STUDIES ON NERVE CELLS.

I. THE MOLLUSCAN NERVE CELL, TOGETHER WITH SUMMARIES OF RECENT LITERATURE ON THE CYTOLOGY OF INVERTEBRATE NERVE CELLS.

BY

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WITH PLATE I AND THIRTEEN FIGURES IN THE TEXT.

I. INTRODUCTION.

The purpose of this paper is twofold: First, to summarize and correlate the more important contributions on the structure of invertebrate nerve cells exclusive of the neuro-fibrillæ (a special problem which cannot be adequately treated in the space allotted to this review); and, second, to present our own studies on the structure of the gasteropod nerve cell with special reference to the problem of the so-called NISSL bodies, whose nature is still in controversy. It has been maintained that these bodies are arte-facts. Inasmuch as we have been able to cause them to appear by feeding experiments and have been able to photograph them in the living and unstained nerve cells, we feel reasonably sure of their actual existence and shall make suggestions as to the manner of their development, as well as their probable function. In a

later paper we hope to show structural and physiological simi-
larities between the nerve cells of invertebrates and vertebrates.

The various terms employed to describe the stainable and non-
stainable substances of the cytoplasm of vertebrate nerve cells have
been in large measure carried over to the description of the inver-
tebrate nerve cells.   Since the NISSL bodies were discovered and
known as the visible or stainable part of the cytoplasm, the fol-
lowing words have been used for similar structures; the chromatic
substance, the chromophile part of the cytoplasm, the chromato-
phile elements, the chromophilic particles, the basophile constit-
uents, the tigroid substance, the sigroid substance, the collagenous
substance, granules or granular substance.   The names of most
of the authors who have created this confusing and unnecessary
terminology may be found in ROBERTSON's review.   In a similar
manner the non-stainable substance is designated as the achro-
matic, fundamental, invisible, not formed, unstainable, acidophile
substance, trophoplasm, or kinetoplasm.   The fibrillar substance
is included in these terms although it is a distinct structure and
whether it is considered as a part of the stainable or non-stainable
substance depends largely on the writer.

The pigment found in nerve cells of the central nervous system
is deposited in masses distinct from the NISSL bodies and is pale
yellow or dark brown.   These seem to be unlike, the brown appear-
ing early in life and ceasing to increase after a few years.   It is not
blackened by osmic acid.   The yellow appears in man during
the sixth year, increases with age and is blackened by osmic acid.
Some writers maintain that the yellow is not fat, but that it under-
goes fatty degeneration.   In certain mental diseases there is an
accumulation of this pigment and a breaking down of the struc-
ture of the cytoplasm.   Whether the two processes are related
or not is unknown.   A golden yellow pigment is found in the nerv-
ous system of certain gasteropods and a yellow pigment in other
classes of invertebrates, the origin and use of which are somewhat
problematic.

A further modification of the cytoplasm of nerve cells is found
in the presence of vacuoles, lymph spaces and the actual though
infrequent penetration of nerve cells by capillaries.   The vacuoles
occur in the cytoplasm, nucleus, and nucleolus and are probably
in each case formed in a similar manner even when the exciting
cause is different.   The vacuoles which occur in the nucleolus

are similar to those that occur in this structure in ova in most animals during their growth. The vacuoles that occur in the nucleus are not as common and it is doubtful whether they are normally present. So far as we are aware they have not been seen in the living nerve cells, but are common in cadaveric specimens. Nerve tissue poorly fixed may also exhibit them, which renders it all the more probable that they are artefacts.

The vacuoles in the cytoplasm are present in the nerve cells of many animals both vertebrate and invertebrate. *They can be seen in the living nerve cells of Gasteropods* and have been reported in some vertebrate nerve cells. In well fixed and stained sections, vacuoles are very commonly found which agree in form and appearance with the conditions in the living cells. Considerable work has been done to determine the question whether or not these cytoplasmic vacuoles have a definite wall. It is necessary in this connection to distinguish the vacuoles from the lymph spaces and capillaries. The vacuoles are usually small and irregularly distributed throughout the cytoplasm. They contain a homogenous fluid or differential bodies, and their presence is, we believe, intimately associated with the metabolism of the cell and probably with its constructive phases. These vacuoles vary in number in the same animal and in the same species. This would indicate that they are transitory structures which appear when certain chemical changes occur, and then disappear. A very critical study of the cytoplasm in contact with the vacuoles fails to show any evidence of a separate wall. The vacuole in the living nerve cell forcibly reminds one of the food vacuoles in protozoa which appear to have a wall; but this appearance is really due to the contact of fluids of different refractive index. In stained specimens the vacuoles look as if they were limited by a more deeply staining border, but this may be explained as due to the accumulation of cytoplasmic granules about the enclosed liquid. We believe that it is no more proper to speak of a wall for these vacuoles than it is to say that the numerous vacuoles in a protozoan have walls.

The lymph spaces are of a different character and are usually located in the periphery of the cytoplasm. They are intimately associated with the circulatory system and may contain blood. In some of the larger invertebrate nerve cells the periphery is richly supplied with lymph canals which may occasionally contain corpuscles. These canals or spaces can in many instances

be traced directly into the surrounding neuroglia tissue and appear to be of a more permanent character than the vacuoles. We are inclined to believe that these lymph canals are supplied with definite walls.

A sufficient number of cases has been described to show that occasionally nerve cells are actually penetrated by capillaries. We have observed one instance in Helix. These capillaries terminate in finger-like branches or pass through the cell or even through two or three adjacent cells. They have a definite wall and contain blood corpuscles.

The question as to how the nerve cell is nourished, and how it maintains itself during long periods of excitation, long fasts or hibernation is one which has attracted the attention of scientists and will continue to do so. The appearance and disappearance of the granular particles in the cells at once gives evidence that they are temporary structures. It is natural to think of nerve cells as performing *one* function, and we frequently lose sight of the fact that the cell has a protoplasmic structure which must be nourished just as truly as that of any other cell. The activities of a nerve cell are not all of a nervous character; metabolic processes must go on here just as truly as in the muscle cell or the gland cell. But these processes may be overshadowed or concealed by the more specialized activities of the cell.

We shall attempt to show that these metabolic processes actually take place within the nerve cell, that certain food substances are stored up within the nerve cell, that these substances may remain in the cells for long periods, and that they may be called upon at any time of want or stress to supply material out of which new protoplasm may be built or to act as a source of energy.

Twenty years after the admirable work of NANSEN, we can do no better than to quote from him the following sentence. "If we look through the modern literature having special reference to the invertebrate nervous system, and compare the many different views of the structure of the ganglion cells, we meet with a confusion on the subject which is far from encouraging."

II.   MORPHOLOGY OF THE GASTEROPOD NERVOUS SYSTEM.

Much of the work on nerve cells where a direct stimulation has been employed has been on a certain ganglion through a specific

nerve passing to that ganglion. The nervous system of gastero-
pods does not permit of any such treatment, as the following
description and diagram shows. The nervous system of Limax
may be taken as typical of
the common snails. It
makes its first appearance on
the sixth or seventh day after
the eggs are laid (HENCH-
MAN '90) and is derived en-
tirely from the ectoderm.
The several ganglia which
constitute the nervous sys-
tem of Limax arise separ-
ately to become secondarily
joined by commissures.

In the adult stage, the
central nervous system con-
sists of five pairs of ganglia
and a single ganglion asym-
metrically placed. The rel-
ative position of the ganglia
can be appreciated from the
view shown in Fig. 1. "In
passing from behind for-
ward, the ganglia are en-
countered in the following
order: (1) The pair of pedal
ganglia, which lie under the
radular sac, and are joined
to each other by an anterior
and a posterior commissure;
(2) one abdominal ganglion
a little to the right of the me-
dian plane (which is inti-
mately fused with the right
visceral, and is also in close
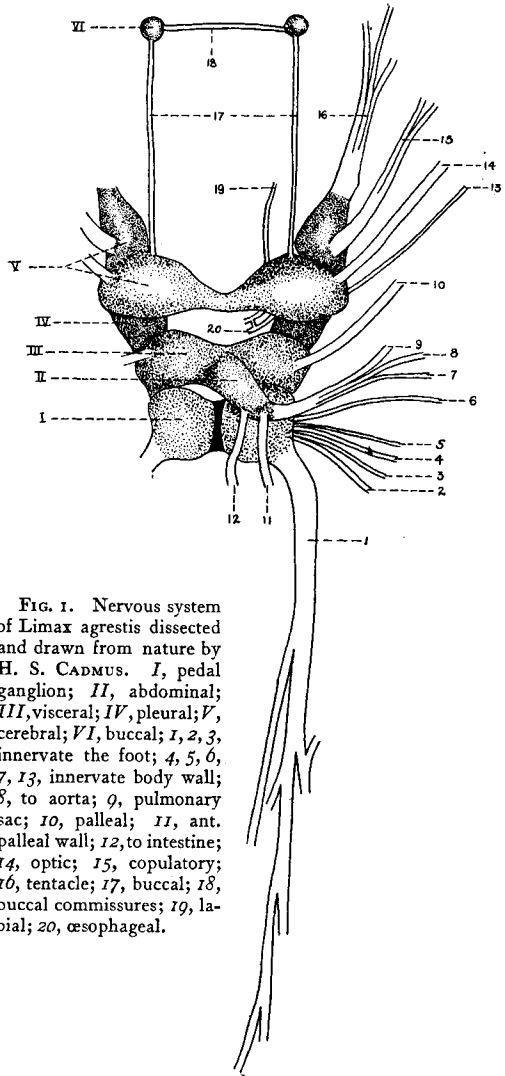connection with the left vis-
ceral ganglion, p. 199); (3)

