

THE NEGRI BODIES IN RABIES.*

By ERNEST M. WATSON.

(From the Bacteriological Laboratory of Brown University and the Hygienic Laboratory of the Johns Hopkins Medical School.)

PLATES I AND 2.

Since Negri, in 1903, discovered the bodies contained within the nerve cells of the central nervous system in cases of rabies, there has been much speculation as to their identity and importance. These structures, or Negri bodies, as they are now called, are constantly associated with rabies and we have come to regard them of prime importance from the standpoint of diagnosis. Their presence is demonstrated in the cerebral or cerebellar cortex, in the hippocampus major, or in the corpus striatum in over 98 per cent. of all cases with the clinical symptoms of rabies. The occasional failure to find them is, probably, due to our imperfect methods, to the fact that the bodies under certain conditions do not take the stain, or that in certain cases they occur in forms too small to be recognized by the one-twelfth inch oil immersion lens.

The nature of the Negri bodies is today a mooted question, and concerning them many and varied views have been advanced. The clinical history and symptoms of the disease, together with the nature of the infection and the properties of the virus, point toward a definite microorganism as the underlying cause. All observers now agree that the bodies described by Negri are definitely associated with rabies. One group of investigators believes the bodies to be definite parasitic organisms, and the cause of the disease. Another group considers them simply cell degenerations caused by the infecting agent, but incapable of producing the disease. Negri himself believed the bodies to be parasites of an animal nature and *ipso facto* the cause of rabies. Other Italian investigators including Volpino, Dominici, Marzocchi, d'Amato, Bandini, Fasoli, and others,

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have corroborated Negri's work and with him agree that the bodies are of a parasitic nature. In this country Williams and Lowden, Calkins, and others believe that the Negri bodies are of protozoan nature. The former authors have worked out a tentative life history, illustrating undoubtedly a multiplicative cycle in the development of the organism and have classed it among the Microsporidia. Calkins believes it to be more closely allied to the ameba and has placed it under the classification of the Rhizopods. Other writers in this country who favor the protozoan identity of the Negri bodies are Poor, Stimson, Frothingham, Hadley, Harris, and others.

THE NEGRI BODIES.

In the following observations upon the nature of the Negri bodies the methods and technique employed have been those now generally used in most of the Board of Health Laboratories in this country. The examinations of rabid material were made in the regular smear preparations, and in paraffin sections of the cerebral and cerebellar cortex, and of the hippocampus major and corpus striatum. In general it was found that the smear preparation under proper manipulation gave the better results. The morphology of the bodies by this method can be brought out definitely and their internal structure shows clearly, much more so, in fact, than in the paraffin sections, while the possibility of changing the position of the bodies within the cell and of mutilating them in any way by pressure, is reduced practically to nil after a little experience. By the smear method the general contour and shape of the bodies is the same as that noted in the paraffin sections, and their arrangement in the cell shows no appreciable displacement of the cellular protoplasm. A further advantage in the smear method is that upon the slide the layer of brain material is of varying thickness, which fact, after staining, aids materially in the final conclusions which are based on a comparative study of very thin, medium, and thick areas.

The stains used have been the Van Gieson stain for rabies, which at times was modified by the substitution of basic fuchsin instead of the rose anilin violet, the other proportions remaining the same. Mann's method of staining was also used in attempts to bring out more definitely the inner structure of the bodies.

Shape.—In general it may be said that the Negri bodies tend to assume an oval shape. Sometimes, however, they appear round and occasionally rather irregular, appearing to be in the process of division. Usually the outline of the bodies is smooth. Less frequently the edges appear irregular.

At times forms resembling a process of budding are noted. There seems to be a pretty general distribution of the different shapes in a single animal. If anything the oval shape predominates, while the division forms are least frequently encountered.

Size.—The size of the bodies seems to vary within rather wide extremes, from 0.25 to 0.5 to 21 microns. Although in general the very small ones and the very large ones are met with less frequently than are those measuring two to nine microns across their longest diameter. All sizes may be present at the same time in one animal and frequently in one nerve cell (from Ammon's horn) bodies measuring one micron and others measuring ten to fourteen microns are present at the same time.

