them an important part in the maintenance of the conduction paths within the central system.

Golgi's Pericellular Net.

The network of fine fibers which GOLGI first described as surrounding the nerve cells of the central and peripheral system has been treated by subsequent writers as both nervous and non-nervous. The more recent work, however, by HELD, BETHE and others demonstrates that this net is continuous with the terminals of medullated axones. HATAI ('03) confirms this position and shows further that the fibrillae of the net are of the same nature as those of the axone. That is to say, they are a modified neurosomic reticulum. We have treated the relation of the net to the nerve cell in the foregoing section upon the gemmules.

HATAI's observations would seem to be in harmony with HOLMGREN's ('99) views regarding the pericellular net of the spinal ganglion cell of *Lophius*. This net lies between the capsule and the cell and between the lamellae of the capsule. It is continuous with fibers which come from other regions of the spinal ganglion and with fibrils which penetrate deeply into the cell. But these fibrils do not become continuous with the protoplasm of the cell into which they penetrate. A light area always separates them from the surrounding protoplasm.

Intracellular Canaliculi.

In 1886 FRITSCH first discovered an intracellular system of vessels in the nerve cell. His observations were made upon certain large cells in the medulla of *Lophius*. He interpreted the structures as genuinely vascular. HOLMGREN ('99) discovers similar structures in the spinal ganglion cell of *Lophius* and claims that he is first to confirm the observations of FRITSCH. But during the same year of HOLMGREN's publication NELIS ('99) introduces "un nouveau detail" in the protoplasmic structure of the nerve cell, which has many features in common with the intracellular vessels of FRITSCH and HOLMGREN. These structures, the "Gefässe" of FRITSCH, the "Kanälchen" of HOLMGREN and "l'état spiremateux" of NELIS, we shall for convenience designate as intracellular canaliculi.

HOLMGREN ('99, '00) asserts that the canaliculus is continuous with the pericellular lymph space and that it is accompanied by trabeculae of the connective tissue capsule of the cell. Along with it occur also the nuclei of its membranous walls and connective tissue nuclei which have migrated in from the capsule of the cell, while corpuscles of the lymph circulate through the canaliculus.

KOLSTER ('00) observes canaliculi also in the nerve cell of the spinal cord and spinal ganglia of *Petromyzon*. He has demonstrated them successfully in unstained sections of cells fixed in osmic acid. He traces them from the periphery of the cell into the deepest part where they seem to be continuous with a perinuclear space of the same nature. A slight invagination of the endothelial capsule may occur where the canaliculus enters the cell and free nuclei are found in the protoplasm which are interpreted as nuclei of the capsule; but KOLSTER, even with the technique employed by HOLMGREN, fails to find a nucleated membranous wall surrounding the lumen of the canaliculus. It is bordered simply by the granular protoplasm of the cell. Still, in a later work, HOLMGREN ('00) confirms his first observations by demonstrations of the canaliculus in the nerve cells of mammals and birds with all the features originally described for *Lophius*. He further shows that electrical stimulation of the nerve cell causes an expansion of the canaliculi.

HOLMGREN's interpretation of the canaliculi receives positive support from the observations of PUGNAT ('01) upon the embryological development of the canaliculus in the nerve cell of the chick. PUGNAT finds that the canaliculi appear first in the outer zone of the spinal ganglion cell on the eleventh day. By the fifteenth day they have reached the central zone. These canaliculi, according to PUGNAT also, have membranous walls and are continuous with extracellular vessels of the same nature.

Canaliculi have been recognized also by BOCHENEK in the largest nerve cells of *Helix*. As to the structural and topographical features of the system, BOCHENEK agrees in the main with HOLMGREN. He finds the connective tissue fibrillae and cells very conspicuous in the protoplasm of the nerve cell and even invading the basal portion of the axone. He explains the structure as a simple invagination of the capsule into the body of the nerve cell or as clefts in the cell. His figures and descriptions would not give one the idea of a clearly defined membranous wall about these clefts, yet he says "Si, dans cet exposé des faits, nous sommes en complet accord avec le travail de HOLM-

GREN, nous ne pouvons pourtant pas souscrire a ses déductions théorétiques."