FIG. 1. Nervous system
of Limax agrestis dissected
and drawn from nature by
H. S. CADMUS. *I,* pedal
ganglion; *II,* abdominal;
*III,*visceral; *IV,*pleural;*V,*
cerebral; *VI,* buccal; *1, 2, 3,*
innervate the foot; *4, 5, 6,*
7, 13, innervate body wall;
8, to aorta; *9,* pulmonary
sac; *10,* palleal; *11,* ant.
palleal wall; *12,*to intestine;
14, optic; *15,* copulatory;
16, tentacle; *17,* buccal; *18,*
buccal commissures; *19,* la-
bial; *20,* œsophageal.

a pair of visceral ganglia occupying the posterior angle formed by
the outgrowth of the radular sac from the œsophagus. They are

separated by the abdominal ganglia from which connectives pass to them; (4) a pair of pleural ganglia, not joined by a commissure and not giving off nerves.   They are united by means of connectives to the pedal, visceral, and cerebral ganglia of the same side; (5) a pair of cerebral ganglia with their supra-œsophageal commissure and connectives to the pleural, pedal, and buccal ganglia; (6) a pair of buccal ganglia, with a commissure under the œsophagus posterior to its connection with the sac of the radula.''   (Quoted from HENCHMAN '90, p. 193.)

A comparison of this drawing with those of pond snails by LACAZE-DUTHIERS shows a number of differences in respect to the origin of the nerves and the announcement of two nerves that are not shown in his figures.

<div align="center">III.   LYMPH CANALS.</div>

Structures known as lymph canals we differentiate from vacuoles, although both have a similar appearance in the fixed cell. This distinction is made after a study of the living nerve cell. In a subsequent section on vacuoles it is suggested that in certain instances the lymph canal, trophospongium, etc., are not real lymph spaces, but isolated and independent vacuoles. That lymph canals do really exist in nerve cells seems to be well established, as the accompanying review indicates.   Our study of fixed material in Helix and Aplysia shows that the outer border of the cytoplasm is frequently penetrated by spaces, as well as numerous processes from the neuroglia.   Many of the drawings of RHODE and HOLMGREN indicate a similar state of the cytoplasm so that we believe that these lymph canals have a rather general distribution in invertebrate nerve cells.   HOLMGREN in his several papers has given an elaborate account of lymph-spaces.   Apparently the same class of structures had been previously described under the caption "intercellular neuroglia" by RHODE.   RHODE observed these structures in various animal classes, making a special study of Aplysia, Helix, and Doris.   His results are interpreted in terms of his theory of work on the part of the neuroglia cells.   The neuroglia cells are not considered as intruders but as cells which by their activity build up the nerve cell.

In order to give some conception of the extent and importance of the work on lymph canals, the following rather full review is made.

Our review of the work of HOLMGREN can give us at best but an inadequate conception of its amount and quality. His numerous papers, while somewhat controversial, contain a large range of observations on *fixed* nerve cells, both vertebrate and invertebrate. His main contention seems to be centered around the character of the cytoplasm. Whence come the numerous spaces in it, and what of their character? It seems to us necessary to include here a review of some of his studies upon the nerve cells of vertebrates, since he makes this his starting point. A good summary of HOLMGREN's ideas concerning the structure of the nerve cell may be found in vol. 11 of MERKEL and BONNET's Ergebnisse.

HOLMGREN ('01) makes the first mention of the "Saftkanälchen" in the spinal nerve cells in his paper on Lophius piscatorius, where he makes the following statement, "localized endocellular nets of 'Saftkanälchen' are seen especially well in the rabbit." A thick network of fine tubules is to be seen in the cytoplasm surrounding the nucleus, and usually near the poles of the cell. The sectioned lumina of the tubules are always circular in outline and are always sharply marked off. Here and there one can find how these networks of tubes are connected with the pericellular tubes. In these places the walls are clearly marked. Within the cells the author could see no definite walls to the canals. Most of the cells of the spinal ganglia possess such networks, but they do not always seem to agree with each other with respect to the breadth of the lumen or the wall of the canal.

In the cells the author distinguishes two cytoplasmic zones, an inner canalicular and an outer extra-canalicular zone. These canals are supposed to have walls— at any rate something which appeared to be a wall stained red with erythrosin. In addition to the observations just cited upon the rabbit, the author studied the dog, cat and various birds. In these animals he found remarkably strong dilated canals winding in a corkscrew manner through the ganglion cells. From the perior extra-cellular tubes more or less numerous canals force their way into the ganglion cells. Inside of the cell they often divide in the characteristic finger-form manner, and they turn in manifold ways, not infrequently in spirals. By this means there exist glomerulus-like collections of tubes in the cell. In the case of the birds there were seen canals so strongly dilated that the protoplasm appears only as islands or thread-like heaps between the tubes. These dilations or tubes are not localized in any particular part of the cell but may be found in any part. He says that these tubes must correspond to the bands which were described by NELIS, with the exception that NELIS did not make any mention of bands going out of the cell. Such connections do not exist in all cases, but are nevertheless general. HOLMGREN could find these cells in the sympathetic and central nervous system of birds. He considered the canals which may be continued beyond the limits of the nerve cell as lymphatic passages.

As opposed to STUDNICKA, HOLMGREN says that the lymph canals come from the anastomosis of vacuoles or alveoli, and again he states that the canals in the case of Petromyzon are bounded by intensely staining walls which continued rectly outside of the nerve cell into the walls of the extracellular paths.

If one stimulates the spinal ganglion cells by means of weak induction currents, almost all parts of the whole canal are strongly widened. This agrees with the statement of NELIS that the bands occur in altered cells. "The nerve cells are permeated with a very rich canal system hitherto unsuspected, and only the more dilated parts of these networks are the passages which I was able to see before."

The great dilations of the canals are certainly only accidental, and so one can understand without anything further the great variability of the canals.

After working upon a variety of animal forms both vertebrate and invertebrate, and especially upon Lophius, the author concludes that his former position in harmony with that of FRITSCH ('86) is a mistaken one and that the vessels are not blood vessels within the nerve cells but are to be considered as lymphatic in their nature, and that they press their way into the nerve cells and there branch about. Among the invertebrates he finds Astacus and Palæmon, next to Lophius, excellent material for clearing up the true nature of the lymph canals.

In very young animals he finds the canal net to be remarkably simpler than in the case of older animals. Often this net is to be found at one pole of the very eccentric nucleus. The sympathetic nerve cells of the mammals show the canal nets only within the cell body. The same nerve cells of the bird, like the central nerve cells of all the vertebrates studied, possess continuations of the net also within the dendrites. An electrically stimulated nerve cell of the bird will show, according to HOLMGREN, the presence of the lymph canals in the neurites.
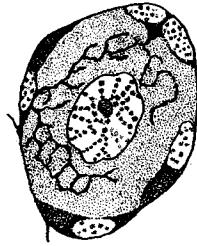

FIG. 2. The intracapsular cells surround the nerve cell. The trophospongium branches as a net of coarse threads through the endoplasm and at two points reaches the surface connecting itself with the colored bodies of the intracapsular cells. After HOLMGREN ('04, Fig. 1).

The question as to the morphological and genetic character of the lymph canals has been much discussed and various opinions held. NELIS considered them as achromatic hyaline bands, but he seems to be somewhat uncertain in his meaning. To him they are riddles as to morphology and function. HOLMGREN and his followers believe them to be canal-like, fluid carrying structures. According to HOLMGREN and his followers the bands of NELIS are only modified parts of the lymph-canals. HOLMGREN opposes the view that they are formed out of the nerve cells but holds that they press into the substance of the nerve cells from without in the form of hollow processes (Kapselfortsätse). He further claims to have seen unmistakable nuclei-bearing capsule processes in the spinal nerve cells of Lophius and other teleosts, also in the gastric ganglion cells of the Crustacea, within which there were sap spaces. According to his view these canals do not represent drainage tubes but are rather the morphological expression of certain phases of the penetration of nerve cells and the intracapsular cells belonging to them. The trophospongium has pseudopodia-like mobility whose intensity is supposed to depend upon intracellular chemical processes (Fig. 2).

The lymph-canals are of a lymphatic nature and are certainly associated with

the nourishment of the cell. NELIS claims that as the nerve cells change there is a decrease of the tigroid substance which is accompanied with an increase in the amount of the transparent bands. HOLMGREN believes that the localization of the tigroid substance should coincide with the appearance of the canals, that the canalicular zone of the cell should be the tigroid layer free of ectoplasm. The tigroid substance stands in a causal relation to the lymph clefts and is associated with their activities. Where the clefts are especially dilated, a rich accumulation of tigroid substance takes place. In more protracted periods of activity the clefts become smaller and the tigroid substance vanishes; but in such places where the tigroid substance remains, the clefts remain dilated. Electric stimulation points to the same conclusion. The nerve cells, as a result of such a stimulus, receive new supplies of tigroid substance and at the same time become somewhat larger; accompanying this, there is a dilation of the lymph clefts. This leads one to believe that the electric current calls forth an alteration of the circulatory relations. HOLMGREN cites a number of investigators whose work bears directly on the interpretation of these structures as follows:

ADAMKIEWICZ ('86) from his researches with injections could have made the same report, that the nerve cells are furnished with their own blood vessels and that the nuclei of these cells should present venous spaces, but these discoveries have nothing to do with the sap canals which do not carry blood. From the work of other investigators it is evident that blood vessels very rarely enter nerve cells.