Number.—The number of bodies present in any individual case seems to be subject to considerable variation. Sometimes the large cells from the hippocampus and the cortex of the cerebrum and the cerebellum are literally filled with bodies, and at other times a search of several minutes is necessary to reveal a single body. In these latter cases, however, further search, in the writer's experience, has always been rewarded with the finding of an appreciable number of bodies, although they may be well scattered. When the bodies are few in number they seem to be uniformly small in size and almost without exception are quite regular in their morphology. For the most part the bodies are found with greater regularity in the horn of Ammon and in the corpus striatum than in either the cerebral cortex or the Purkinje cells of the cerebellum. A specimen brought into the laboratory some years ago from a case of human rabies showed nine well developed bodies in one of the Purkinje cells of the cerebellum.

Structure.—Concerning the structure of the Negri bodies there has been much speculation and much has been written in attempts to identify and determine the rôle of the various parts. With the Van Gieson stain, and also with the basic fuchsin modification of it,

the bodies take a characteristic pink stain, lighter and of a more delicate hue than the eosin red color imparted to the red blood cells which are frequently seen in the same section. With proper staining solutions, this typical color varies but little from day to day.

The Negri bodies are essentially intracellular parasites and we can speak of them with certainty only when they are found within the nerve cells. They never have been demonstrated along the longer and larger nerve trunks or along the fiber tracts in the cord. There is, however, good reason to believe that the infection reaches the central nervous system through the above mentioned channels. Within the nerve cells the pink color of the bodies is broken by the regular appearance within the body of the parasite itself of cellular inclusions termed chromatin granules. These granules are a constant part of the typical Negri body. They take a dark slate blue stain with all the stains which have methylene-blue or hematoxylin as a base. Their number in the body is variable, being dependent for the most part upon the size of the parasite. There is usually one slightly larger and more deeply stained than the rest which occupies a position more central than the others. This granule has been regarded as the nucleus and is present in practically all forms which are large enough to permit a structural examination of their inner cytoplasm. In the very small forms only the central chromatin granule or nucleus is discernible, while in the larger forms the granules vary from three or four to ten or twelve. In the larger forms the rather concentric arrangement of the chromatin granules around the parent nucleus appears like nuclear fragmentation preparatory to a subsequent division of the cytoplasm and these types have been believed by many to represent a preparatory stage to direct cell division by fission.

Williams and Lowden have described at length the succeeding stages in the growth and reproduction of this type of Negri body. According to them, the bodies are first found as definite tiny forms 0.5 to 1 micron in diameter, with one chromatin granule or nucleus taking a deep azure blue stain in the center and enclosed in a delicate pink staining cytoplasm, while around the whole and blending into the cell cytoplasm is a definite rim, or ectoplasm, staining a little deeper pink than the rest of the cell protoplasm. In addition to

these extremely tiny forms there are larger ones which are similar in shape and staining reactions, but which contain an extra chromatin granule or two, probably fragments of the nucleus. Still larger forms are also noticed which are, in general, similar to the bodies last described, but which begin to show evidences of division, *i. e.*, constrictions giving rise to hour glass forms. The various steps in the process of fission have been observed. In the last, only a fine filmy bit of protoplasm connects the two organisms. In the next stage, the two bodies have become entirely separate and lie side by side. In some cases the ectoplasm of the two bodies is in close proximity, but in others it is separated by a small space through which the protoplasm of the nerve cell shows as a blue staining line between the pink staining ectoplasmal rims of the two now separate individuals.

The above description outlines briefly one undoubted phase in the life history of the organism. It represents a stage of multiplicative reproduction,—a schizogonous life cycle, or, in speaking of the Myxosporidia, a stage of plasmotomy carried on within the cells of the host. This condition we expect on account of the vast numbers of parasites that are found in a given host and even in a single cell of a host, and the great difficulty of conceiving that each parasite could have arisen from a separate and individual spore infection. From the above commonly observed conditions, and from the nature and frequency of the findings, we have good reason to believe that this plasmotomous life cycle is supplemented, either within the body of the host or elsewhere, by another cycle of a different nature, this other cycle being concerned with a sexual reproduction.

