A STUDY OF THE SPINAL CORD BY NISSL'S METHOD IN TYPHOID FEVER AND IN EXPERIMENTAL INFECTION WITH THE TYPHOID BACILLUS.*

By JOSEPH LONGWORTH NICHOLS, M. D., Late Fellow in Pathology, Johns Hopkins University.

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

Plates II–IV.

This paper presents the results of the study of certain changes noted by means of Nissl's staining method in three cases of typhoid fever and in a series of experimental inoculations of rabbits with Bacillus typhosus. My observations relate mainly to the alterations shown by this method in the motor cells of the ventral horns of the spinal cord and in the nerve cells of the dorsal root ganglia. With the Nissl method only one constituent of the cell body is stained by the basic dye, and hence this is called the stainable or chromatic substance. In the normal nerve cell of the motor type this consists of coarse, spindle-shaped masses which are regularly distributed throughout the body of the cell, and, with their long axes more or less parallel, run from process to process. On closer examination these masses, called the " Nissl bodies," are seen to be composed of an aggregation of small deeply staining granules (Held, 14). Into the dendrites these masses are continued less thickly distributed and drawn out into thin threads, plastered against the wall or angle of some branch, or coursing through the middle of the process. The axone on the other hand is entirely clear of stained particles, as is also a small area about its origin, known as the " axone hillock." The nucleus occupies the centre of the cell and, with the exception of the nucleolus, contains normally no substance stainable by Nissl's method. The nucleolus is small, sharply outlined and very intensely stained.

The points to be emphasized, as regards the normal cell, as seen by

* Received for publication April, 1898.

this method, are the fairly constant size of cell body, nucleus and nucleolus, the even, regular distribution and distinct character of the Nissl bodies, the central position of the nucleus, the clear nuclear substance and the small deeply staining nucleolus.

The stainable constituent of the cell body is now generally believed to represent a nutritive substance, previously soluble in the fluid portion of the cell, but precipitated by fixing agents as incrustations upon the achromatic or unstained portion. The achromatic portion of the body of the cell is regarded by Marinesco (22, etc.) as an unstained network prolonged into the processes as minute fibrils, which represent the conducting portion of the cell. Van Gehuchten (9) would account for the regular shape and arrangement of the chromatic bodies by supposing them to be incrustations, especially at the points of intersection of this network.

It obviously makes no difference in the results of our study of pathological effects whether we believe these structures to exist definitely as such in the cell during life, or to appear only after death as the result of fixing agents. What is of importance is that they possess in the normal cell a definite arrangement, constant for a variety of fixing agents and stains, though best shown by the Nissl method (Flatau, 6).

The normal cell shows variation from this type chiefly in the amount of chromatic substance. When this is present in larger amounts, the condition has been termed by Nissl (29, 30) "pyknomorphism," and has been thought to represent a state of rest. When, on the other hand, the nutritive element has been used up and chromatic substance is scanty, he has termed the condition "apyknomorphism." This variation in amount of chromatic substance does not alter the regular shape or regular distribution of the Nissl bodies. When these are found broken apart and destroyed, the condition is pathological, and for it Marinesco (21) has suggested the term "chromatolysis."

METHODS.

In the cases of typhoid fever to be described sections were taken from the cervical, thoracic, and lumbar regions of the cord and their respective dorsal root ganglia when practicable. Small pieces of the tissue

were placed at once in 95 per cent. alcohol and allowed to remain there from 12 to 20 hours. They were then transferred to absolute alcohol, and thence to a mixture of equal parts of absolute alcohol and xylol, remaining in each 12 to 20 hours, the longer period being more desirable, as it produces less distortion. After 5 hours in xylol they were kept in melted paraffin at about 55° C. for from 3 to 4 hours, and then embedded in paraffin having a melting point of 52° C.

The sections were stained in Nissl's methylene-blue solution, and differentiated in 0.1 per cent. alum solution, as recommended by Held (14). For mounting benzine colophonium was used, the benzine being driven off with as little heat as possible.

THE HUMAN CASES. SPINAL CORD.

Of the three human cases the first was of ordinary character, but a very severe infection; the second a severe infection ending in perforation and sudden death; the third a very severe infection in an old man, unrecognized before autopsy. The experimental material was derived exclusively from rabbits.

Case I. Man, aged 28 years, who died in the hospital after a severe attack lasting 11 days from date of onset. The ordinary signs of typhoid fever were present, and there were no complications except unusual nervousness and delirium, and a short time before death, difficulty in swallowing, which may be accounted for by ulcers in the œsophagus found at autopsy.

The autopsy was made 6 hours after death, the body having been preserved on ice. In addition to intestinal ulceration, ulcers were found in the gall bladder, stomach, œsophagus, larynx, and on the tongue.

The bacteriological examination showed pure cultures of Bacillus typhosus in the liver, spleen, mesenteric and retroperitoneal lymph glands, and urinary and gall bladders. The ulcers of the œsophagus and larynx contained streptococci and staphylococci.

The number of altered nerve cells in the cord is very numerous, but in most of these the alterations are not marked, except in the lumbar region of the cord. The size of both cell and dendrites is increased; in the more advanced stages the cell body is considerably enlarged. In the cell there has been a breaking apart and partial or complete solution of the chromatic substance or the Nissl bodies,

advancing from the region of the nucleus out toward the periphery. The component granules of these bodies not merely are separated and partly destroyed but also appear more or less diffused in the fluids of the cell, so as to form when precipitated pale, blurred flocculent-looking masses. [Plate II, Fig. 1.]

This process has not gone on to the same extent in all cells. Some, notably in the cervical and thoracic regions, vary hardly at all from the normal type. Others, and these in great numbers in the lumbar region, show an advanced stage of this form of chromatolysis. In this region wherever the axone with its hillock is accurately determined, the dissolution of the granules is especially marked in that portion of the cell, and, wherever pronounced, the nucleus has migrated somewhat toward the opposite side of the cell. In these cells the slightly enlarged dendrites are almost free from chromatic substance, rendering the determination of the axone, although not a more difficult problem, yet one requiring more care. [Plate II, Figs. 1 and 2.]

The achromatic substance has been altered in some parts but very slightly, and in such a way as to stain very faintly with the methylene-blue, a condition which, with the absence of the chromatic substance, serves to show more clearly its structure. In the dendrites and body of the cell, this staining is of a more indefinite nature; about the axone hillock, the staining is granular or net-like; in the axone, in the form of very few and fine, parallel, granular streaks. (Marinesco, 22.)

The nucleus is not enlarged in the cells of less advanced chromatolysis. Under the low power in the nuclei of most of these cells there is apparently a diffuse blue stain. This, under the high power, resolves itself into minute, faintly staining granules. In the more advanced stages the nucleus, in addition to being often eccentric, has become considerably enlarged, while the granular deposit is not increased and therefore is less thickly and more unevenly distributed within it. In all stages the nucleolus is greatly enlarged and less deeply stained than normal. In many of the cells it is so faintly stained and so vacuolated as to be scarcely visible, while in others it is undergoing complete disintegration.

Case II. Woman brought to the hospital suffering from typical typhoid fever. The disease ran an ordinary course until the morning of the 10th day, when the patient sank rapidly with profuse sweating, vomiting, dull delirium, distended and tender abdomen and died at 7.30 that night. There was a leucocytosis of 22,600.

At autopsy, 14 hours after death, a perforation of the ileum, with a consequent general, sero-fibrinous peritonitis, was noted in addition to the usual post-mortem appearances of typhoid fever.