FRITSCH ('86) found that blood vessels were constantly to be found in the giant ganglion cells of Lophius piscatorius. HOLMGREN uses the results of FRITSCH to confirm his own belief that lymph spaces exist in the cell, but makes the additional statement that the blood capillaries are supposed to be drawn into the cell through endocellular branching processes. In 1900 HOLMGREN came to the conclusion that these spaces in the cells were not to be considered as blood vessels but rather as lymph spaces in so much as they do not carry corpuscles. STUDNICKA in the same year expressed the same belief, though more indirectly.

NELIS ('99) describes in nerve cells homogeneous non-staining bands of a skein-like appearance found within the cell. These appear in various places in the cell body. They exhibit various forms, half moon, spiral, corkscrew, and hang together at the ends, but do not form a true reticulum. They are to be found in the cells of the spinal and sympathetic systems as well as in the brain. They are particularly prominent in animals which have been poisoned. HOLMGREN claims that these structures are the same as are called "Saftkanälchen."

STUDNICKA ('99) held that the canals are formed from the running together of vacuoles which had formed in the cell in a row.

BETHE ('00) opposes this view on account of the fact that he had observed single canals which passed completely through several nerve cells and their capsules at the same time.

FRAGNITO ('00) regarded the canals as the remains of the interstices between the neuroblasts, through whose melting together the single nerve cells are supposed to come into existence.

PUGNAT ('97) believes that the canals force their way into the nerve cells from without, as lymph capillaries.

PEWSNER-NEUFELD ('03) studied the finer anatomy of the nerve cells in the nervous system of the white rat and guinea pig. He does not find that there are

distinct zones in the plasma of the cell. Small canals are scattered throughout the cytoplasm, no region being free from them. They do exist in the nucleus (Fig. 3). The canals may or may not occur in the protoplasmic processes of the cell. The canals run about the NISSL flakes, sometimes passing through them, at other times merely surrounding the flakes, or they may be free in the cytoplasm. Some of the small canals approach the nuclear membrane, but in no place were they seen to penetrate it. The size and extent of the canals is dependent on the physiological state of the cell. The canals do not have a distinct wall but a linear boundary due to the arrangement of the cytoplasmic granules. The intracellular lymph canals of the central ganglion cells open into channel-like spaces.
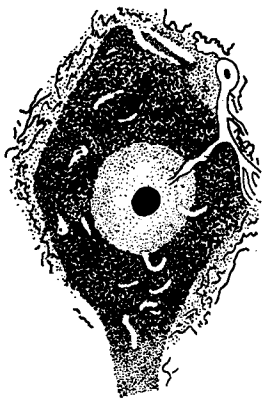

FIG. 3.   FIG. 4.

FIG. 3.   Ganglion cell of white rat.   Illustrates penetration of cytoplasm and nucleus of nerve cell by sap canals.   The isolated clear spaces are the cut ends of sap canals.   After PEWSNER-NEUFELD ('03, Fig. 3).
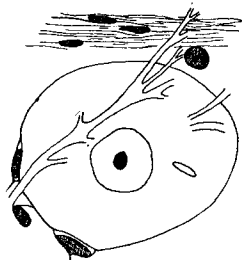FIG. 4.   A large ganglion cell with tubes formed from the capsule extending entirely through it.   After BETHE ('00, Fig. 2).

STUDNICKA ('99) presents a discussion of the origin and use of the canals in ganglion cells. The little canals can very often be followed in the body of the cell some distance, indeed, often through the half of the entire cross section of the cell. They are seen in such a study to branch freely. These little canals which are identical with those described by HOLMGREN, arise very likely through the union of a row of vacuoles. Many of the canals have smooth outside walls. Some separate vacuoles are found which are explained as being the cross sections of the branches of such vacuoles as have not yet fused into canals. He is unable to define the contents of the canals and alveoli, but suggests that they are during life, no doubt filled with a fluid which may be identical with that in the pericellular space with which the little canals are united. Some of the greater alveoli contain a homogeneous substance which colors more intensely with eosin and is to be considered a special deposit.

BETHE ('00). We have here to do only with dependent canals (blood vessels) which can be proven only by injections. No nuclei are to be found in the walls of these canals. The canals result from the fusion of separate vacuoles. The canals have nothing in common with the neuro-fibrillæ (Fig. 4).

IV. VACUOLES.

The presence of vacuoles or vacuolar-like structures in the cytoplasm of nerve cells is a common structural character. They have been recorded as follows:

HODGE's ('92, '94) work is of great importance to all interested in the question of fatigue and the accompanying structural changes in the nerve cells. The spinal ganglion cells of the frog, cat and dog, under electrical stimulation and the spinal ganglion and brain cells of English sparrow, pigeon and swallow show the following changes. The nucleus undergoes a marked decrease in size and changes from a smooth and rounded structure to one having a ragged outline. Its reticulate appearance is changed and the whole structure takes a denser stain. The cell protoplasm gives evidence of slight shrinkage and the formation of vacuoles. These vacuoles appear quite constantly in the ganglion cells of birds. The vacuoles have a sharp outline and a definite shape in the rested animal but are indistinct in the bird that has been at work during the day. Vacuoles also appear in the honey bee under the following conditions. Honey bees were collected in a raspberry patch as soon as they appeared in the morning. The first six bees were quickly decapitated, the brains removed, and three were dropped into one-half per cent osmic acid, and three into saturated mercuric chloride solution. At about seven o'clock at night six more bees were captured and treated in the same manner. After the morning and evening bees had been paired at random, each pair was stained and studied and an attempt was made to measure the nuclei and work out the amount of shrinkage. The minimal shrinkage was 9 per cent, and the maximal 75 per cent. The author does not attach much value to these figures, although they express the fact that a wide difference exists between the two. The average in diameter of the morning bees is more uniform than for the evening bees. These results indicate first, that the nerve cells of a number of bees' brains are in a more uniform condition in the morning than in the evening. Secondly, they differ in appearance, or condition, from one another, somewhat in the morning and a great deal in the evening.

MONTGOMERY ('97) finds in the nemerteans, Cerebratulus and Lineus, chromophilic corpuscles under the following conditions: The cytoplasm of the medium sized cells is of a coarsely vacuolar structure; sometimes the hyaloplasm fills the whole proximal portion of the cell as far as the nucleus. But a thin, peripheral layer of spongioplasm is always present, and a similar layer envelops the nucleus. These cells are much larger in Cerebratulus and the cytoplasm is much denser, *i. e.*, there is a proportionately greater amount of spongioplasm, and a coarsely vacuolar structure is seldom found. The large cells of the brain are of an elongated pyriform shape, largest and rounded proximally, seldom nearly spherical. It may be noted that while the cell bodies vary considerably in size, their nuclei remain of nearly uniform dimensions. The cytoplasm is, as a rule, coarsely vacuolar

(vesicular), especially so toward the distal pole. A thin peripheral layer of finely granular cytoplasm is always present. The vacuoles do not seem to have any definite grouping, but such groupings as exist are explained as corresponding to the different physiological states.

Certain bodies occur in these ganglion cells in Lineus which are absent in all of the cells in Cerebratulus. These bodies are frequently larger than the nucleolus and of a spherical or oval shape, and are not refractive. After the use of a double stain they stain usually with eosin, sometimes with hæmatoxylin, but always more intensely than the surrounding cytoplasm, though seldom as deeply as the nucleolus. Structurally, they are homogeneous, with a peripheral membrane, which may be scarcely discernible or in other cases, of considerable thickness; this membrane always stains more intensely than the enclosed portion, and forms a boundary against the surrounding cytoplasm (Fig. 5). These bodies do not occur in all cells, but only in about one-sixth of the total number; when they are present, it may be but a single one, more frequently four or five, apparently never more than
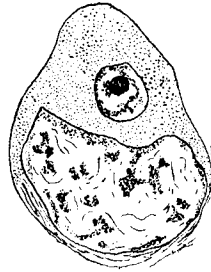

FIG. 5.   FIG. 6.

FIG. 5. Lineus gesserensis. Ganglion cell of the third class, showing the presence of vacuoles, some of which contain differentiated granules. After MONTGOMERY ('97, Fig. 9).

FIG. 6. Nereis, brain cell of sixth class. Nucleus lies in narrow end surrounded by granular cytoplasm, while in the other end there is a large vacuolar space. After HAMAKER ('93, Fig. 17).

fifteen. There is also no regularity in their distribution, such as a concentric or radial arrangement, and in the same cell they are usually of various sizes and of different staining power. To these cytoplasmic bodies may be applied the term chromophilic corpuscles, to distinguish them from the chromophilic granules in the ganglion cells of other animals.

RAND ('01) reports vacuoles and gives an analysis of the cytoplasm as follows: Very little can be said as to the finer structure of the cell protoplasm in the Lumbricidæ. The most careful examination fails to reveal its precise nature. It varies in degrees of homogeneity somewhat according to the size of the cell. In the smaller cells, it usually appears compact and fairly homogeneous. In larger cells, it is much less homogeneous, and there is a tendency toward the formation of large vacuolar spaces. The substance of the fixed cytoplasm, as it appears to the eye, may be said to be of four kinds. There is (1) a perfectly homogenous "ground," represented by the lightest areas in the figures; (2) material which gives the impression of being very finely granular; in the smaller cells this is quite evenly

distributed, while in the larger cells it tends to concentrate in regions, giving the cytoplasm a blotchy appearance; (3) rather conspicuous granules or masses staining fairly deeply and often surrounded by an area within which the material of the second class is less dense; (4) a fine fiber irregularly distributed through the cell body, but often appearing to be associated with the more conspicuous granules and sometimes occurring about granules as centers of radiations.