The theoretical deduction of HOLMGREN to which BOCHENEK cannot subscribe is regarding the significance of the canaliculus in *Helix*. HOLMGREN holds that the nerve cells are poorly or richly supplied with canaliculi according to the functional condition. BOCHENEK has observed, however, that the canaliculi of *Helix* are equally developed in winter and in summer; that is, during the periods of activity and inactivity. He believes, therefore, that they are constant features and are to be explained as an adaptation of a large cell for increased absorbing surface.

The "nouveau détail" which NELIS ('99) calls "l'état spiremateux" is in the form of a spireme-shaped or much coiled, continuous band. In material hardened in GILSON'S fluid or 5% formalin and stained in HEIDENHAIN'S iron haematoxylin and eosin or erythrosin these bands appear uncolored and amorphous, and marked off from the colored ground substance by regular, parallel lines. The position of the spireme varies in position and extent in different cells. It may lie near the periphery of the cell, near the center or in close relation to the nucleus. In some cases one of its borders is indistinguishable from the nuclear membrane; although the author considers that the two elements do not in reality coincide.

NELIS finds the spireme in the plexiform ganglion of the dog, and, less conspicuously, in the superior cervical ganglion. It is present in the pyramidal cells of the cerebral cortex and in the spinal ganglion cells also. He considers that this is a normal structure, but that under certain pathological conditions it may become much more extensively developed and more easily demonstrated. As to its significance, NELIS is undecided, but he is inclined to interpret it as a protoplasmic element of the cell.

DE BUCK and DE MOOR ('99), in a work upon the lesion of the nerve cells accompanying experimental tetanus in the guinea pig, find a system of vacuoles which they identify with the spireme of NELIS. These vacuoles may approach very near the border of the cell, but are always separated from it by a thin layer of protoplasm. VAN GEHUCHTEN and NELIS ('00) have observed the structure also under pathological conditions and conclude that it is accentuated by arsenic poisoning, tetanus, etc.

Among these various descriptions of intracellular vessels it is quite easy to identify the type described by KOLSTER with the canaliculus of HOLMGREN, by assuming that KOLSTER has failed to demonstrate the

membranous walls of the vessel. Furthermore, the general form and position of the spireme of NELIS harmonizes well with the canaliculus of HOLMGREN. Though NELIS does not find nucleated membranous walls, he does find parallel walls with a sharp contour. It only remains to demonstrate the continuity of the structure with extracellular lymph vessels in order to identify it with the canaliculus of HOLMGREN. But as to the interpretation of BOCHENEK's clefts we find greater difficulty. He has compared his preparations with the original preparations of the spireme made by NELIS and has decided that the two structures are totally different. He expresses himself as surprised, also, that HOLMGREN should homologize the canaliculi of *Helix* with the spireme. This suggests that HOLMGREN and BOCHENEK may be dealing with altogether different structures. It may be that BOCHENEK has not seen the genuine canaliculus with membranous walls, but that he has demonstrated only deep clefts in the cell which are filled with the capsular tissue.

The Nucleus.

HOLMGREN ('99) finds that the size of the nucleus in the spinal ganglia of *Lophius* varies with the size of the cell. The linin net and chromatic granules, which stain red with toluidin blue and erythrosin, are massed thickly around the nucleolus and radial branches stream out from this to the nuclear membrane which is acidophile also. On the side of the nucleus which lies nearest the center of the cell the contour may become flattened or even indented by a mass of tigroid substance which accumulates at this point. The nuclear membrane of this region thickens and changes its reaction to the stain, for it now stains dark blue in toluidin-erythrosin, deep black in iron haematoxylin and green with the triple BRONDI stain. Simultaneously with this change in the nuclear membrane there come changes in the tigroid mass, which is heaped upon the nucleus in this region. The large tigroid bodies, which, earlier in the process, were packed closely together here, have become resolved into small granular heaps or scattered granules suspended in a homogeneous or purely granular ground substance. The latter stains blue with toluidin-erythrosin, gray or perhaps black with iron haematoxylin and red with the triple acid stain. Following this condition the thickened part of the nuclear membrane disappears either throughout the entire extent or at intervals. Through this cleft the cytoplasm becomes continuous with the karyoplasm. The union takes place through protoplasmic bands (Züge) which radiate from the centrosome into the nuclear substance and become continuous