Typhoid bacilli were cultivated from the bile, spleen, mesenteric glands and kidney; Bacillus coli from the lung, peritoneum, kidney, spleen, and liver.

Obviously the secondary infection of the peritoneum makes this not an absolutely pure case, but in view of the long period of infection with the typhoid organism and the shortness of the secondary infection, the latter can be practically disregarded.

The changes in the ventral horn cells are so nearly like those of Case I that they may be dismissed with a few words. In the numbers of the cells affected and the characters of the degeneration the two cases are nearly identical. The only difference is in a slighter degree of alteration in the nucleoli, these retaining in Case II a deeper stain and more definite outline. In some cells, although the chromatolysis spreads inward from the axone hillock, there are a few large abnormal blocks of chromatic substance filling in the corners formed by the entrance of the axone and the periphery of the cell.

In the two foregoing cases, in spite of the great and early disappearance of chromatic substance from the dendrites, by far the greater number of cells show the central form of chromatolysis. The point of entrance of the dendrites is in nearly all cases blocked by the remains of Nissl bodies, which had been altered much less than those in the more central portion of the cell [Plate II, Fig. 1]. There are a few cells, however, which show a more complete destruction advancing from the periphery and in which the nuclei are not eccentric. It was noted, however, that this appearance is, in some cases, in sections which do not show the nucleus, but have passed through the dendrites at the periphery of the cell, and that, in the succeeding section or sections, as one approaches the nucleus, this appearance gives place to the central form of chromatolysis. In cells showing this peripheral

character of chromatolysis the nucleus when present in the section is not eccentric, but it seems to be undergoing disintegration in the centre of the cell.

Case III. Man, aged 67 years, who entered the hospital in a dull, listless state, soon passing to unconsciousness, and from whom no satisfactory replies could be obtained. Friends stated that he had been ailing for two months with loss of appetite and weight. For two weeks before admission he had pains in the back, indigestion and shortness of breath and was very thirsty. Physical examination showed a large area of dulness in the right lower lobe with friction and tubular breathing. There was no expectoration. There was a leucocytosis of 15,000. The pulse was 128, while the temperature rose toward evening to 104° F. These facts naturally led to the diagnosis of senile pneumonia. The patient died two days after admission, and the autopsy was made within six hours after death.

At autopsy there was found a recent thrombus in the branch of the pulmonary artery supplying the lower lobe of the right lung, and consolidation of this lobe with gangrene and perforation of the visceral pleura. The spleen was enlarged and soft, but no intestinal lesions were present. The bacteriological examination, however, revealed the presence of Bacillus typhosus in the consolidated area in the lung, in the spleen, and in other organs. This case, which will be reported in detail elsewhere, is of especial interest as an example of infection with the typhoid bacillus without intestinal lesions.

Unfortunately the cord in this case could not be removed in its entirety, and therefore only as much as could be taken out through the cranial cavity could be reserved for examination.

In this case the earlier alterations described in the first two cases can be traced in only a few cells. The vast majority of cells show a much more advanced stage of alteration. These cells are swollen and distorted in varying degrees. The central portion of the cell is a mass of ill-defined, extremely pale, flocculent-looking material, studded everywhere with small round refractive bodies, probably representing remains of the normal achromatic network [Plate II, Figs. 3, 4 and 5]. Scattered along the periphery are a few small and large clumps of pale washed-out looking granules undergoing the later stages of disintegration and solution.

The nucleus is large and swollen, and sprinkled with the finely granular deposit. It no longer occupies a position anywhere near the centre of the cell, but bulges from the periphery. Along its internal margin there is often a fine dark line composed of minute deeply staining granules [Plate II, Figs. 3 and 4]. The nucleolus is pale and vacuolated and frequently may be seen to protrude from the prominent nucleus. In some few cells there seems to have been an actual extrusion, the nucleolus lying free with the remains of the crumpled nuclear membrane about it [Plate II, Fig. 4]. This latter appearance, however, may be due to tearing with the knife, although no injury to the surrounding tissue can be made out.

There seems to be a marked disappearance of many processes from the cells, perhaps an illusion due to the great increase in size.

THE DORSAL ROOT GANGLIA IN HUMAN CASES.

The consideration of the dorsal root ganglia in these cases, as elsewhere, is attended with certain difficulties. These are, chiefly, the absence of processes, and the great variation under normal conditions in the size of the cells and in the amount and distribution of the chromatic substance. Thus Lugaro has divided these cells into five normal types. For this reason it has been thought better to notice only such alterations as are well marked, and to discard all those of a doubtful nature. Owing to the refusal of permission to remove the cord in the third case the ganglia could not be studied. The following statements, therefore, are confined to Cases I and II, that is, to the ones showing less alteration in the cells of the ventral horns.

The alterations of a definite nature are identical in both cases and present in only a few cells. They consist mostly in a rarefaction of the chromatic substance and extremely eccentric position and even bulging of the nucleus. A mass of chromatic substance is often plastered against the cellular margin of the nucleus, which, though large, is much shrivelled, often full of a granular deposit, and contains a very large pale vacuolated nucleolus [Plate III, Fig. 12]. In addition a small number of cells show absence of chromatic substance in a central zone between a ring of large globular-looking bodies about the

periphery, and a collection of similar bodies immediately about the nucleus (as in Rabbit VI, Plate IV, Fig. 16).

EXPERIMENTAL CASES. SPINAL CORD.

In order to determine the constancy and mode of progress of the previously described lesions in typhoid infections the following inoculatory experiments were made on rabbits:

Inoculations were made into the ear vein, using bouillon cultures of the typhoid bacillus derived from the second human case. The following table shows the character of each experiment:

TABLE

SHOWING HISTORY OF INOCULATED RABBITS.

Number of Animal.	Dose.	Remarks.
I.	2 cc. 80-hr. culture.	Very intense reaction. Died in **2 hours.**
II.	2 cc. 70-hr. culture.	Ordinary reaction. Killed in **7 hours.**
III.	2 cc. 96-hr. culture.	Ordinary reaction. Killed in **33 hours.**
IV.	1st day, 2 cc. 2-day culture. 3d day, 2 cc. 5-day culture.	Ordinary reaction after first dose. After second dose animal rapidly succumbed in a few hours, *i. e.* **52 hours** after first inoculation.
V.	1st day, 2 cc. 2-day culture. 3d day, 2 cc. 5-day culture.	Ordinary reaction after first dose. After second dose animal extremely weak; lost weight for several days. At end of first week seemed very feeble in hind legs. As symptoms of convalescence began to appear, animal was killed **9 days** after first inoculation.
VI.	First 5 days, 1 cc. 6th and 7th days, 2 cc. 8th day, 15 cc. into peritoneum.	Animal very resistant. Blood agglutinated rapidly at end of 7th day. On 8th day 15 cc. were injected into peritoneal cavity without effect. On 23d day paralysis of hind legs first noted. Animal killed and autopsy made **24th day** after first inoculation.
VII.	2 cc. 72-hr. culture.	Animal passed through first effects and was allowed to live. About 29th day paraplegia of hind legs first noted; great emaciation of rump and legs. As symptoms of recovery set in, animal was killed on **64th day** after first inoculation.

As will be seen by consulting the table an attempt was made to get the degrees of toxic effect at different periods.

In *Rabbit I*, 2 hours after inoculation, the changes though noticeable are slight and confined to a few cells. They consist of slight swelling of the Nissl bodies and a tendency to disintegration and disturbance of their orderly arrangement.