HAMAKER ('93) shows in one type of the nerve cells in Nereis the following: In the posterior half of the brain there are several pairs of very large cells which have a very striking characteristic. The nucleus lies in the narrow end of the cell, and is surrounded by the granular cytoplasm. At the other end of the cell, there is a large vacuolar space containing a number of deeply staining bodies of irregular form, embedded in an indistinct coagulum (Fig. 6). Other cells have very finely granular substance occupying a similar position, the granules being much smaller and staining less deeply than those of the body of the cell. In these cases the nucleus shows no signs of degeneration.

LENGENDRE ('05, '06) in a series of short papers during the years 1905 and 1906 has given us reports of an investigation on nerve cells of Gasteropods. He has studied the cell from the physiological point of view, with the idea of determining whether the structures described by HOLMGREN and others are in any way related to the nutritive functions of the cell. He follows the work of HOLMGREN, BOCHENEK, McCLURE, RHODE, and others. A study is made of the effects of various fixing reagents and he finds that RABL's solution is a very poor reagent for the study of nerve cells. Consequently many of the results which have been obtained through the use of this fluid are to be considered as artefacts and not as actual structures which exist in the living cell. He questions the work of RHODE and does not believe that the fibrils of the nerve protoplasm are continuations of the processes of the neuroglia cells on account of the difference in size and staining qualities. He finds in the cells of Helix pomatia vacuoles of various sizes, arranged in various ways in the cell. Sometimes they communicate with one another and sometimes open to the outside of the cell. These vacuoles are without definite walls and contain a homogeneous fluid without granules. The chromophile granules are always found in the protoplasm when present at all and never appear in the vacuoles. LEGENDRE does not admit the theories of HOLMGREN concerning the nutritive functions of the nerve cells. He advocates in his first paper that the vacuoles represent accumulations of excretory products and that they are in no way connected with the constructive metabolism of the cell (Fig. 7).

In these papers he calls attention to the following points: He describes the appearance of living nerve cells that have been immersed in water for a considerable time. The result is a rapid increase in size due to osmotic exchange. In the protoplasm of the cells thus treated the meshes of the spongioplasmic net become greatly enlarged and more clearly visible. The nucleus becomes large and numerous vacuoles appear in the periphery of the cytoplasm. He also advances the idea that the HOLMGREN canals in the trophospongium are to be interpreted as pathological rather than nutritive and that they act more like the phagocytes in that they destroy cell substance rather than build it up.

PFLÜCKE ('95) notes the presence of a few vacuoles in the cell plasma which he does not regard as true vacuoles but as accumulations of unstainable substance.

EWING ('98) takes an extreme position in regard to the presence of vacuoles, claiming in the majority of cases that they are cadaveric or artificial products.

The formation of vacuoles has long been recognized as one of the necessary imperfections in most methods of fixing of nerve cells.   The writer cannot agree with the statement often seen that the vacuolation may be regarded as pathological only when it is found in advanced degree.   Among the present cases, extreme vacuolation when found, was always plainly referable to post-mortem processes. The study of cadaveric changes in ganglion cells indicates that vacuoles are one of the most constant of post-mortem products; and that they frequently form in considerable numbers and of large size within a few hours, often preceding other post-mortem changes.   Especially when the brain and meninges are œdematus, or when the patient has suffered from general sepsis, vacuolation of cells may be expected unless the tissues are fixed very shortly (one half hour) after death.   The above observations, as well as the circumstances under which vacuoles are usually found in stained specimens, indicate that in the great majority of instances vacuola-
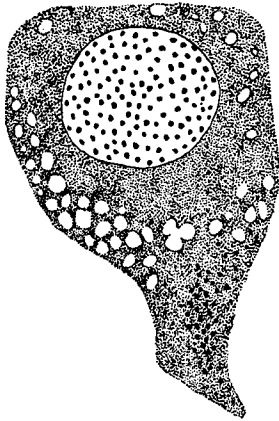

FIG. 7.   FIG. 8.

FIG. 7.   Arion rufus.   Vacuolated condition of cytoplasm and granules in the axone hillock.   After LEGENDRE ('05, Fig. 1).
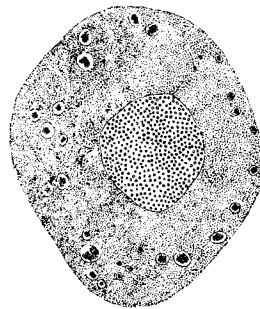
FIG. 8.   Ganglion cell of Tethys with a number of mitochondrien masses either in clear spaces limited by a definite wall or free in the cytoplasm.   After RHODE ('04a, Fig. 10).

tion of ganglion cells is a cadaveric or artificial product, and in any case with the present state of our knowledge, is devoid of definite pathological significance.   It is doubtful if the structures known as nucleolar vacuoles are to be regarded as of a similar character with the vacuoles of the cytoplasm.

RHODE presents numerous facts in his several papers in regard to the structure of the ganglion cell.   The sphere referred to in the following is a differentiation of the cytoplasm of a distinct character and should not be confused with the sphere associated with the centrosome.   According to RHODE ('04a) the sphere in the ganglion cell of Tethys consists of a central part surrounded by a clear layer having the granules arranged compactly and in a radial manner.   The clear layer is made up of a homogenous or fine granular substance which colors intensely (Fig. 8). The outermost bodies in the peripheral layer of granules may fuse completely so

that there is the appearance of a thick membrane which seems to separate the sphere from the cytoplasm. The clear region may be encroached upon and occupied by radially arranged granules which vary in size. All stages in the origin of the sphere may easily be seen in the same ganglion cell. In the frog these same spheres have a nuclear origin, *i. e.*, they are derived from the smallest bodies in the nucleus. In the same manner as in the frog, arise the spheres in Tethys with this difference, that the origin does not take place within, but without the nucleus. The various stages in the development of the spheres are seen in the cytoplasm, which may be compared to similar stages in the development of the spheres in the ganglion cells of the frog.

When the spheres attain a certain size, their destruction occurs as follows: The central body becomes indistinct and the radial zone breaks up into large or small pieces, finally becoming so small that they cannot be distinguished from the cytoplasmic granules so far as their shape is concerned, but they retain their avidity for stain, which gives them prominence everywhere. Some of the large spheres do not go through these regular changes and are described as vacuoles (Bläschen) with a thin wall and a clear center. In the transformation of the sphere into a vacuole this stage corresponds to the term "Mitochondrien." When the peripheral layer of the sphere is broken up into a number of loose threads the term "Chondromiten" is applied to them. The largest spheres are as a rule the oldest and arise out of the smallest, structureless globules (Küglchen) of the cytoplasm. These may be seen to grow and to differentiate themselves into a light inner zone and a dark outer band. The larger the sphere, the more plainly the granules, which finally assume a radial arrangement in the outer zone, appear. The last stage in the formation of the sphere shows the central body assuming its complete shape and size.

SMALLWOOD ('06) reported the presence of numerous vacuoles in Haminea, Venus, Planorbis, Limax, Helix, Littorina, Melantho, Montagua and Aplysia which were designated as lymph spaces. A more extended study suggests that this term should be reserved for the larger peripheral spaces and that the term vacuoles more correctly describes them. There is no definiteness about their position or size in the cell (Fig. 7). Animals examined during all seasons of the year show them to be present in living nerve cells.

From this review, we learn that the nerve cells of Nemerteans, Annelida, Crustacea, Insecta and Mollusca among invertebrates exhibit a highly modified cytoplasm. A sufficient number of specimens have been examined in each of these great groups to indicate the very general appearance of differential structures in the cytoplasm other than fibrillar. In the introduction eleven different terms are cited as having been given to this stainable substance in the cytoplasm which of itself suggests that the problem is one of great difficulty; certainly a doubt must have existed

in the minds of the various workers who have coined these terms as to their significance and relationship.

It is rather hard to make a classification of these structures as described by the various authors because in most instances the cytological study was not followed or preceded by an examination of living nerve cells.   Our results have been so clear and satisfactory that we are tempted to try to correlate some of the previous facts with them.   Probably the commonest structure present in the cytoplasm of the invertebrate nerve cells is the *vacuole*. These vacuoles are present in all of the great groups already cited, although usually described under the terms "lymph space," "Netzapparate," "Saftkanälchen," "Trophospongien," etc.   The vacuole can be determined in the following manner in the living cell: Isolate a nerve cell and study it in a 1–500 solution of methylene blue or neutral red in normal salt solution under the oil immersion lens.   At first, but little can be determined; but as the stain progresses the vacuoles become more distinct and their contents often take on a differential stain.   The experienced worker can make out these vacuoles without any stain.   The time that it takes to stain these vacuoles will vary; but usually from 5 to 20 minutes will be the limit, as after that time the nerve cell is apt to become overstained and undergo some changes in its general appearance and the character of its parts.   This gives about 15 minutes when a critical study may be made.   During this time the vacuoles are readily made out as isolated spherical bodies containing a fluid. It is impossible to trace any connection between vacuole and vacuole.   The size is also further evidence of their individuality, for they range from the very minutest bodies recognizable with the oil immersion lens to structures a third the size of the nucleus. Studying these vacuoles in Planorbis and Limax for two years, in which we examined almost weekly the living nerve cells from hundreds of specimens, we are convinced that these vacuoles are transitory structures, that they vary in number from time to time, and that they are not limited by a distinct wall.   The vacuoles move about in the cytoplasm when the nerve cell is put under pressure, which would be impossible if they were part of lymph spaces that had grown in from the surrounding neuroglia tissue.