with the linin net. The part of the linin net which enters into the radiating bands contains granules which stain a darker red than the other acidophile elements and black with iron haematoxylin. In the radiating bands beyond the limits of the nucléus there occur granules which stain black also in iron haematoxylin but dark blue in toluidin-erythrosin. They are sharply differentiated from the tigroid elements by their reaction to DELAFIELD'S haematoxylin and the triacid stain. In the former they stain blue-black, while the tigroid elements stain faint blue; in the latter, they appear green while the tigroid elements appear red. This reaction places them in the category of basichromatin and they must be considered as such elements which have migrated out from the nucleus. They become basophile during their migration from the nucleus and represent the nuclear chromatin.

While these changes are going on the nucleus enlarges and migrates towards the periphery of the cell, till, in some cases, a mere film of protoplasm separates it from the cell membrane. In the meantime, also, the acidophile granules of the nucleus have increased greatly in number and during the process also the nucleolus sends off fragments into the cytoplasm.

KOLSTER ('00) also contributes interesting facts upon the general morphology of the nucleus. In a large series of preparations he finds that only a part of the nuclear border has a regular outline and limiting membrane. As studied in serial sections the nuclei, practically without exception, lose their membrane in a particular region and the karyoplasm pushes out in pseudopodia-like processes into the cytoplasm. This appears to the author to be a constant feature and not due to any peculiar physiological condition. He interprets it as concerned in the nutrition of the nucleus. But, compared with HOLMGREN'S work, KOLSTER'S results are noteworthy from the fact that the side of the nucleus which is marked by this irregular contour may lie opposite the centrosome while HOLMGREN finds it directed toward the centrosome.

Irregularities in the border of the nucleus have been observed also by BOCHENEK ('01) in certain large nerve cells of *Helix*.

The idea that the nuclear membrane breaks down and that there is an interchange of formed substance between the nucleus and the cytoplasm, especially as described by HOLMGREN, is opposed by SCOTT ('99). He believes this appearance is due to the action of the knife in cutting. However, it hardly seems probable that both HOLMGREN and KOLSTER should be utterly deceived in this manner. Moreover, it does not seem that SCOTT'S fundamental thesis or his results

exclude the possibility of such ruptures in the nuclear membrane as HOLMGREN and KOLSTER describe.

The Nucleolus.

The behavior of the nucleolus in the spinal ganglion cells of *Lophius* as described by HOLMGREN ('99) has already been mentioned in the section relating to the nucleus. Regarding the finer structure and chemical nature of the nucleolus the works of KOLSTER, HATAI and SCOTT are noteworthy.

In the spinal ganglion cell and the FREUD' schen cells of *Petromyzon*, according to KOLSTER, the nucleolus appears homogeneous only in preparations fixed in sublimate and stained in iron haematoxylin. In all other methods which the author used he found two rather sharply differentiated zones, a dark, relatively large central portion surrounded by a shell of substance which stains more faintly than the central body. In some preparations there appeared a granular, intermediate zone between the central core and outer shell. KOLSTER is inclined to interpret the nucleolus, not as a solid mass, but as a vacuole with peculiar liquid contents. The reaction of the contents to reagents accounts for the structural features which appear by different methods. PUGNAT, on the other hand, considers that the central, granular appearance of the nucleolus is due to the presence of formed bodies.

SCOTT ('99) and HATAI ('03) both demonstrate an oxyphile center with basophile peripheral zone in the nucleolus. Only the basophile part represents the chromatin, while the oxyphile center is the true nucleolar substance.