In *Rabbit II* these alterations, already in 7 hours, have become marked, and notably so in the lumbar region of the cord. They correspond in nature, if not in degree, to those already described in the first and second human cases, and consist, as before, in the pale washed-out form of chromatolysis starting from the axone hillock and displacing the nucleus slightly to the opposite side [Plate III, Fig. 7]. The nucleus shows slight enlargement and the finely granular deposit. The nucleolus is large, pale and vacuolated. The enlargement of the cell and dendrites, the disappearance of chromatic substance from the latter, and the alterations in the achromatic substance are not pronounced.

In *Rabbit III*, which had been subjected to infection for the still longer period of 33 hours, the number of normal cells is greatly reduced, and it becomes evident at once that we have to deal with two different kinds of alteration. Most of the altered cells present the same appearance of central disintegration and solution of the granules spreading from the axone hillock, with the accompanying changes in nucleus and nucleolus, already described in the human cases and the second animal.

An appreciable number of cells, however, present the type of peripheral destruction observed in a few cells of the first two human cases. In some of these the cell body and processes are somewhat contracted and their outline is no longer regular. In the periphery of the cell any distinction between chromatic and achromatic portion is almost lost, the whole substance appearing granular and shred-like, with here and there small chains of disintegrated granules [Plate II, Fig. 6]. Toward the centre of the cell these chromatic masses become more and more abundant, until about the remains of the nucleus they are quite densely packed. The appearance in some of these cells is as if, progressing from the periphery, the Nissl bodies had been broken apart and destroyed *in situ*, not washed out into the surround-

ing substance. The nuclear membrane has disappeared, and the only sign of the position of the nucleus is a slightly rarefied area containing a dark, disintegrating nucleolus.

In some of these cells single or multiple clear areas resembling vacuoles may be observed [Plate II, Fig. 6]. These correspond, presumably, to those described by many observers in a variety of experimental intoxications, and seen by Babes (1) in typhoid and in other experimental infections to contain the organism used for inoculation. If present in large numbers such appearances may be significant. In my study this appearance was observed in one cell only, and in this animal, and is depicted in Plate II, Fig. 6. Other cells of this type show very little irregularity of outline or contraction, while the achromatic substance does not seem much altered. The granules are paler and more washed-out looking, though more numerous and in larger groups about the nucleus, which also is not much altered.

The whole gray matter of the cord of this rabbit is infiltrated with leucocytes, mainly small mononuclears, which are very abundant in the small dilated capillaries, in which they may be seen in the act of migration, and thus to invade the pericellular lymph spaces.

In *Rabbit IV*, which succumbed after a period of 52 hours, nearly all the cells are affected; practically no normal cells can be found. The type of chromatolysis which begins at the periphery, however, has almost disappeared, while the other or central form has become very prominent. The former lesion, that characterized by peripheral destruction, in addition to affecting fewer cells than in Rabbit III, differs also in the absence of any greatly contracted cells and of the appearance of vacuolization described in the foregoing animal. The cells resemble the other variety of this type. They are perhaps slightly enlarged, pale, diffusely blue, with a few flakes of chromatic substance grouped about the nucleus, which is little altered.

The latter type of lesion, that characterized by central chromatolysis, in addition to affecting a greater number of cells than before, has advanced considerably in the individual cells. These are large and swollen as well as their dendrites, which are nearly free from chromatic substance. At times one of two dendrites, which join to enter

the same cell, is almost entirely deprived of chromatic substance, while the other contains more or less well-formed Nissl bodies, a difference which exists even after their juncture, and before the cell body proper is reached. The disintegration and washing out of the granules has progressed pretty thoroughly throughout the cell, leaving but a faintly marked zone of slightly larger collections of granular debris at the periphery. Where the axone is cut this alteration as before may be seen to extend outward from the axone hillock.

The nuclei are only slightly eccentric, and show the same general appearance of a deposit, grouped especially about an irregularly swollen nucleolus [Plate III, Fig. 8].

Rabbit V lived for 9 days after the first inoculation and during this time lost much weight and nearly all control of the hind legs. The animal was killed as symptoms of recovery began to appear. The ventral horn cells in the lumbar region showed, contrary to expectation, very few cells similar to those already described, although great care was taken to cut in sections all parts of this region. Nevertheless, in that portion just above the entrance of the sciatic nerve, groups of large swollen cells were found with slightly eccentric nuclei, but in which Nissl bodies of characteristic shape and distribution were arranged somewhat concentrically about the nucleus, with a slight intensification of single granules in that region. These granules are bright and freshly staining, and their arrangement is very regular [Plate III, Fig. 10]. From their position in the cord these cells probably send fibres into the sciatic nerve. Alterations found in this nerve and the large size of these cells seem to indicate that they must have undergone previously some change and probably that of the central type already described [Plate III, Fig. 8]. The newly formed, regular appearance of the Nissl bodies, taken in consideration with the fact that this animal was recovering, suggests strongly the idea that these cells are undergoing a process of restitution. There is no infiltration with round cells demonstrable.

Rabbit VI proved very resistant to repeated inoculations and was allowed to live. There developed gradually paralysis of both hind legs, which was first noted on the 23d day. The emaciation of the

muscles of the rump and legs was very marked. On the 24th day the animal was killed and autopsied. The alterations found in this case are of interest both on account of their character and their distribution.

In the cervical cord there are scarcely any pathological changes. The cells, however, are in an apyknomorphic state, that is, the chromatic material seems to have been used up to a considerable extent, but the normal arrangement still remains. There are, moreover, some cells which are larger than others and present a slight suggestion of chromatolysis about the axone hillock and in the dendrites.

In the thoracic portion of the cord there is nothing of note.

In the lumbar enlargement most of the cells are of the normal type, and, in contrast to those of the cervical portion, are in an extreme state of pyknomorphism. The Nissl bodies are very numerous, in many cells slightly smaller than usual, and connected by small threads of granules forming a dense network of chromatic substance. A very few cells are much enlarged, and the chromatic substance is disintegrated and undergoing dissolution pretty evenly throughout the cell. The nuclei and nucleoli in these, as well as in some of the cells of more normal type, present the same general changes as those described in the previous cases.

But in the immediately adjacent portion of the lumbar enlargement, just above the entrance of the sciatic nerve, there is a localization of marked alterations, corresponding, it may be assumed, to the area of nervous control of the paralyzed muscles. A number of cells are still normal or only slightly changed, but here and there mere shadows of degenerated cells may be seen, with a number of small lymphoid cells apparently about to invade their territory.

In addition to these two extremes, the one of health, the other of extreme degeneration, altered cells are numerous, and indeed in a very advanced stage of pathological change. The cell and processes are enormously swollen, and the latter, many of which have apparently disappeared, are nearly completely free from chromatic substance. In the central portion of the cell the chromatic substance has been almost completely washed out, leaving a few flakes and pale, minute granules

scattered about in a faint, diffusely blue background. The periphery is bordered by a zone where these flocculent, pale granules are slightly more numerous [Plate III, Fig. 9]. The nucleus in the majority of these cells is partly protruding from the periphery, and encloses a very irregular, disintegrating nucleolus, surrounded by the finely granular blue deposit already mentioned. Outside the nucleus and along its cellular margin there is generally a fine layer of more deeply staining granules [Plate III, Fig. 9].