The Chronodromiten and Mitrochondrien of RHODE, the Trophospongien of HOLMGREN as interpreted by BERGEN, present in Helix but not figured by McCLURE, the chromophilic corpuscles

of MONTGOMERY, the vacuolar spaces of HAMAKER, the granules within clear spaces of RAND, the numerous vacuoles described in Arion by LEGENDRE, all, we believe, are to be classified as nerve cell vacuoles. The significance of these vacuoles is discussed further on.

V. THE NISSL BODIES.

RHODE ('04a) has called attention to certain similarities of structure in the ganglion cells of vertebrates and invertebrates. Both have the following facts in common: (1) a homogeneous hyaloplasm, (2) a spongioplasmic groundwork which consists of coarse and fine fibrils, (3) a *stainable substance* which in the case of the invertebrates and a part of the vertebrates is lodged in the coarse fibrillar spongioplasm. In the remainder of the vertebrates it clumps and forms the NISSL bodies, which are, indeed, independent of the spongioplasm, which appears between them in almost colorless fibrils.

The structures known as NISSL bodies or granules furnish a most interesting field of research. The great degree of variability in the appearance of nerve cells from different animals has led to the belief that structures existing in one nerve cell may have no counterpart in another. Among the invertebrates the failure of some authors to identify structures closely similar to those found in vertebrates has led to the supposition that such structures were lacking. It seems evident that such bodies as NISSL granules must be present in the cell for some specific purpose. The nerve cells of invertebrates have fundamentally similar functions to perform as the cells of vertebrates. If this be true, may we not expect to find some structure, perhaps even morphologically and chemically different, which takes the place of that structure known as the NISSL granule? We are of the opinion that such bodies do exist.

The *stainable structures* of the cell, referred to above, have received various names, as they have been observed and described by different authors under dissimilar conditions. The terms chromatic substance, chromophile substance, tigroid substance, sigroid substance, basophile constituent, etc., have all been employed to designate the structures recognized by us as NISSL bodies or NISSL granules. Various authors have recognized the fact that

these bodies may vary in size, in number and in capacity for taking up various staining agents.

NANSEN ('87) described the structure of the nerve cells of Patella vulgata, Nereis, Lumbricus, Homarus vulgaris, Nephropa norwegicus and six different Ascidians which he classed with the above. He found in the cells of the Nereidæ structures which correspond very closely in description to the granules commonly known as NISSL bodies. Some of the granules were very large and prominent and were situated in the mesial part of the protoplasm. In preparations fixed with osmic acid and stained with hæmotoxylin they were very dark, almost black in color, and consisted of a fatty (myeloid ?) substance (Fig. 9).
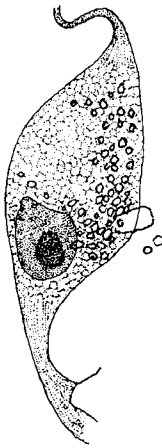

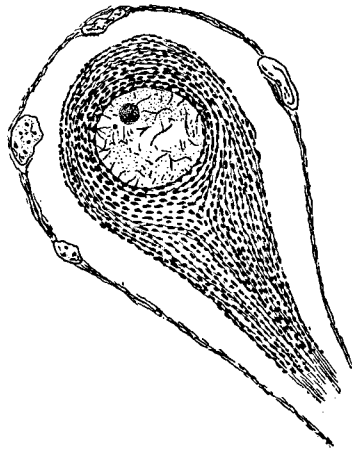FIG. 9.   FIG. 10.

FIG. 9.   The yellow granules are scattered through the cytoplasm and are drawn with heavy outlines. After NANSEN ('87, Fig. 54).

FIG. 10.   Crayfish. Shows the chromophile bodies spindle shaped and apparently associated intimately with the fibers. After PFLÜCKE ('95, Fig. 10).

Nissl bodies in invertebrates.—The question as to the existence of NISSL granules in the nerve cells of invertebrates has more than once been raised. PFLÜCKE ('95) undertook the investigation of the finer anatomy of the nerve cells of the crab, snails and worms. In the crab he succeeded in demonstrating granules which appear like the commonly accepted NISSL bodies. In the snails and worms he failed to identify such structures (Fig. 10).

McCLURE ('97) found (chromophilous) granules in the nerve cells of Helix and Arion, and expressed the opinion that this chromophilous substance is homologous with that found in the nerve cells of vertebrates.

FLOYD ('03) was unable to differentiate by means of methylene blue any NISSL bodies in the ganglion cells of the common cockroach. In well fixed material, however, he found varying quantities of deeply staining granules and masses.

Distribution.—These deeply staining granules were found by RHODE ('04a) in both vertebrates and invertebrates to occupy a zone of the cytoplasm surrounding the nucleus but not extending out to the cell wall. A rather broad zone (the spongioplasm) at the periphery of the cell is free from these bodies, so that the ganglion cell resembles the Amœba in that it has a light ectoplasm and a dark entoplasm. Only the finely granular hyaloplasm enters into the axis cylinder.

McCLURE ('97) found the granules to be arranged chiefly in rows, but at certain points in the cell body they appeared to be collected into spindle-shaped groups, having their long axes parallel to the periphery of the cell (see Fig. 11). A statement of McCLURE's is of particular interest: "The cell bodies stain a deep blue, while the axis cylinder processes are only partially affected by the stain, and thus appear light in color. The cause which produces this difference is fundamentally the same in both cases: namely that the intense staining capacity of the cell body, and the lack of the same for the axis cylinder process in Limax are due respectively to the presence and absence of the chromophilous granules. The Flemming-iron-hæmotoxylin preparations are especially interesting for the reason that they show with great clearness, not only the same chromophilous granules but also certain spindle shaped structures in the cell body, which in all probability are collections of some small chromophilous granules. The above results concerning the presence of chromophilous granules in the nerve cells of Gasteropods point toward the acceptance of the view that this chromophilous substance is homologous with that found in the nerve cells of vertebrates (NISSL bodies)."

PFLÜCKE ('95) found that in the crab the chromophile granules of the nerve cells are arranged in rows, and in the nerve processes they were few in number. The granules were especially numerous about the nucleus, being regularly distributed. Under high magnification they were found to be spindle-shaped and to be arranged in parallel concentric rows.

FLOYD ('03) finds the granules disposed in areolar fashion in the cell, deposited upon the cyto-reticulum.

Physical constitution.—Among vertebrates the NISSL bodies have been found by FLEMMING, VON LENHOSSÉK, MARINESCO, VAN GEHUCHTEN, HELD, CAJAL, PFLÜCKE, EWING, CARRIER and others to have a granular structure—to be in reality aggregations of minute particles of deeply staining substance. FLOYD and McCLURE have presented evidence of the same structure for the NISSL bodies of the invertebrates.

Resistance to degenerative change.—The work of EWING ('98) upon cadaveric changes taking place in the ganglion cells of brains and cords of rabbits which were allowed to decompose in the air from 48 to 72 hours may give evidence as to the function of the NISSL granules. During the first twenty-four hours there was noticed a granular disentegration of the chromatic substance. This disintegration was evidently due to the separation from each other of the granules which made up the NISSL bodies. As the degenerative changes proceeded, the granular disintegration became more and more marked. During this time the individual granules retained all of their natural capacity for stains. Later when putrefaction changes were set up in the cells the NISSL granules exhibited a remarkable resistance to the action of the bacteria and still retained distinct outlines even when the cells were becoming filled with vacuoles or when the cell consisted merely of a nucleus with a narrow fringe of granules (see Figs. 12–13).

Do NISSL granules exist in the living cell? The existence of the NISSL granules in the living cell has been seriously questioned by several prominent observers and various answers have been published. DOGIEL, HELD, RUZICKA, FLEMMING hold to the view that they are an aggregation of material produced in the cell at the time of fixation, by the reagents employed. OLMER ('01) contends that the material of which the NISSL bodies are composed is scattered through the cells, and that these particles are clumped and precipitated by the fixing agent.
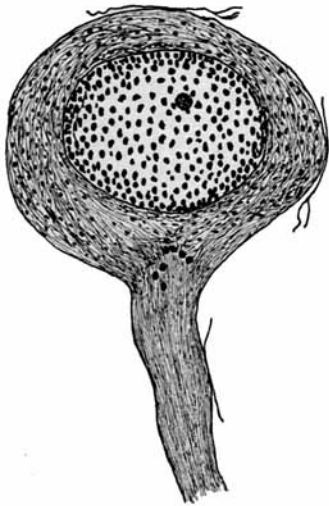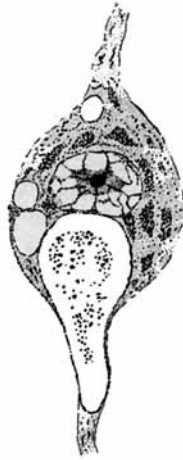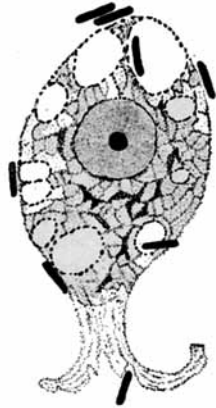

FIG. 11.   FIG. 12.   FIG. 13.