The behaviour of the nucleolus of the nerve cell during mitosis has been carefully worked out by HATAI. While in the adult nerve cell the larger part of the nucleolus stains blue with toluidin-erythrosin, in the germinal cells the entire nucleolus stains a deep red. In the later telophase stage of mitosis the nuclear substance, which has become closely massed around the chromosomes, dissolves and accumulates again in small spherical masses which collect near the center of the nucleus. Each granule of this group sends out a process from either pole. These processes from the various granules anastomose to form a net with granules at the angles of the meshes. The linin and the basophile nuclear substance now collect around this group of acidophile granules to form the nucleolus of the adult nerve cell. But if the cell is to divide again, the linin which has accumulated around the nucleolus breaks up in the early prophase and the nucleolar granules separate. As the spireme forms they collect upon

it and ensheathes it, and form groups in the nuclear net. That which clings to the chromosomes become modified to form the "Halbspindel fasern." As the spireme splits, nucleolar substance still persists around the daughter spiremes. This tends to collect at the middle of the curved chromosomes which are turned with the convexity towards the centrosphere. As the daughter spiremes separate, nucleolar substance unites with the linin to form the rays of the central spindle. The linin in this phase stains slightly deeper than the cytoplasmic reticulum but not so deeply as does the nucleolar substance. It is only in the telophase stage that the nucleolar substance, which has been associated with the linin, becomes indistinguishable from it.

There seems to be conclusive evidence, therefore, that the nucleolus of the adult nerve cell is a heterogeneous structure with an oxyphile center which is structurally and chemically allied to the linin, and with a peripheral zone of basophile chromatin.

The Centrosome.

HOLMGREN finds that the centrosome in the spinal ganglion cell of *Lophius* is located in the center of the cell. It forms the center of the concentric circles and radial "Züge" of the cytoplasm. HOLMGREN suggests that, since its reproductive function must have ceased, and since it holds this constant relation to the trigroid substance, it is probably concerned in the nutritive functions of the metabolism of the cell. The object which LENHOSSÉK first interpreted as the centrosome in the spinal ganglion cell of *Rana* is, according to HOLMGREN, nothing other than a section through an invaginated trabecula of the capsule.

KOLSTER identifies the centrosome in the nerve cells of *Petromyzon* even in unstained preparations, but it is not located in the center of the cell. The centrosphere is surrounded by an irregularly shaped mass of granules which are arranged in the form of a dense reticulum, which we have already discussed in connection with the ground substance of the cytoplasm. The interior of the body in unstained preparations appears as dark, circular lines separated by bright points. In other methods, it appears as a circular space in which the centrosome lies.

The centrosome in the nerve cell of the dog and rabbit infected with rabies has been studied by NELIS. He holds that the organ is not visible in the normal nerve cells of mammals, but that it is brought into plain view during chromatolysis which accompanies rabies. He suggests that this reappearance of the centrosome immediately before the nucleus atrophies indicates a tendency toward cell division at that

time. Such a hypothesis is supported also by the fact, observed by several investigators, that karyokinetic figures occur in the nerve cells of animals infected with rabies.

HATAI, however, finds the centrosome present in the nerve cell of the adult rat, though it is not so generally found in the adult as in the young. The centrosphere is here densely surrounded with neurosomes which go out in radial lines from it, somewhat as KOLSTER finds in *Petromyzon*. Within the clear centrosphere HATAI finds, also, radii of extremely fine granules centering in the centrosome and staining like it. In some cases the place of the single centrosome may be taken by a number of smaller granules, but in such cases the radial arrangement in the centrosphere is lost. HATAI ('02) describes also the behavior of the centrosome in the mitosis in the embryonic nerve cell. One of the two centrosomes seems to migrate to the opposite pole of the nucleus and then each divides, giving two centrosomes in each centrosphere during the mitotic process.

The Tigroid Substance and Chromatolysis.

I. Structural and Chemical Features.—The studies of SCOTT ('99) upon the chemistry of the tigroid substance of the nerve cell are especially noteworthy since they are based upon both embryological and comparative methods, and since he has employed both cytological and micro-chemical technique. He has not confined himself to the use of the NISSI method, but has used toluidin blue and eosin to differentiate the oxyphile and the basophile substances.