In certain of these cells, notably in those where the nucleus is not bulging from the periphery nor very eccentric, the fine deposit within the nucleus assumes a metachromatic, pale violet stain. By the concentration of these fine violet granules along the internal surface of the nuclear membrane, the nucleus is thrown into sharp relief against the pale blue of the more central portion of the cell. Some of these nuclei are large and only slightly irregular in outline, others small and greatly shrunken and distorted. As in the others the nucleoli are pale and undergoing the last stages of disintegration. In some of these latter cells, three zones of chromatolysis may be sharply distinguished, a very clear one immediately about the nucleus, a second not quite so clear separating it from the third or the border zone of larger masses at the periphery already referred to.

Rabbit VII, the last of this series, was first noticed to be paralyzed on the 29th day. Symptoms of recovery becoming marked, the animal was killed 64 days after the first inoculation.

In the cervical cord the ventral horn-cells do not differ in great degree from the normal type, although a number of slight variations exist. These consist for the most part in a slight increase in size of the cell, and a little irregularity in the shape and distribution of the Nissl bodies. This irregularity seems to consist, not in a breaking apart and destruction of the granules, but rather in the addition of new sharply staining granules to those already present, causing a little interference with the regular striped appearance of these bodies. This is usually accentuated about the nucleus, which is a little swollen and contains a few bluish granules, but is otherwise normal. Some cells are very deficient in the chromatic substance, especially about the

periphery. The chromatic granules about the nucleus in these cells are distinct and stain brilliantly with the methylene-blue.

At about the level of the second lumbar vertebra the cells are for the most part well formed and appear vigorous. The chromatic substance is dense and abundant, and characteristically arranged. The nuclei of these cells are of normal size and assume a very finely granular, almost homogeneous stain. Here and there are a few smaller cells with the chromatic substance distinct but somewhat finely divided.

On reaching approximately the level of the third lumbar vertebra a very different and striking picture is obtained. Corresponding doubtless to the paralyzed area are found large groups of cells which have a strong resemblance in their great size, eccentric nuclei and large clear dendrites to the cells in about this region in the previous experiment [Plate III, Fig. 9]. Here, however, the resemblance ceases. Instead of the pale, glassy, washed-out centre, the distorted, shrunken or swollen nucleus, and disintegrating nucleolus, the cell is filled with brightly staining sharp chromatic granules arranged in streaks shaped like the Nissl bodies, and traversing in a parallel direction the body of the cell toward the dendrites, or concentrically disposed about the nucleus, where the chromatic substance is especially abundant, being often especially dense along the inner edge of the nucleus [Plate III, Fig. 11]. The nucleus, instead of being greatly altered, is large, regularly spherical or oval, contains only a slight granular deposit and a normal deeply staining nucleolus. Many gradations in the amount of chromatic substance may be seen, but all these cells show this regular, apparently new formation of chromatic substance.

That these cells, as well as some of those described in the cervical region, are in a state of regeneration or restitution, is highly probable from their appearance alone, which corresponds also with that described as such by van Gehuchten (9), Marinesco (21) and others. In connection with this should also be taken into consideration the fact that this animal showed marked improvement, although the clinical symptoms and the alterations in the Nissl bodies are not always correlated.

A few cells seem to have lost their nuclei and to have completely degenerated. These are pale, shrunken forms contained in clear spaces, with a few blue flakes scattered within them, and at times invaded by wandering cells.

The part played by the nucleus in the stages of degeneration and of restitution is interesting. As is well known, if the nucleus be intact the cell may retain its power of regeneration. Should the nucleus, however, become completely degenerated or extruded from the cell, this power is lost (Nissl, 28). In many of the most altered cells, the nuclei which show marked signs of degeneration, as for example the metachromatic alteration in the granular deposit, are surrounded by a zone entirely free from chromatic substance, while in regenerating cells about the normal-looking nucleus, new granules are especially abundant [Plate III, Fig. 11]. In other words, as the nucleus gives out, the granules disappear from about it; as the nucleus recuperates, a new crop of granules appears along its cellular margin. This looks as if the nucleus controlled their formation, and thus, upon the supposition that they represent a nutritional element, presided in some way over the nutrition of the cell. The appearance of granules within the nucleus of altered cells may have something to do with this function, and may represent an exertion to replace the excessive destruction of the chromatic substance.

THE DORSAL ROOT GANGLIA IN EXPERIMENTAL CASES.

The dorsal root ganglia showed changes of a marked nature in the last four of these animals. In the ganglia from the lumbar region the altered cells are numerous. They are chiefly of two kinds and correspond in part to those already described in the human cases.

A few cells show a clumping of the chromatic granules into large swollen masses arranged in a row around the periphery and gathered about the centrally placed and only slightly altered nucleus. Between these two situations is a zone entirely free from chromatic substance [Plate IV, Fig. 16]. Others show no peripheral zone, but the chromatic substance is massed about the nucleus in the centre of the cell [Plate IV, Fig. 17].

The majority of the altered cells, however, show eccentric nuclei. In some few of these the chromatic substance is scattered at intervals in large flakes through the body of the cell [Plate IV, Fig. 15]; in others, the chromatic substance is finely divided, and in some of the latter the destruction seems to begin in one or more small areas [Plate IV, Fig. 13]. The nucleus is very eccentric, frequently bulging from the periphery, and encloses a pale, very irregular nucleolus. Altered cells, showing in particular eccentric nuclei, are most abundant in Rabbit IV, where most of the cells of the ganglia are thus affected.

In Rabbit V, on the contrary, there are few alterations, but there is great uniformity in the appearance of the cells, which are for the most part rich in chromatic substance, especially about their nuclei. This difference in the ganglia in these two animals corresponds very closely with the difference in the same animals between the conditions of the ventral horn cells.

In Rabbit IV, which died under the influence of an acute attack, the chromatic substance in both situations is much reduced; Rabbit V was on the road to recovery and an apparent restitution of chromatic substance is observed. This correspondence of external manifestations and internal alterations is not always so exact. The Nissl bodies are in a state of extremely unstable equilibrium and very easily influenced quantitatively. When such correspondence does exist, however, it is worthy of consideration.

The similarity of these alterations in the inoculated animals with those found in the human cases needs no further comment. The lesions are evidently uniform and constant. In both the human and the experimental series, the ventral horn cells show two forms of lesion. One is indefinite and characterized mainly by contraction or slight, irregular enlargement of the cells; by a chromatolysis marked in the periphery of the cell and at the entrance of the processes, with disintegrated granules more numerous about the nucleus which is either normal or together with the nucleolus is undergoing destruction in the centre of the cell. In some of these cells a process of vacuo-

lization is noted, and an apparent degeneration of the achromatic portion.

The other type of lesion is definite and well characterized by a regular enlargement of both cells and processes, a pale washed-out chromatolysis starting from the axone hillock and surrounding the somewhat altered nucleus, which is displaced to, and often protruding from, the opposite side. The achromatic portion is but little altered.

The first type of lesion is at no time predominant. It is most marked, however, in Rabbit III, and decreases somewhat in Rabbit IV. Both these animals were killed when the influence of the toxic substance on the whole system was at its height.

Without entering into a full discussion of the direct effect of toxic substances upon the nerve cell, attention may be called to the general resemblance between the alterations of this first type and those which have been produced by a number of investigators in different experimental intoxications, such as by arsenic, strychnine, alcohol, etc. These changes are doubtless due to the direct action of poisons on the cell. For a discussion of this subject reference may be made to the excellent articles of Marinesco (21), Lugaro (16), Flatau (6), and Goldscheider and Flatau (12). Although slight differences exist in the descriptions given by different authors, yet the lesions are essentially of the same type, and no doubt in our typhoid cases, too, they may be attributed to the direct action of the typhoid toxine.