FIG. 11. Helix. Cell from infra-œsophageal ganglion. FLEMMING's sol., prog. iron-hæm. Concentric arrangement of fibrils and granular rows. Spindles. Pigment granules at base of process. After McCLURE ('97, Fig. 12).

FIG. 12. Medullary stichochrome of infant, 3 hours after death. LANG's fluid. Methylene blue. Very rapid and extreme vacuolation. Coarsely granular appearance of chromatic bodies. After EWING ('98, Fig. 1, plate 2).

FIG. 13. PURKINJE cell of rabbit, after 48 hours exposure to air. LANG's fluid. Methylene blue. Extreme vacuolation. Growth of putrefactive bacteria. The chromatic reticulum and bodies are reduced to a series of coarse dark granules. Complete nuclear chromatophilia. Shrinkage and destruction of dendrites. After EWING ('98, Fig. 3, plate 2).

The admirable work of CARRIER ('04) gives strong evidence for the belief that the NISSL bodies are not due to postmortem changes but actually exist in the living cells. In support of the same view may be mentioned the results by ARNOLD, VON LENHOSSÉK, CAJAL, TURNER, etc.

Our own work, done upon the living nerve cells, has convinced us beyond any possibility of doubt of the actual existence of these structures in the living cell. The detailed discussion of this feature appears later in the paper.

Studies upon the molluscan nerve cells.—In a previous paper in this *Journal* SMALLWOOD ('06) described certain morphological characters of molluscan nerve cells. Without indulging in vain repetition, it is perhaps well to call attention here to certain of these facts. There were found in the nerve cells of Haminea solitaria, Venus mercenaria, Planorbis and Limax cytoplasmic vacuoles containing a colorless, transparent liquid, also solid bodies of various sizes, irregularly rounded forms of varying numbers. The solid bodies were of different appearance in the different genera named, and somewhat different in distribution, those occurring in Limax being always found within the limits of the vacuoles, while in the other forms the bodies or granules were only rarely to be seen in the vacuoles. Attention was called to the fact that these bodies could be seen in the living nerve cell, and hence could not be considered as artefacts. The fact that the number of these bodies present in a given cell varies from time to time convinced us that a morphological study could not satisfactorily account for their presence and variable appearance.

In our discussion of our work upon the bodies mentioned above we do not wish to be understood as maintaining that these structures are in every sense homologous with the NISSL granules of vertebrates. Morphologically and chemically they may not correspond to the NISSL granules of vertebrates, and may even differ much among themselves in these respects. We are convinced, however, that the question of function is more fundamental and believe that these structures will be found to fill the same place in the economy of the invertebrate nerve cell as does the NISSL body of the vertebrate nerve cell.

Since the bodies found in the cells of Limax more nearly correspond to those found in vertebrates we will first describe our experiments upon this form and later discuss our work upon the other forms under the caption "Pigment."

Experimental.—The experimental work in connection with our study of the molluscan nerve cells has been carried out with a view to determine, if possible, the nature of some of the structures which have been found to exist in the cells. In order to insure a certain

degree of accuracy in the work it was found desirable to bring the animals into the laboratory and keep them under definite environmental conditions, which could be more easily controlled. The temperature and surroundings were generally more uniform than they would have been outside of the building. The animals were kept in moist boxes or glass dishes. Some were fed upon grass or chestnuts; others were starved. At intervals animals were taken from both the fed and starved groups and their nerve cells studied, either in sections or in the live condition.

Limax.—The remarkable appearance of the vacuoles and granulations in the nerve cells led us to make a series of tests with a number of fixing agents in order to assure ourselves that we were dealing with actual structures and not artefacts due to faulty fixation or preservation.

The following agents were employed: CARNOY's fluid, PETRUNKEVITCH's solution, picro-nitric acid, FLEMMING's strong solution, osmic acid and absolute alcohol. The vacuoles and the bodies contained within them appeared with a constancy that was remarkable.

Effects of starvation and feeding.—Specimens of Limax taken in the early spring as soon as they emerge from their hibernation exhibit in the cytoplasm of the nerve cells collections of vacuoles of various sizes, scattered about in various parts of the cell. Sometimes the whole cytoplasm appears to be peppered with them; sometimes they are packed together with their thin walls touching each other in such a way as closely to resemble in appearance a mass of soap bubbles. In some of the vacuoles small granules of various shape may be found. The granules are, however, not to be found in all of the vacuoles at this time. Fig. I of Plate I is a photograph showing the strongly vacuolated condition which may be seen in the cells and also indicates the presence of some of the granules mentioned in certain of the vacuoles.

The other cell structures do not show any especially important features. The nucleus is large and well defined. In some cases the cytoplasm appears to be somewhat shrunken, but this is far from being a constant character.

Later in the spring animals taken into the laboratory and studied, or animals which have been kept in the laboratory and fed upon grass show that the number of solid bodies within the vacuoles has increased. This increased number is found to hold throughout the summer and fall of the year.

Two possibilities for the increase in the number of bodies in the vacuoles present themselves, either the bodies are to be considered as storage products which may be called upon in time of stress to supply energy for the nerve cells or they are to be considered as degeneration products which have accumulated in the cell during the increased activity of the animal in the active season. If they are of the former class, any great increase in the activity of the animals should have the effect of breaking them down and should cause them to disappear. If they are of the second class, prolonged activity should bring about an increase in their number and size.

Fatigue.—HODGE and others have noticed that the nerve cells of animals respond to excessive stimulation in definite ways. HODGE found that the cytoplasm of the cells took on a different appearance and that the nucleus became shrunken. Our work upon Limax has failed to confirm these particular observations and has convinced us that we have here conditions which may have escaped notice.

An active, living, specimen of Limax was taken and by means of an induction current applied to the posterior part of the body forced to crawl until it could no longer draw itself away from the point of stimulation—a period varying somewhat with different specimens, but usually from one-half to three-quarters of an hour. The nerve collar was then dissected out, fixed, sectioned and stained in the usual manner. The nerve cells of an animal treated in this way differ in a very marked degree from those of the normal rested animal. In the periphery of the nerve cells are to be found the vacuoles to which attention has already been called. These vacuoles are usually numerous, but differ from those found in the normal, well fed, rested specimens in that they contain no dark solid bodies. The limits of the vacuoles are sharply marked. The vacuoles appear in various parts of the cytoplasm and may occupy nearly all the space between the nucleus and the cell wall, when at their greatest development. It is evident that these vacuoles are filled with a liquid substance, for when the cells are placed in a medium of higher concentration than the body liquids an osmotic action takes place which draws out water from the vacuoles and finally ends in their collapse.

One may say that the disappearance of the dark bodies from the vacuoles is not the result of the fatigue of the animal, but rather

the effect of the current upon the nerve cells.   To avoid the possibility of this criticism another experiment was devised.

A number of well fed snails which had been living upon damp earth were taken.   A part of these were killed at once and the rest were fatigued by poking them with a sharp needle until they would no longer withdraw from the point of stimulation.   This process was somewhat slower than the fatigue by means of the electric needle and took from two and a half to three hours.   A comparative study of the two sets of animals revealed conditions entirely in harmony with the previous experiment.   The nerve cells of the rested animals show the presence of the vacuoles with the bodies in them, the nerve cells of the fatigued animals show the presence of the vacuoles but the solid bodies have disappeared. Evidently there has been some change in the cells of the animal due to the excessive amount of work which the animal was called upon to do.

Up to this time in our work no attempt had been made to ascertain whether it were possible to see these structures in the living nerve cell.   It was our good fortune to find that with care in manipulation and careful observation it was possible clearly to distinguish these several structures in the living nerve cell.   A trace of methylene blue added to the salt solution in which the cells were examined brought out the bodies with great distinctness within a few seconds and they could be easily studied.

The next step in our work was to study the disappearance of the bodies in the nerve cell under the microscope—to watch the process.   The results were even better than we had hoped.   Small electrodes of platinum foil were attached to a slide and the nerve cells mounted between these electrodes.   The electrodes were connected with the secondary coil of an inductorium.   Under the $\frac{1}{12}$ inch oil immersion lens the bodies in the vacuoles showed with great clearness and sharpness of outline.   When the current was first applied there was no change in the appearance of the bodies but within a few minutes a change appeared.   The outline of the body lost its sharpness.   The body seemed to grow larger in size. The line of demarcation between the solid body and the liquid became less and less distinct and finally disappeared.   The substance of the body appeared to be going into solution in the liquid of the vacuole.   At the same time, there was a slight change in color, the body taking on the color of the liquid.   This process

was allowed to continue until the body had been completely re-
placed by the more transparent liquid mass. At this time the
current was stopped. A continued study of the cell showed that
in the same vacuoles where the disappearance of the bodies had
been noted there was later a reconstruction of the solid body.
Within an hour or two the solid masses had again become estab-
lished in the cells. These bodies were, however, not the same
bodies as had existed in the cells previous to the stimulation, as
they exhibited entirely different forms.

That we have here substances in the cell which are intimately
connected with the normal activities of the cell seems to be demon-
strated. As to the chemical nature of these bodies we have only
little knowledge. The fact that they are more or less darkened by
osmic acid would indicate that they are of a fatty nature. Fur-
ther we can not say at the present time.