Bodies corresponding to a sporogonous life cycle of this type have in two instances in the past few years come under the writer's observation, and a general description of these findings is reported at this time. The two cases and the specimens which showed these sporogonous types presented rather similar and singular histories. The dogs came from sections of the state some thirty miles apart and during life presented the usual clinical picture of uneasiness, restlessness, and signs of evident distress, and became very irritable. During this last stage both animals had bitten people. The dogs were consequently confined, and in approximately twenty days after

the initial signs of malaise both animals died, the reported cause of death being distemper. Unsuspecting the seriousness of the bites both dogs were buried, and several days elapsed before they were dug up in order that their heads might be sent to the laboratory for examination.

In these two cases the cells of the cerebral cortex, the Purkinje cells, and the giant cells of the horn of Ammon showed the presence of the typical Negri bodies with their characteristic nuclei and chromatin granules as described above under the usual cycle of an asexual intracellular development. In addition to these were certain forms quite different from any of the preceding, yet taking the stain readily and being closely associated with the former, many of them being in the same cells with the plasmotomous type of body. These new bodies were seen to vary in size. The smallest ones measured 0.25 to 0.5 of a micron in diameter (plate 1, figure 4, A). Some were possibly smaller than this, the difficulties of identification in these extremely small types being considerable. The smallest forms present are slightly round or oval, have a definite morphology, and are regular in outline. They take a deep pink, almost a crimson stain, and when treated with acid alcohol seem to hold the stain longer than those of the plasmotomous type. Their protoplasm stains with no indication of a nucleus or of chromatin granules. At one end, by careful focusing and with most of the light coming from the mirror, the condenser being cut out, a small refractive area is seen which takes the stain less readily than the other portions. As nearly as could be determined with the immersion lens this light spot presents an oval outline and gives every indication of being a capsule, and the whole body with its uniform and homogeneous consistency seems to have every appearance of a spore.

Bodies of this type are found scattered more or less diffusely throughout the slides, both inside and outside of the nerve cells. Forms similar to these in every way but slightly larger are also found, but are less plentiful than the very small ones (plate 1, figure 1, E, F; figure 2, E, F, H, J). The next larger body corresponding to these forms presents quite a different picture. They measure 1 to 1½ or 2 microns in diameter, stain a brilliant pink, are very regular in outline, and about them a definite membrane, or rim of

ectoplasm, can be made out, while their interior contains two, three, and sometimes four of the definite, tiny, regular oval spores described above. All these stain a brilliant pink and occupy completely the interior of the body, there being no nucleus and no chromatin granules, nothing in fact which takes the blue stain, and but little of the residual protoplasm of the parent body which takes a faint pink stain and shows up in marked contrast to the spores. Larger forms than this are also observed which include a definite cell membrane, within which are eight to ten, and sometimes twelve, of the spore-like bodies (plate 1, figure 2, H, E). They all stain similarly to the smaller forms and show only a little of the residual pink staining protoplasm of the original cell and no nucleus or chromatin granules. Larger forms than these show a broken ectoplasmal rim with the spores protruding and some are even quite outside the body itself and in the substance of the nerve cell (plate 1, figure 1, B; figure 2, E, H, I; figure 3, D). They present the same picture as the tiny round or oval spores described above. Some forms contain as many as twenty to thirty and these were observed with the ectoplasm intact and the spores completely filling the inside of the body. These forms measure eight to ten microns in diameter. In the still larger forms the membrane surrounding them becomes less distinct, until finally the definite structure of the rim-like band is lost completely. After losing the membrane the groups of spores in many cases are seen remaining close together as before (plate 1, figure 1, B). In general, however, after the disappearance of the cell membrane there is a marked outpushing of the spores from the center, making the body appear much larger than in any of the preceding forms and leaving in the center a small light pink staining area formerly occupied by the spores (plate 1, figure 2, I; figure 3, D). In these forms nothing which resembled a nucleus is seen nor are there any chromatin granules present. A later step in the development of the organism is seen when the spores become further removed from the center and occupy a much larger area. They form a circle with the pink staining residual protoplasmic remains of the original Negri body, possibly too a portion of the ectoplasm, on the inside and the blue staining cytoplasm of the nerve cell on the outside. The final step in the dissemination of the spores is seen when the circle of spores has

been broken up, and in certain nerve cells they are then seen scattered diffusely over the entire field (plate 1, figure 4, A).