Babes (1) has studied the changes in one case of typhoid inoculation in connection with a study of other infections, and describes only this first form of lesion, which he believes to be due to an actual invasion of the cell, as well as the tissues of the cord, by typhoid bacilli. Probably to this class belong especially the irregularly contracted and vacuolated cell forms with disintegrating nuclei.

Goldscheider and Flatau (10) and Moxter (25) have produced by experimental elevation of temperature, and Goldscheider with Flatau (11) and with Brasch (13), Déjerine (4), and Marinesco (20) have found in certain affections with high temperature in man, an alteration which corresponds closely with the pale blue non-vacuolated variety here described. Perhaps these forms may be referred to this

effect, though the temperature of the animals, when taken, was never particularly high.

Whether this lesion is due to direct toxic action, to high temperature, or to some other condition or to a combination of these need not be further discussed here. It is the more indefinite and not the predominant and characteristic lesion.

The second and characteristic lesion is that which predominates in all the human cases, and is especially advanced in the last of these. It is present to a greater or less degree in the whole animal series. It first shows itself in Rabbits I and II, to increase in III, to become particularly abundant in IV, when the other lesion begins to disappear. Its traces may be seen in the enlarged, apparently restituted cells described in Rabbit V, in which recovery from a half paralyzed condition was taking place. It is particularly advanced, though confined to the lumbar region, in Rabbit VI, which developed a paralysis of both hind legs. In Rabbit VII, paralyzed but recovering, it was manifested in the large cells, with eccentric nuclei, which were apparently undergoing regeneration.

This lesion, in its mode of onset, its general characteristics and progression, is similar in every way to the alterations produced in the corresponding cells in consequence of experimental section or other interference with the function of the axone, as described by Nissl (26, 27), Onufrowicz (31), Marinesco (21), Dutil (2), and many others. Specimens made in this way by Mr. Erlanger of the Johns Hopkins Medical School were kindly lent to me for purposes of comparison.

Moreover, an identical lesion has been discovered in human beings, where the axone has been injured or its function disturbed. Thus, Flatau (7) found this condition in two cases of amputation, and in one of thrombosis of the femoral artery; Adolf Meyer (24) in the facial nucleus, where the nerve had been compressed by inflammation in the internal auditory canal; and Barker (3) after injury to the fibres of the direct cerebellar tract in spinal meningitis found the same change in the cells of Clark's column.

Alterations in the dorsal root ganglia have also been studied after section of their peripheral nerves. Although this branch does not

correspond to the axone of the motor cell, yet it is apparently the only one which, when severed, produces alterations in the appropriate ganglion, as Lugaro (15) has shown by section of the cord above the ganglion examined, and by section of its peripheral nerve. By the latter procedure Lugaro observed alterations similar to those of cells with eccentric nuclei described in our typhoid cases, and shown in Plate III, Fig. 12, and Plate IV, Figs. 13, 14 and 15. R. A. Flemming (8) and Sadovsky (32) have described, in addition, cells with the chromatic substance massed about a centrally placed nucleus, as in Plate IV, Fig. 17.

From the character of the alteration in the motor cells and dorsal root ganglion, and its correspondence with the changes due to injury to the peripheral nerves, it seemed desirable to search outside of the nerve cells and cord for the primary lesion. This resemblance, coincident in both localities, cord and ganglia, at once suggested examination of the peripheral nerves. Unfortunately this was not done in the three human cases* nor in the first three rabbits or Rabbit VI.

THE PERIPHERAL NERVES IN EXPERIMENTAL CASES.

As the lumbar portion of the cord in all cases seemed chiefly involved the sciatic nerves were the ones excised, with some muscular connections, and in Rabbit V in connection with the cord.

Some parts of these were examined fresh, teased in glycerine, and stained with osmic acid. Other portions were hardened in Müller's fluid, and subsequently stained by Marchi's and Weigert's methods; and still others, hardened in Flemming's solution of formaline, were stained with carmine, safranin, polychrome methylene-blue, iron-hæmatoxylin and erythrosin. Some of the nerves hardened in formaline were stained by the method used by Kolosoff for heart muscle, which was found to give excellent results.

Degenerations were found in Rabbits Nos. IV, V and VII, the earliest case examined being Rabbit IV, which lived 52 hours after

* Since the completion of this paper I have examined portions of the sciatic nerve from a fatal case of human typhoid fever and have found definite parenchymatous degeneration similar to that described in the rabbit's nerves.

inoculation; numerous nerve fibres in the sciatic were found degenerated. These degenerations consisted in varicose swelling of the fibres, and breaking up of the neurokeratin and myeline sheath. In these vesicle-like spaces numerous small lymphoid cells and the shred-like remains of the structural network occur, while the axis cylinder is swollen, twisted, and no longer clear and homogeneous. About these areas the small-celled infiltration is quite noticeable.

In the later animals, especially in Rabbit VII, the altered myeline is broken up into balls and a deeply staining, granular detritus, which is collected for the most part into regular, oval or spherical bodies, suggesting the so-called "compound granular corpuscles" (Plate IV, Fig. 18). This suggestion is strengthened by the fact that, in sections hardened in formaline and Flemming's solution and stained with polychrome methylene-blue, safranin, etc., there may be seen lying within these swollen, degenerated areas, in addition to small lymphoid cells, large swollen cells with rather pale vesicular nuclei, placed somewhat eccentrically, in a granular-looking protoplasm. In such nerves the axis-cylinder is broken, twisted and much enlarged, the swollen club-like extremities projecting into the vesicular spaces. In Rabbit VII there is seen about the more degenerate spots a proliferation of the nuclei of the sheath of Schwann and of the interstitial tissue.

These lesions are especially marked in the gluteal, and some other lower branches of the sciatic nerve, and apparent especially in the intramuscular branches. The corresponding muscles are, in Rabbits V and VII, more or less affected, showing a fatty degeneration, staining black with osmic acid, loss of cross striation, atrophy of fibres, with, in the latter animal at least, some proliferation of the interstitial tissue.

Sections of the cord in Rabbits IV and VII were examined by Marchi's and the Pal-Weigert method, both in transverse and longitudinal section. A few nerve fibres, scattered indefinitely through the white substance, showed changes pointing to some slight degeneration of the myeline sheath but so slight in comparison with that of the peripheral nerves that they do not seem of much importance.

Marked degenerations are essentially peripheral and are such as are found in typical neuritis of the parenchymatous form, and call to mind especially those described by Sidney Martin (23) in his studies on diphtheria.

It would seem as if so profound an alteration of the nerves and muscle, a true Wallerian degeneration of the former, could scarcely be produced by primary lesions of the nerve cells, of the nature we have described. Such an interpretation of an alteration so superficial and slight as the disintegration and destruction of the Nissl bodies is known to be seems out of the question. It should be remembered that, except in a few cells, the achromatic substance was not much altered. Moreover, in one of the rabbits at least, the cells were quite restored to integrity, and in another undergoing a process of active restitution.

The changes could hardly have been primary in the muscles, as in Rabbit IV these were not much altered, while the nerves were quite extensively degenerated. Again, although ascending degeneration may take place in peripheral nerves, it is a process of longer duration. We must therefore conclude that we are dealing with a condition similar in its effects to section of a peripheral nerve, that is, with reaction on the nerve cell at a distance, brought about by changes in the nerves, the direct result of the action upon the latter of the typhoid poison.