VI. PIGMENT.

NANSEN ('87) was, so far as we are aware, the first to give an accurate account
of the yellow pigment granules existing in certain of the invertebrate nerve cells,
although such granules had been observed before. He found in the nerve cells of
Patella plenty of large yellow granules lying in the cytoplasm. These granules
had a variable size, and no regular shape, being sometimes spherical, sometimes
square or polyhedral. They looked as if they had been produced by the coagula-
tion of a homogeneous yellow substance. The granules were sometimes found
scattered through the whole mass of protoplasm, but more frequently were con-
centrated in special parts of the cells, especially in the neighborhood of the nucleus.
Plenty of similar smaller and larger granules were also to be found outside the
ganglion cell. They frequently occurred in such numbers that one, for a time,
could feel disposed to believe that they belonged to a substance extending through
the whole nervous system. NANSEN was convinced that they were either exuded
from cells, or that they sprang from destroyed cells. He had observed such a sub-
stance exuded from the protoplasm of the cell. Fig. 9 represents such a case. The
substance here occurred inside as well as outside the cell. The granules were
concentrated toward the part of the cell surface where they were probably to be
exuded. Outside the cell they were united into larger pieces of irregular shape.
The granules were situated not only near the surface of the cell but also occurred in
the mesial parts of the protoplasm. NANSEN recognizes that the granules gave
the yellow color to the nervous system of Patella, as well as other molluscs.
He thought the yellow color to be due to a substance allied to or similar to hæmo-
globin, and also believed that the granules contained fat. He found difficulty in
recognizing these granules in the sections of nerve cells. As to function, he believed
them engaged in the nutrition of the cell.

McCLURE ('97) in connection with his studies of the chromophile granules
mentions the existence of pigment granules in the cells of gasteropods, but gives
them no further attention.

LEGENDRE ('06) found in the nerve cells of Helix aspersa, Helix pomatia and Arion rufus pigment granules of various sizes, sometimes isolated, sometimes grouped together in irregular masses. The granules were most frequently located in the cone of origin of the axone, though they were sometimes arranged in concentric rows in the peripheral layer of the cytoplasm. Frequently they extended out along the axis cylinder. Osmic acid alone or in combination attacked the granules and stained them black at times; at other times they were unaffected. Hæmatoxylin gave them a brown color. These reactions resembled those of the lipochrome pigments observed in the nerve cells of a large number of vertebrates and some invertebrates. The number of granules varied in different individuals, and the author had failed to establish any connection between their appearance and the physiological state of the animals. He says, "The rôle of the granules is not known. One may consider them as a food, a reserve material, a functional precipitate, a product of disassimilation, a degenerative product. The multitude of hypotheses tells us nothing concerning their composition, their variation or their functions."

Planorbis.—In the preliminary study of the nerve cells of Planorbis the same general methods were employed as in the case of Limax. A number of fixing fluids were used and their comparative effects carefully studied. The various cell structures appeared almost equally well in the cells fixed by all the different agents. From a study of a large number of sections it appeared that absolute alcohol was at least as good as any other. For clearness and sharpness of detail it could hardly he surpassed. One feature should be mentioned. A long continued stay in alcohol is not good for this material, as it tends to swell the pigmented bodies in the nerve cells and to remove from them a portion of their color, changing it from a bright golden brown to a lemon yellow. These bodies are, however, clearly distinguishable in our sections, even when the stay in the alcohol was somewhat prolonged.

The vacuoles which formed so constant a structure in the nerve cells of Limax are rarely found in the cells of Planorbis. When present they are usually located in the end of the cell farthest from the axone and very seldom contain pigmented granules, though specimens have been found in which even in the living cell it was possible to see these bodies within the limits of the vacuole. The contents of the vacuole is a liquid of low viscosity, for the little brown granules could be seen dancing with the characteristic Brownian movements. In other parts of the cell where the bodies do not appear in the vacuoles they lie perfectly at rest.

Effects of starvation and feeding.—In Planorbis the number and size of the pigmented granules depends upon the general

nutritive conditions under which the animal is placed. The changes in appearance, however, of the nerve cells are so slow that it has been necessary for us to extend our observations over a period of two years in order to satisfy ourselves of their correctness. Specimens have been taken from their natural habitat at various times of the year, have been kept in the laboratory under fairly constant conditions, have been fed or starved as we wished, and have finally been killed and their nerve ganglia examined.

In the summer and autumn specimens, these golden brown bodies are rounded granules of somewhat irregular shape, and varying in diameter from 1 to 5 μ. In specimens kept in the warm laboratory for a considerable time (up to three months) without feeding a distinct change is noticed in the appearance of the cells. The pigment bodies become distinctly smaller, in some cases becoming so small as not to be easily distinguished from each other even with the $\frac{1}{12}$ inch oil immersion lens. Under these conditions it is of course impossible to measure them. No bodies as large as 5 μ were found at all and only an occasional one so large as 2 μ. The substance is in the process of being broken down. It becomes very finely divided and seems to become actually less in amount in the cells. These changes take place so slowly that it is a difficult matter to follow them and only by a long series of observations can one be at all sure of any change in the condition of the pigmented matter.

In specimens taken early in the spring, which have passed the winter in hibernation, the bodies are not as a rule numerous, though some still remain in the cells. Judging from the appearance of the nerve cells of animals which had been kept in the warm laboratory during most of the winter and those which were taken early in the spring, it would seem that the processes of metabolism had been much greater in the specimens kept in the warm room and that the total amount of matter stored up was in both cases somewhat in excess of the amount which would ordinarily be needed for the use of the cells.

Fatigue.—On account of the fact that this snail, like many others, withdraws into its shell when disturbed, it was found impossible to subject it to the same conditions for producing fatigue as in the case of Limax. It was possible to remove the ganglia, to place them upon a slide between electrodes and to stimulate the nerve cells directly by means of induction currents. As a result

of such stimulation it was found that, unlike the granules found in Limax, these bodies are extremely resistant and would not change in appearance during the time which the cells would live under these unusual conditions.   This fact, as well as their different appearance in the cell, indicates that they are of a different nature from those in Limax.   They are, however, a storage product and have to do with the nourishment of the cells during times when proper food is unavailable.

Nature of the bodies.—Many experiments have been made to determine the chemical nature of the golden brown bodies, and while we cannot say definitely just what the substance is we are in a position to state to which general class of substances it belongs. It is even possible that the bodies are not of constant composition. Most of the tests used require a long time for their action, and in some cases even failed to act at all.   Osmic acid blackens the bodies after a long time.   In many of the specimens the blackening was merely superficial, indicating that the substance is a highly resistant or that it is not a fat but some substance which may break up into a fat and some other substance.   The tests with Sudan III and with cyanin indicate the same thing.   With Sudan III the bodies assume an orange color for a short time.   The color soon disappears, however, and leaves the body a sort of yellow lemon color.   With cyanin the action is slow.   The bodies stain a deep blue, which is sometimes temporary and sometimes more lasting.   In ether the bodies swell up and clump together, becoming gradually dissolved and diffused throughout the cell.   The resistance of the granules is shown by the fact that it requires frequently an hour or more to dissolve a granule 1μ in diameter.

On account of the difficulty in making these tests it was thought for a time that they might be proteid in character, but all attempts to digest them with pepsin have so far failed.   The results of the tests seem to indicate that they are some sort of a fat.

Further tests with concentrated sulphuric acid indicate that the pigment is one of the lipochrome group, the bodies assuming a bright blue color as soon as the acid touches them.

Venus.—Our experiments upon the nerve cells of the edible clam, Venus, have been few in number and serve only to add emphasis to what has already been stated.   We find in the nerve cells certain yellow spots, whether solid or semifluid in character we are at present uncertain.   The color is not the same as that of

the bodies in Planorbis and they are of larger size. When tested with Sudan III and cyanin they give the colors which are characteristic for fats.

The cells of *Limnea* contain granules so closely similar to those of Planorbis that we have yet to find any way of distinguishing them. The pigmented granules are of the same color, size, and position in the cell. They also react in the same way to the various tests. We have not had opportunity to observe any seasonal changes in their appearance.

In the cells of *Melantho* we find a pigment of a light yellow color. The granules are generally smaller than those found in Planorbis and Limnea. This is evidently a different sort of substance, for it does not give a blue test with sulphuric acid. We have not yet made sufficient study to make a definite statement as to its chemical nature.

VII. THE CENTROSOME IN NERVE CELLS.

A few years ago the centrosome was all the fashion among biological works. The question of its origin, use and fate furnished the basis for many papers. With the accumulation of a considerable number of facts, it became evident that no general homology was to be established for the centrosome; nor did its detailed structure permit of reducing all centrosomes to a common form. About the only feature generally agreed upon was that the centrosome was at the center of radiation. In order to be sure that the dark staining granule or granules or vesicle when found in various parts of the cytoplasm has any claim to be regarded as a centrosome, it must have astral radiations. The question of the sphere substance which immediately surrounds the centrosome is more indefinite and less clearly defined than that of the centrosome. It may assume a variety of appearances and probably plays an unimportant part.

While centrosomes were being recognized in a great variety of cells, VON LEN-HOSSÉK ('95) was the first definitely to announce the presence of centrosomes in nerve cells. His observations were on the moderate sized spinal ganglion cells of the frog. He found the nucleus occupying in some cells an eccentric position and flattened or slightly concave on the side nearest the cell center. In this larger region of the cytoplasm there was a concentric figure in the center in which he located minute granules.