By the haematoxylin method for the Prussian blue reaction after treatment of the tissue with acid ferrocyanide, and by the ferrous sulphide reaction after treatment with ammonium sulphide and glycerine, the basophile and oxyphile nuclear substance and the tigroid bodies show the presence of iron. By the oxide of molybdenum reaction after treatment with a nitric acid solution of ammonium molybdate followed by phenylhydrazin hydrochloride the same elements of the cell show the presence of phosphorus. In digestive tests SCOTT finds that immersion for several days in 0.2 per cent hydrochloric acid, at 37°C., does not affect the oxyphile nuclear substance, but after digestion in pepsin and hydrochloric acid the oxyphile substance cannot be demonstrated by the most vigorous stains. In the pepsin experiments the nucleolus sometimes disappears, but SCOTT considers that it is only loosened from the slide by the digestion of its oxyphile center by which it may have been attached.

While treatment of the nerve cell with acid alcohol aids in dem-

onstrating the presence of iron, prolonged treatment will extract all the iron and render the tissue colorless under the toluidin blue stain. Yet after all the iron has been extracted phosphorus is still demonstrable in the tigroid substance and in the oxyphile and basophile nuclear substance. Treatment with alkalies removes the iron from the tigroid substance but not from the nucleolus and the oxyphile nuclear substance, excepting when the treatment is prolonged, while the nuclei of neuroglia cells in the same preparations stain normally in eosin and toluidin blue. Prolonged treatment in the alkalies, however, does not affect the phosphorus of the cell. The author finds that fresh defibrinated ox-blood, owing to its alkalinity, has the same effect as potash of soda upon the nerve cells fixed in alcohol.

By these differential methods SCOTT concludes that the tigroid substance is one of at least three nuclein compounds found in the nerve cell, the other two being the "basophile covering of the nucleolus and the oxyphile nuclear substance." The descent of the three compounds was traced by SCOTT from the chromatin of the germinal cell. "The chromatin," he says, "divides into two parts, each containing iron and phosphorus, but the one is oxyphile and remains in the nucleus, while the other is basophile and diffuses into the cell body and becomes the NISSL granules." This position would seem to be supported, also, by VAN GEHUCHTEN ('97) who is inclined to think that the nuclein (chromatin) of the karyochrome cell is equivalent to the chromatin substance of the somatochrome cell.

If the nuclear chromatin is the source of the first chromatic elements in the cytoplasm of the embryonic nerve cell, does it continue this role in the adult cell? If it does, in what manner is the distribution of the chromatic elements from the nucleus to the cytoplasm brought about?

HOLMGREN ('99) has described an elaborate process, which we have discussed in the section relating to the nucleus, by which the nuclear wall breaks down and the oxyphile nuclear substance migrates into the cytoplasm and becomes at the same time metamorphosed into basophile tigroid substance. By the same process also the basophile covering of the nucleolus breaks off in large masses which are carried out into the cytoplasm. SCOTT, however, since he considers that the breaking down of the nuclear membrane and the displacement of the nucleolus is an artifact, is convinced that, if the transference of chromatic substance from the nucleus to the cytoplasm continues during adult life, the process is diffusion and in no sense a transposition of formed chromatic bodies. However, the nuclear origin of the tigroid

substance, at least in the adult, is opposed by VAN DURME, who believes that the tigroid substance is derived from the nucleo-albumins of the lymphocytes.

VAN GEHUCHTEN ('97), accepting the reticular structure of the ground substance, believes that the tigroid substance accumulates at the nodal points of the net. These accumulations enlarge in certain regions and form masses which appear homogeneous when they become sufficiently dense to obscure the reticular framework. A mesh of the reticulum which remains unfilled produces a vacuole. VAN GEHUCHTEN attributes the formation of these bodies to the affinity of the protoplasmic net for a special chemical substance. It is, therefore, the form and disposition of the cytoplasmic net that determines the size and distribution of the tigroid bodies; and this, in turn, is governed by the function of the neurone.

SCOTT ('99), on the contrary, argues that the shape and distribution of the tigroid bodies are determined by the modification in the shape of the cell during growth. The tigroid substance diffusely permeates the whole cytoplasm in the early history of the cell. But the growth of the cell and especially the development of the protoplasmic processes break the substance up, by a purely mechanical process, into separate bodies. The distribution of these bodies would seem, therefore, to be governed by the proportions and shape assumed by the cell.