Ballet (2) and Marinesco (17, 18, 19), in the cases of peripheral neuritis examined by them, found similar changes in the nerve cells, but are unwilling to infer definitely a primary alteration in the nerves, if much time has elapsed and the degeneration in the cells is so extensive that the achromatic portion is involved. This difficulty is obviated in the experimental lesions, where the whole development of the process may be traced, and which tend to show that some reliance is to be placed upon this form of lesion as an indication of the involvement of the peripheral nerves. Indeed, the peripheral nerves would not have been examined in this instance had not the lesion found proved so constant and characteristic, and in spite of the fact that it was expected that a direct toxic lesion would be discovered.

So far all experiments involving disturbance of the function of the axone produce constantly this one characteristic lesion. The fact that by infections, poisons, the use of high temperatures, the cutting off of the circulation from the cord, etc., this lesion is at times produced, along with other changes, proves nothing against its specificity, as all these injurious conditions might act as well directly on the peripheral nerves as on the cells. It is also held that in any morbid condition the disturbance of function of any one or all organs of the body produces abnormal conditions, which would mask the specific effect of the infectious agent. But it is well known that all organs or the same organs are not affected alike in the course of the same infection in different individuals, and hence such conditions and the lesions they might produce would not be constant. The lesions found in typhoid fever are constant. Therefore, where the lesion in question is predominant and constant it seems as if it should be referred to a peripheral effect of the infectious agent, until such effect can be proved to be excluded by examination of the peripheral nerves. The exclusion of these, however, is not an easy problem, as it has been shown by Nissl (26) that even such slight disturbance as contact of nerves with a grain of salt is sufficient to produce reaction upon the cells. Nissl also observed these cell alterations 6 hours after removal of part of the nerve, while Dutil (2) first notes degeneration in the proximal nerve stump by Marchi's method in 37 days. Thus an area of injury might be overlooked.

At least in these cases of typhoid infection it would seem that the toxine acts primarily upon the peripheral portion of the neurone, so far as this can be affected more in one portion than another, and there seems to be no reason why a unit which differs structurally in its parts should not differ as to these in its vulnerability. This means that the typhoid toxine is a powerful peripheral nerve poison, and that its effect is felt early and continuously, although it may be so slight as not to become manifest clinically, or be so slightly manifested as to be readily overlooked under existing means of observation in the height of the disease. Thus a slight loss of muscular control might well be veiled. At times, however, some complaint on the part of the

patient attracts the attention of the physician, and the condition is recognized. Such, for example, is probably the condition of " tender toes " not uncommon at this stage of the disease, as suggested by Dr. Osler in Vol. V of the Johns Hopkins Hospital Reports. Should the lesion be of a grave nature and produce a paralysis lasting into convalescence, then for the first time when the patient attempts to use these muscles, the true condition becomes apparent, and " develops " as one of the many varieties of post-typhoid neuritis. Among these occurs, though rarely, a diplegia, which is very resistant and slow to improve. By some this is, for clinical reasons, held to be a primary degeneration of the nerve cells, a true poliomyelitis. In two of the rabbits the same phenomenon developed but was due evidently to a peripheral nerve lesion, and it is not impossible that some of these nerves may fail to recover their peripheral connection, so that there ensues a complete degeneration of their appropriate cells (Flatau, 5; Marinesco, 18).

The aim of this investigation, the determination of the Nissl changes in typhoid infection, and, if found to be uniform, the assignment of some cause for this uniformity, is thus attained. I desire to express my thanks for valuable advice and assistance to Professors Welch, Flexner and Barker.*

Conclusions.—(1) The application of the Nissl method to the study of the motor cells of the spinal cord, and the nerve cells of the dorsal root ganglia in typhoid fever, shows that these cells regularly suffer pathological changes in the course of the infection.

(2) The alterations in the motor cells are more constant and of a severer grade than are those in the cells of the sensory ganglia. The more characteristic changes consist of disintegration, solution and destruction of the chromatic substance of the cell starting from the

* Since writing the above, a thesis by C. Voinot, delivered at Nancy, July 31, 1897, and entitled " Recherches anatomo-pathologiques sur la moelle épinière," fell into my hands. Of twelve cases of typhoid fever among other infections, five were examined by Nissl's method, and evidently with results much as above. The author, however, seems to lay stress upon alterations, perhaps definite, but slight, found in the cord and root fibres, the peripheral nerves not having been examined, and concludes that this disease belongs, with the others described, in the category of acute infectious myelitides, and that the alteration of the cells is coincident merely.

axone hillock and proceeding toward the nucleus. Coincidently the nuclei of the affected cells seek the periphery. Alterations are also suffered by the nucleus and nucleolus.

(3) While this central form of chromatolysis is the prevailing type of pathological change, disintegration, etc., of the Nissl bodies situated in the periphery of the cell and in the dendrites is also observed (peripheral chromatolysis).

(4) In experimental infection with typhoid bacilli in rabbits a similar series of lesions in the corresponding nerve cells in the spinal cord and ganglia is encountered.

(5) The main or central type of lesions discovered is identical with that found in man and animals after section, destruction, or even slight injury of the peripheral nerves.

(6) The examination of the peripheral nerves arising from the lumbar segment of the cord (the site in man and rabbit of the most profound changes) in rabbits inoculated with typhoid bacilli showed well-marked evidences of parenchymatous degeneration.

(7) It is probable that lesions of the peripheral nerves in typhoid fever in human beings are common and that the post-typhoid hyperæsthesias and paralyses are due to this cause.

(8) Restitution of the chromatic granules may take place in the affected nerve cells, the new formation beginning about the nucleus and extending through the protoplasm.

DESCRIPTION OF PLATES II–IV.

All figures were drawn with a Zeiss drawing apparatus; Figs. 3, 4 and 5 with Zeiss apochr. obj. 3 mm., oc. 4; the rest (except Fig. 18) with Zeiss apochr. oil immers. 2 mm., oc. 4.

[Measurements given are the longest and shortest diameters.]

PLATE II.

Fig. 1.—First human case: Cell from ventral horn, lumbar region, showing increase in size, characteristic form of chromatolysis, fine deposit in nucleus, vacuolated swollen nucleolus, and absence of chromatic substance in dendrites.

Size: cell, 78x36 μ; nucl. 24x18 μ; nucleol. 6x6 μ.

Fig. 2.—Similar to Fig. 1, showing also extension of process from axone hillock and slight dislocation of nucleus. Size: cell, 64x34 μ; nucl. 20x15 μ; nucleol. 7x7 μ.

Fig. 3.—Third human case; cell from ventral horn showing progression of the lesion shown in Figs. 1 and 2. Extreme eccentric position of nucleus with crumpled membrane and chromatic granules arranged along cellular margin. Nucleolus swollen but not much altered.

Size: cell, 63x33 μ; nucleol. 6x6 μ.

Fig. 4.—Similar to Fig. 3. Shows bulging of nucleus and extrusion (?) of nucleolus.

Size: cell, 75x15 μ.

Fig. 5.—Similar to Figs. 3 and 4. Somewhat more extensive chromatolysis, and swelling of cell.

Size: cell, 75x15 μ.

Fig. 6.—Rabbit III. Ventral horn cell. Indefinite "toxic" type of alteration; one small vacuole is shown containing a small oval body, resembling a bacillus.

Size: cell, 70x24 μ; nucleol. 4x4 μ.

Plate III.

Fig. 7.—Rabbit II. Characteristic central lesion in earlier stage. Central chromatolysis beginning about axone hillock, and spreading toward nucleus, which is slightly eccentric. On the opposite side the Nissl bodies are swollen and disintegrating.

Size: cell, 49x32 μ; nucl. 18x12 μ; nucleol. 4x4 μ.