LEWIS ('96) describes in the giant ganglion cells of an annelid centrosomes on one side of the nucleus—the one toward the center and the one which tends to be

flattened or concave. The sphere varies somewhat in size, but its diameter is approximately one-third that of the cell. In some cases it is quite sharply marked off from the surrounding protoplasm of the cell; in other cases the transition to the surrounding protoplasm is so gradual that it is impossible to define its limits with precision. In the center of the sphere there is a highly refractive body, or occasionally two or three such bodies. From this central corpuscle there are in many preparations radiations which transverse the whole sphere. The rays are due to the close arrangement in radiating lines of granulations of the ordinary size. Some of the rays are very distinct, others much less clear. They are few in number, usually separated by rather uniform intervals, but often interrupted over an arc of many degrees. The central corpuscle (or corpuscles) is very distinct. It is sometimes spherical, sometimes elongated so as to look like a short rod. It shows a remarkable affinity for stains, being always colored much more deeply than any other part of the sphere.

McClure ('97) finds in certain cells in the ganglia of Helix structures which he has been pleased to designate as centrosomes. In certain unipolar cells of Helix which have a transverse diameter ranging between .17 and 22 μ, the nucleus was found in longitudinal sections to have an eccentric position. In addition to this, in such cells the side of the nucleus directed toward the axis cylinder pole of the cell was often flattened, or more frequently invaginated, so that the nucleus presented a kidney-shaped appearance. The flattened or invaginated side of the nucleus was never found to be directed exactly opposite to the base of the axis cylinder process, but always to a point one side of it. In the body of the cell, directly opposite the invagination, a disk-shaped structure was found. The contents of the disk was finely granular but so far as could be determined there was no evidence of radiation. At about the center of the disk two or three small granular bodies were present which stained much deeper than the surrounding granules and which are taken to be centrosomes (Mikrocentrum).

Hamaker ('98) described in the nerve cells of Nereis structures to which the term centrosome was given. He found from two to as many as ten in a single cell, each one consisting of a deeply stained granule. *No radiations were seen.*

Kolster ('00) represents in Cottus scorpius deeply stained granules with no radiations, which are designated as centrosomes.

Rand ('01) states that there is commonly present in the nerve cells of Lumbricidæ a centered system consisting of centrosome and radiations. The single centrosome (or rarely two, or even three, small granules lying close together) is found in the axis of the cell, on the side of the nucleus opposite the nerve process, and therefore on the side of the greatest cytoplasmic mass. It is generally not far from the nucleus and approximately at the center of the cell as a whole. Radiations consisting of fibrils bearing minute granules extend from the centrosome toward the periphery of the cell. Calling these "primary radiations," there may also be distinguished secondary radiations, which arise from certain of the large granules in the course of the primary radiations. In rarer cases tertiary radiations may be found arising from granules in the secondary radiations. The centered system is, therefore, a complex one, consisting of a chief center or centrosome, and numerous inferior centers situated throughout the cytoplasm, all with their corresponding sets of radiations, the whole system forming a network whose complexity increases toward the periphery of the cell. In most cases no structure which could be called

a centrosome is present. The centrosome, when present, as well as each of the inferior centers, is generally surrounded by a small clear space.

The structure which LENHOSSÉK designated as a centrosome received its correct interpretation only when the toad was studied during hibernation. LEVI ('98) in describing the changes in the nerve cells during hibernation gives a minute account of the so-called concentric figure or vortex as it occurs in the toad. During hibernation the deeply staining granular substance does not appear and the other parts appear more clearly. The centrosome is nothing more than a transverse section of the axis of the vortex which is composed of fibrils. These results of LEVI throw serious doubts on the correctness of other observations which were published soon after LENHOSSÉK's. Furthermore, we do not believe in the light of all that has been recently discovered in the cytoplasm of nerve cells that the structures described by McCLURE, HAMAKER, and KOSTER are centrosomes at all, but probably belong to one of the classes of granules. The fewness of the radiations in the results of LEWIS and RAND is of itself enough to suggest a reasonable doubt as to their actual presence, while the secondary and tertiary systems of radiations as figured and described by RAND are not in harmony with the ordinary aster structure. That the centrosome is not usually found in adult nerve cells is abundantly shown by numerous investigations; that it does appear in some nerve cells cannot be doubted, as HATAI ('01) has shown in the young rat. The centrosome is more easily seen in the young nerve cell than in the adult, which he believes indicates a slight tendency to the degeneration of this structure. Most of the results referred to above are so questionable that we are inclined to believe that there is very little positive evidence in favor of the centrosome in adult nerve cells.

SUMMARY.

1. The nervous system of gasteropods does not permit of direct stimulation of a specific ganglion because of the compactness of the nerve collar and the numerous nerves arising from the different ganglia.

2. Lymph canals are not identical with the cytoplasmic vacuoles. They really exist, and have a rather general distribution among the nerve cells of invertebrates.

3. Vacuoles are present in the cytoplasm of nerve cells of Nemerteans, Annelida, Crustacea, Insecta, and Mollusca. The vacuoles can easily be seen in the living cells as independent structures filled with a fluid or differential bodies. They are transitory structures, vary in number and are not limited by distinct walls.

4. NISSL bodies exist in invertebrate as well as vertebrate nerve cells. They are found to occupy a zone of cytoplasm next to the nucleus but not extending out to the cell wall in most instances. They are chiefly arranged in rows or in spindle-shaped groups.

The NISSL bodies are aggregates of extremely minute particles and exhibit marked resistance to degenerative changes. They actually exist in the living nerve cell. Those occurring in Limax are always found within the limits of the cytoplasmic vacuoles. They can be caused to appear in the cell by rest and feeding and can be made to disappear through hibernation, fatigue and electrical stimulation. They are probably of a fatty nature.

5. Pigment granules are found very generally in molluscan nerve cells. They do not readily respond to starvation experiments, can be increased in size and number through feeding, are practically unchanged by fatigue or electrical stimulation, but do show occasional variations in size and number. These bodies respond to the tests indicated for lipochrome substances or fats.

6. The centrosome has been described in many of the invertebrate nerve cells, but there is considerable doubt as to its persistent presence in adult nerve cells.

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PLATE I.

FIG. 1.   Photograph of a section of ganglion of Limax, fixed in absolute alcohol and stained by iron-hæmatoxyln.   The cells show many vacuoles of various sizes in the cytoplasm, some of which contain solid bodies.

FIG. 2.   Same as above, under higher magnification, $\frac{1}{12}$ inch oil immersion lens used in making photograph.

FIG. 3.   Photograph of a living nerve cell of Planorbis under $\frac{1}{12}$ inch oil immersion lens.   Note the very large nucleus and mass of pigment granules at the axone hillock of cell.

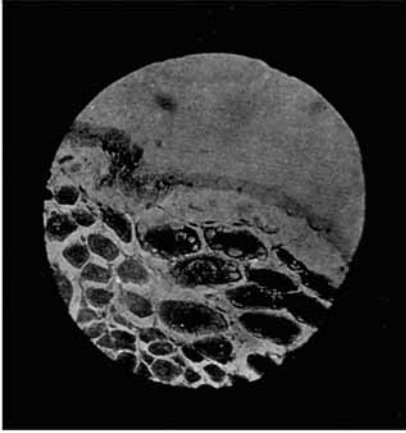FIGS. 4 AND 5.   Photographs of sections of ganglion of Planorbis, fixed in osmic acid, unstained. The dark bodies are the same as those shown in Fig. 3.
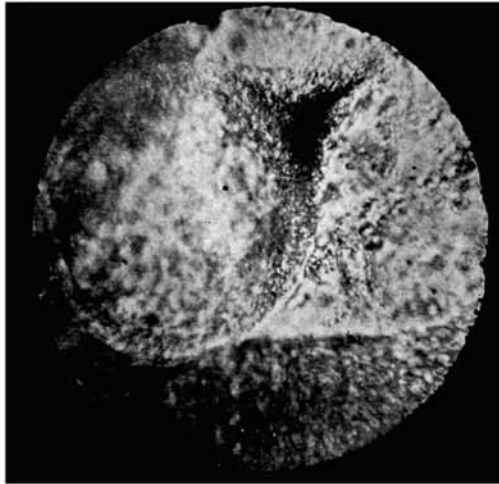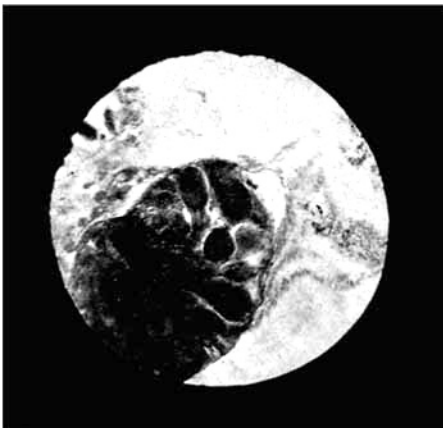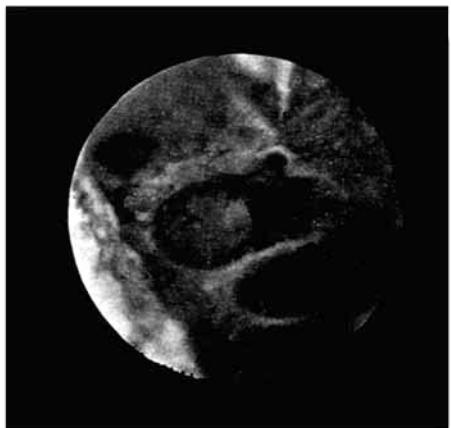
Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.