SCOTT takes the position, furthermore, that the tigroid substance cannot be considered as a part of the cytoplasmic net since it diffuses into the cytoplasm after the net is formed. Though the two substances may be intimately associated, they are structurally distinct. He considers that the granules are homogeneous and that appearances to the contrary, including vacuoles, are to be explained by irregularities in their surfaces.

In *Lophius* HOLMGREN ('99) finds that the tigroid body may be resolved into two constituents: a homogeneous ground substance, which stains bluish gray in iron haematoxylin and which tends to stain in both colors with toluidin-erythrosin; and granules which are suspended in the ground substance and which stain black in iron haematoxylin and deep blue in toluidin-erythrosin. The ground substance forms in areas of varying shape and size and the granules may be diffusely distributed through it or massed into solid bodies of different proportions. HOLMGREN does not discover any definite relation of these bodies to a formed ground substance of the cytoplasm.

Although the substance occurs in comparatively small amounts in

the nerve cells of *Lophius*, HOLMGREN describes an interesting feature of its distribution in the cell. Its ground substance has a two-fold arrangement relative to the centrosome; in radii which widen as they approach the periphery of the cell, and in concentric circles around the centrosome. Both the radial and circular bands are more or less irregular in outline. This typical arrangement, however, is often found modified or obscured. The circular bands may overlap each other and those which come nearest the nucleus are more or less diverted from their symmetrical course so as to encircle the nucleus. And on the side of the nucleus nearest the centrosome the tigroid substance collects into a mass of unusual size and becomes involved in the process of transfusion of nuclear substance into the cytoplasm as we have described in the section relating to the nucleus.

HOLMGREN ('00) believes that the distribution of the tigroid bodies is determined by the arrangement of the canaliculi. He has noticed that the tigroid substance of a given cell is most abundant in the region of the most conspicuous canaliculi; also, that it is very abundant in the nerve cells of animals which are characterized by numerous canaliculi. Furthermore, electrical stimulation of the nerve cell is accompanied by an increase in the tigroid substance and also by an expansion of the canaliculi.

Although HOLMGREN's interpretation regarding the increase in tigroid substance under electrical stimulation of the nerve is open to serious objection, his observation would nevertheless support his thesis that the condition of the tigroid substance is correlated with that of the canaliculi. This idea received further support from the observations of PUGNAT ('01) who finds that the canaliculi appear synchronously with the tigroid bodies in the embryonic nerve cell of the chick.

Regarding the function of the tigroid substance, its relation to the ground substance and its embryogenesis point to the same conclusion: that it is a nucleoproteid whose kinetic energy is transformed into potential energy by the metabolism of the cell. The distribution of the substance through the cytoplasm may, as SCOTT points out, contribute to a more prompt and rapid metabolism than if the activities were restricted to the nucleoproteids within the nucleus. This interpretation seems to be born out further by the facts of chromatolysis.

II. Chromatolysis.—In the strict sense "chromatolysis" applies only to a progressive diminution of the chromatic substance of the cell, but other phenomena which seem to be concomitant with this change will be, for convenience, included in this discussion.

VAN DURME ('01) has studied with the NISSL method the PURKINJE cells and the cells of the cerebral cortex of the rabbit under conditions of rest, fatigue and exhaustion. In the cerebellum of the normal specimen at rest he finds cells of two types: "chromophiles," with relatively large amount of chromatin; and "chromophobes," with relatively small amount of chromatin. Both types vary greatly in size. In the chromophiles the protoplasm is uniformly blue with sharply colored chromatic bodies of various form and size. The larger ones lie near the nucleus and a crescent of chromatic substance rests upon the side of the nucleus. The nucleus is of oval form and the karyoplasm stains uniformly blue. NISSL bodies occur also in the proximal portion of the axone. The reticular structure of the cytoplasm cannot be seen. In the chromophobes, however, the cytoplasmic reticulum is apparent, while the cell body is on the average larger than the chromophiles. The peripheral zone is in many cases comparatively free from chromatic substance and the axone is entirely free from it.