Fig. 8.—Rabbit IV. Same lesion further advanced. As yet not much eccentricity in nucleus. Compare with Figs. 1 and 2.

Fig. 9.—(Rabbit paralyzed.) Great enlargement of cell, and destruction of chromatic substance. Loss of processes. Eccentric nucleus. Disintegrating nucleolus. [Note double nucleoli not uncommon in rabbits.] (Compare with Fig. 4.)

Size: cell, 100x36 μ; nucl., 28x14 μ; nucleol., 5x4 μ.

Fig. 10.—Rabbit V. Type of large cells in ventral horn found above entrance of sciatic, and apparently nearly restored to integrity.

Size: cell, 90x60 μ; nucl. 26x20 μ; nucleol. 6x6 μ.

Fig. 11.—Rabbit VII. Type of cell of ventral horn in altered area apparently showing first stages of regeneration. (Compare with Figs. 8 and 9.)

Size: cell, 62x82 μ; nucl. 20x20 μ; nucleol. 5x5 μ.

Fig. 12.—Second human case; cell from lumbar dorsal root ganglion. Destruction of chromatic substance and eccentric nucleus.

Size: cell, 56x40 μ; nucleus, 16x10 μ; nucleolus, 5x6 μ.

Plate IV.

Fig. 13.—Rabbit V. Similar to Fig. 14. Cell from lumbar dorsal root ganglion.

Fig. 14. Rabbit IV. Shows destruction of chromatic substance in two areas in cell body. Lumbar dorsal root ganglion.

Fig. 15.—Rabbit VII (paralyzed). Remains of chromatic substance scattered as large shreds through body of cell. Bulging of nucleus from periphery. Lower lumbar ganglion.

Fig. 16.—Rabbit VI (paralyzed). Clear zone separating peripheral collections of granules. Exaggeration of normal condition (?). Lumbar dorsal root ganglion.

Fig. 17.—Rabbit VII (paralyzed). Massing of chromatic substance about nucleus. Condition found in a number of cells in Rabbits V, VI and VII, but not always so well marked. Lowest lumbar root ganglion.

Fig. 18.—Rabbit VII. Sciatic nerve, hardened in Müller's fluid, stained by Marchi's method. Myeline sheath broken up, and detritus contained for the most part in granular cells. Zeiss objective D, ocular 4.

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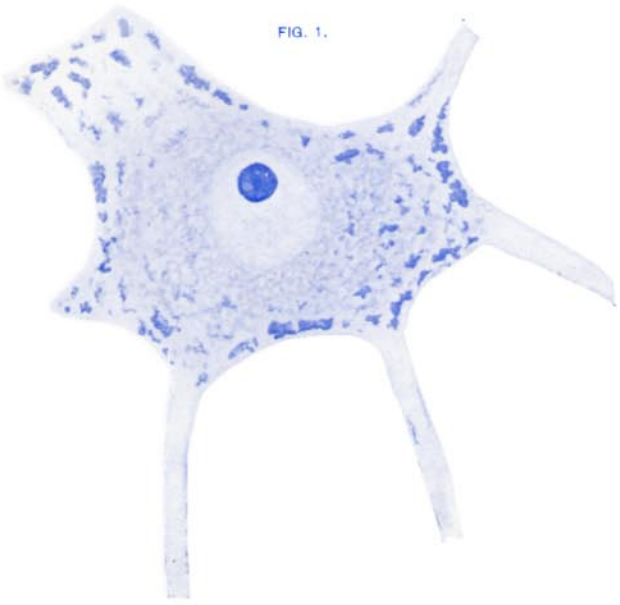
FIG. 1.



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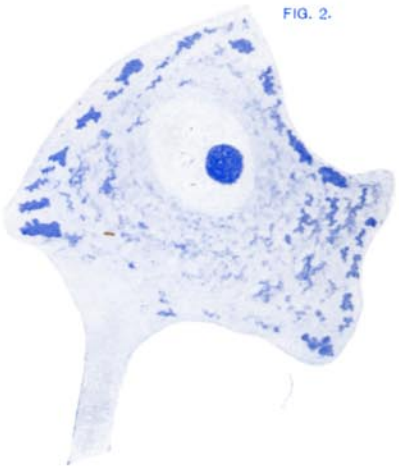

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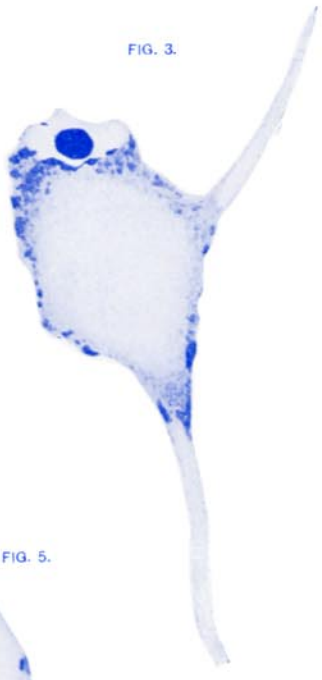

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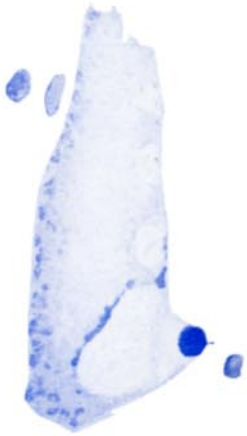

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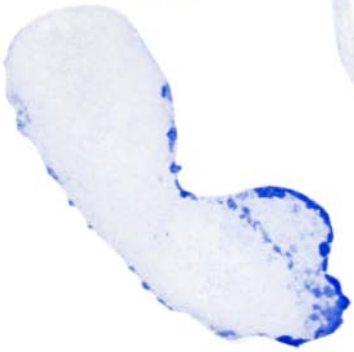

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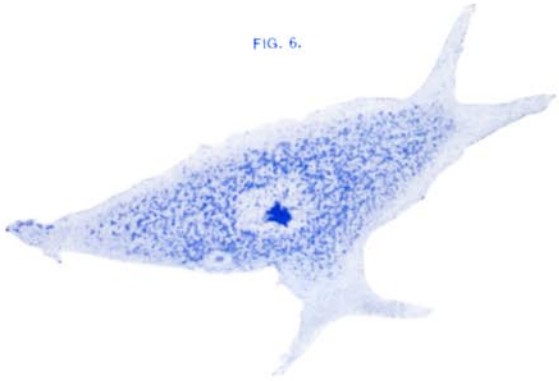

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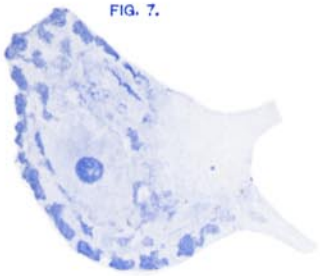

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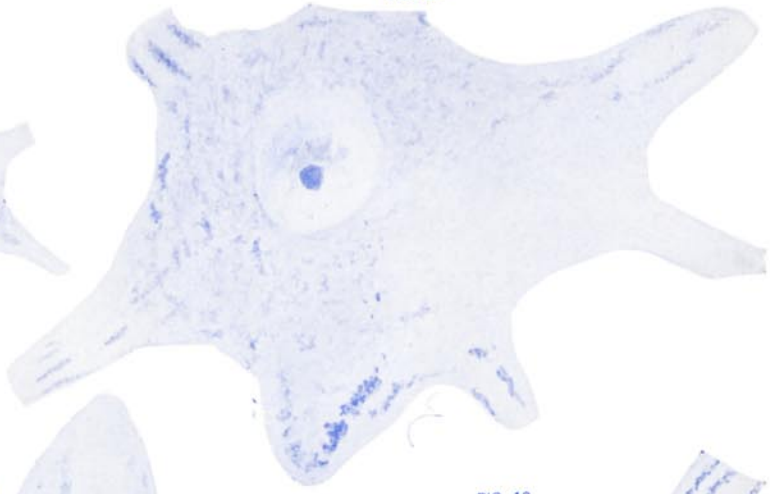