Whether these two types are actual or due to functional conditions VAN DURME is not positive, for, as he points out, it is impossible to find all the cells of the nervous system in a condition of absolute rest. He finds, accordingly, that in rabbits which have been killed in the early morning there is great variation in the proportion of the two types of cells.

For studying the condition of the cerebral and cerebellar cells during activity and fatigue VAN DURME stimulated these regions indirectly through the spinal cord with electricity. He examined the cerebrum and cerebellum after continuous stimulation of the cord for periods of five minutes, thirty minutes, two and one-half and seven hours. He concludes from his experiments that abundance of chromatic substance and an oval nucleus are characteristic of the condition of rest. Activity is accompanied by a reduction of chromatic substance in both the cell body and the nucleus, and an increase in volume of the cell body and nucleus. Fatigue, in like manner, is characterized by the presence of cells extremely impoverished of chromatic substance and rich in vacuoles. The author's explanation of this process is noticed in a following paragraph.

Regarding functional changes in the nerve cell of the cerebral cortex, GEERAERD has experimented upon the guinea pig. To produce fatigue he employs natural methods in preference to artificial stimuli such as electricity, which, he believes, is highly objectionable. His argument against it, indeed, seems rational. He recognizes that under natural conditions there is a physiological barrier to over-stimulation

of the central nervous system, but electrical stimulation may drive the central cells beyond the limits of natural activity into morbid processes. From a series of experiments he concludes that activity causes a reduction in size and number of NISSL bodies in the cortical cells, and a diffusion of the chromatic substance into the cytoplasm. There is no noticeable change in the nucleolus. This condition is initial to fatigue and becomes more and more accentuated. Finally the cell, making a last effort, comes into a state of fatigue which is accompanied by increase in volume of the cell body and disappearance of nearly all the chromatic substance of both the cytoplasm and the nucleus.

GEERAERD followed these studies with experiments upon recuperation. By similar methods he examined the cortex of animals which, after complete exhaustion, had been allowed to rest for periods varying from five minutes to an hour. The first indication of repair was discovered after thirty minutes of rest, when the contour of the cell body is found to have regained its normal condition. After three-quarters of an hour a blue zone appears around the nucleolus, which is finely granular with conical projections reaching out to the nuclear membrane. But while the process of repair seems to appear first in the nucleus, the process in the cytoplasm advances from the periphery towards the nucleus. The first tigroid bodies appear next to the cell membrane and gradually invade the deeper regions of the cell. He finds further that while the large pyramidal cells are last to be affected by fatigue they are first to recover.

GEERAERD calls attention to the fact that in the earlier stages of activity the cytoplasm stains a deeper blue than normal but that this is due, not to an increase in the tigroid substance, but to the breaking up into small granules. He believes that this fact accounts for the erroneous position taken by certain authors that activity causes an increase in the tigroid substance.

In comparing the retina of a bird which had been subjected to a bright light for a prolonged period with the retina of another which had been confined for a like period in a dark room, CARLSON ('03) finds there is a "*constant difference in the amount and appearance of the Nissl substance in the cells of the ganglionic and bipolar cell layer.*" The ganglion cells of the stimulated retinae are poorer in NISSL's substance, the NISSL's granules present are less distinct than in the resting retinae, and the protoplasm of the cell bodies takes a diffuse blue stain." This difference is not equally marked in all preparations nor in all regions of the same preparation.

The lesions of the nerve cell accompanying anemia have been

studied by DE BUCK and DE MOOR ('00). Their experiments consisted in an examination of the lumbar cord after temporary and repeated compressions of the abdominal aorta in the rabbit for from five minutes to one hour, and after permanent ligature. They find that following a ligature of one hour no lesion can be discovered if the animal is killed immediately; but if it survive for one hour and a half after the ligature is removed, lesions are apparent. One-half hour is sufficient period of ligature to cause a marked lesion. The chromatic elements break up and ultimately disappear, leaving the cytoplasmic reticulum in view. The nucleus is more resistive than the cytoplasm but finally undergoes homogeneous atrophy. Lesions of this character are more marked in prolonged, continuous ligature than in repeated, temporary ligature. In twenty-four hours after a ligature of an hour many cells were found to be completely destroyed. To all these processes the spinal ganglion cells are more resistant than the cells of the cord. The authors conclude that these changes relating to the cytoplasm cannot be considered as characteristic of anemia, for similar modifications arise from other causes, such as infectious diseases and toxins. The nuclear changes, however, they think, may be characteristic.