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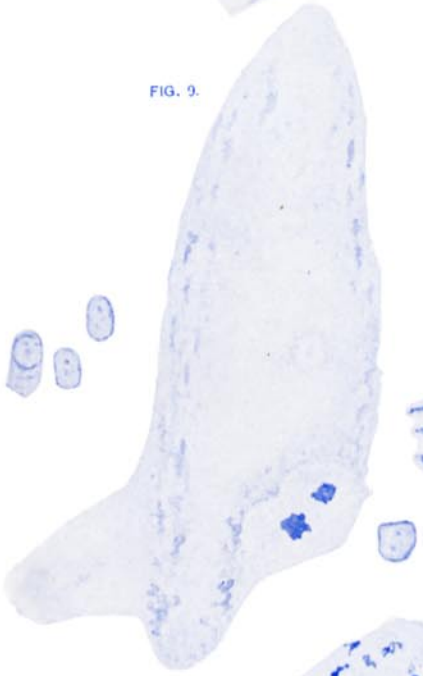

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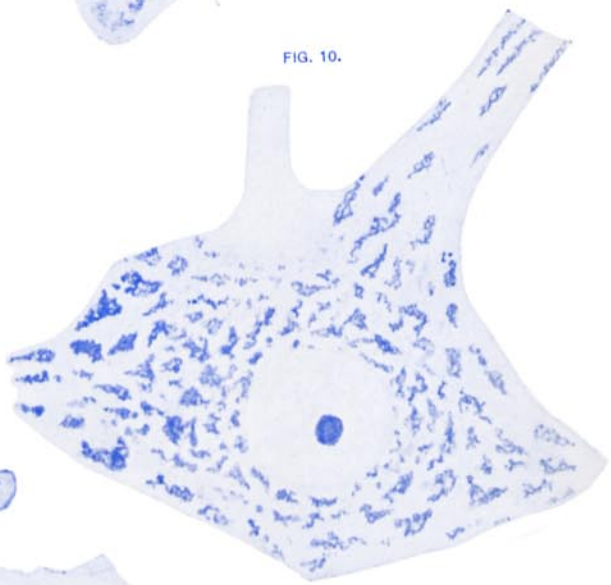

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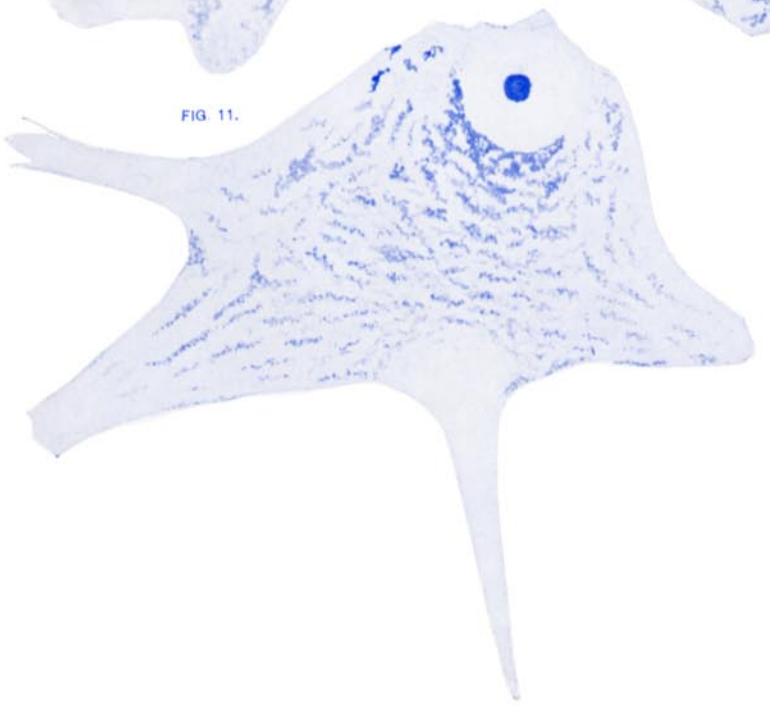

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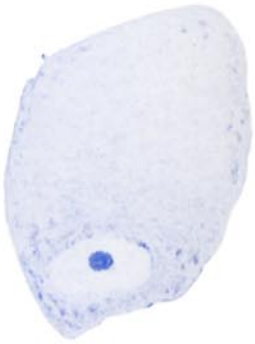

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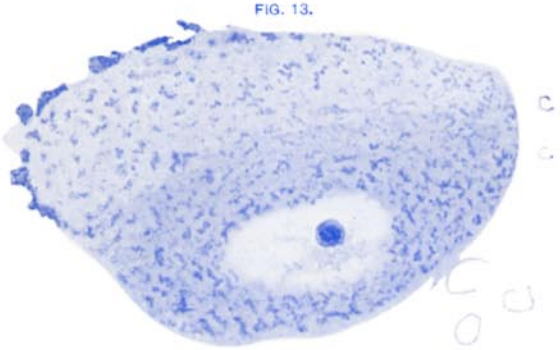

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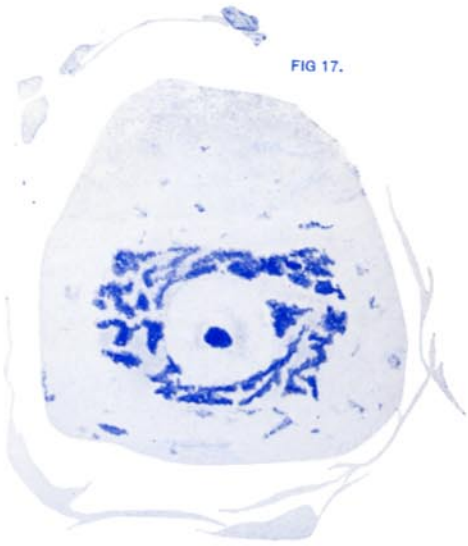

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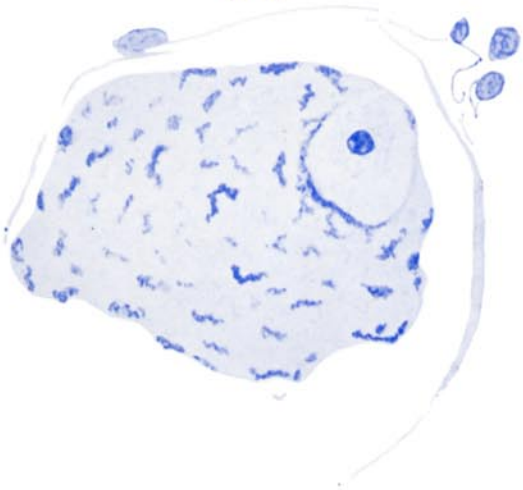

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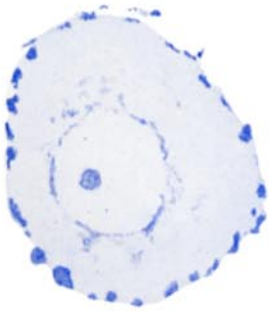

FIG. 14.