VAN GEHUCHTEN's earlier position regarding the lesion of the nerve cell resulting from section of the axone was that all such cases were followed by chromatolysis in the cells of origin. His more recent work ('98), however, leads him to the conclusion that section, or ligature, or a nerve will not always produce chromatolysis in the cells of origin. He observes such a case in the section of the sciatic nerve of the rabbit, in which case the cells of origin are found in the pyknomorphic condition but not in a state of chromatolysis. This condition he attributes to the traumatism. Later researches, in collaboration with VAN BIERVLIET ('00), convince VAN GEHUCHTEN that the lesion of the cell of origin following injury to the nerve varies both according to the intensity of the injury and according to the nerve involved. The cranial nerves appear to be much less resistant than the spinal nerves. The authors conclude also that the cell of origin which is affected by section of the axone may recuperate without regeneration of the axone.

Regarding the comparative cellular lesion which follows mere section of the nerve and extraction of it, DE BEULE has experimented upon the rabbit by extracting and sectioning the hypoglossal nerve. The cells of origin were examined at from one to thirty-five days after the operation. He found that on the fourth day the cells were still increasing in size, but on the sixth day they had begun to grow smaller,

though they had not yet returned to the normal size by the tenth day. By the fifteenth day more than half the cells had disappeared, while at the end of thirty-five days there was not a trace of a cell to be found in the position of the nucleus of origin of the affected nerve. The author believes that while, in case of section of a nerve, the cells of origin enter upon a phase of reaction, this is followed by recuperation; but in "arrachment" the phase of reaction is followed by progressive atrophy of the cell.

Following poisoning by arsenic SOUKHANOFF finds that changes of varying intensity appear quickly in the spinal cord and spinal ganglia, and that in many preparations scarcely a normal cell would be found. The lesions of the cell body were marked by diffuse coloration, by loss of regular contour of the chromatic bodies and by turgescence of the cell. More accentuated lesions were characterized by clear spots around the periphery of the cell, owing to the loss of chromatic substance. This was followed by a still more marked lesion expressed by vacuolization of the cytoplasm. The degree of vacuolization varies with the duration of the poisoning. SOUKHANOFF finds no evidence of peripheral chromatolysis which has been described by other authors as characteristic of arsenic poisoning. In the nucleus there appears a diffuse coloration, obscurity of the nuclear membrane and shrinkage.

In his paper upon the finer structure of the nerve cell, VAN GEHUCHTEN ('97) took the position that chromatolysis is essentially a dissolving of the tigroid substance. This results in turgescence of the cell which, beginning at the center, mechanically forces the nucleus towards the periphery of the cell, and causes expansion of the cell. A reconstruction of the chromatic bodies reverses the process. VAN DURME ('01) explains the turgescence of the cell during chromatolysis upon the hypothesis that the katabolic products in the cell, notably sarcolactic acid, increase the osmotic power of the cell and that this produces turgescence.

Chromatolysis itself, VAN GEHUCHTEN ('97) holds, need not be considered as a lesion in the cell. He suggests also, through VAN BIERVLIET ('99), that chromatolysis is, in a sense, a return of the cell to the embryonic condition: that is to say, a condition in which the chromatic substance exists in solution. VAN BIERVLIET also concludes that chromatolysis is perfectly compatible with the normal activities of the cell. DE BEULE ('01) believes that all nerve cells which undergo a non-physiological excitation, which may be traumatic, physical or

chemical, undergo chromatolysis. This is a useful reaction, a utilization of the material to support a special strain upon the cell.

It seems probable, therefore, from the conclusions of these authors, and also from the numerous experiments especially upon poisoning, anemia, and high body temperature, that the nerves may perform their normal function while the cells of origin are undergoing rather marked chromatolysis, and that the cellular lesions resulting from any acute condition may be due in a large measure to general disturbances in the system rather than to the specific disease itself.

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