This outlines briefly the successive stages seen in the growth, reproduction, and dissemination of this new type of Negri body. The succeeding steps in its growth and development, with the typical pictures presented in the different stages, and the multiplicative or schizogonous life cycle previously described, suggest immediately a sexual or sporogonous cycle for this new series of bodies described above.

Other writers have often referred to the possibility of finding a sexual cycle which in a measure would supplement the knowledge of the forms already found and do much toward increasing our knowledge of this protozoan parasite, which we now believe is the causative agent of rabies. The above findings, taken in the light of the multiplicative cycle already observed, are indeed strongly suggestive. Williams and Lowden, as has been stated, have placed the Negri bodies among the parasitic protozoa in the suborder Microsporidia of the Sporozoa. Organisms of this order in their sporogonous life cycle produce numerous oval or pear shaped spores corresponding closely to those described above, each of which possesses one polar capsule. This is not seen in the fresh specimen, but is brought out under suitable treatment with stains and reagents.

From the findings and observations recorded above the writer believes that we are now justified in placing the Negri bodies a little more definitely in the suborder of Microsporidia and that we may regard them as Oligosporogonea, in which forms the trophozoite produces a single pansporoblast. Its position is perhaps among these under the family Glugeidæ, when we bear in mind that in these the pansporoblast produces numerous spores.

The smallest forms observed with a single dark staining nucleus or chromatin granule are undoubtedly on the order of a trophozoite of a multiplicative cycle characterized oftentimes by an ameboid appearance and a dense rim of ectoplasm, with a granular endoplasm containing a nucleus and possibly chromatin granules. These may increase in size very rapidly until there are numbers of bodies of different sizes. During this growth they undoubtedly have the power of endogenous reproduction. This has been observed by several writers and may take place in different ways, all of which

are common to the members of this order. In the adult form (1) simple binary fission may take place, *i. e.*, an hour glass constriction, or (2) a simple budding may occur. This plasmatomous division, or breaking up of the multinucleate cell into numerous parts each having a nucleus with a bit of surrounding protoplasm has been termed, in the first case, a simple, and in the latter, a multiple type of division.

In the youngest stages of the organism there has been described nuclear fragmentation into several daughter nuclei, supposedly by a process of multiple amitosis, and this is similar to, if not identical with, that observed in the young forms of *Glugea lophii*. This type early spreads the infection through the tissues of the host and is probably the most common of all the methods of multiplicative growth. In the well known forms of Myxobolidae and Glugeidae it is undoubtedly the commonest type of growth. In considering the sporogonous or reproductive cycle, spores undoubtedly begin to develop at an early period in the life of the trophozoite. The finding of two, three, and four spores in a single small body, or pansporoblast, would seem to prove this. Among the better known and more closely studied members of the Microsporidia the first step in spore formation is the gathering of cell protoplasm around some of the nuclei of the mother endoplasm to form a primitive sphere (Gurley) or pansporoblast. Whether or not this has been observed in the case of the Negri bodies it is still difficult to say; stages which seemingly show a fragmentation of nuclei have been reported, but these may indicate a stage in the multiplicative, as well as a preparation for spore formation in the reproductive life cycle. The pansporoblasts as observed in the development of the Negri bodies have a definite membrane or envelope around them, and so far at least the spores they contain have been observed to vary considerably in number. Furthermore, when first observed they were rather completely formed so that all steps in their development, particularly the presence of a sporoblast stage, are not as yet completely understood. As to the origin of the polar capsules it has not as yet been observed often enough to state whether or not it arises like many other members of this order from a sphere-like vacuole.

ANALOGIES BETWEEN THE NEGRI BODIES AND THE BETTER KNOWN FORMS OF THE SUBORDER OF THE MICROSPORIDIA.

In general, the forms of the suborder of the Microsporidia show an extremely wide variation in their structure, habitat, and mode of life. The trophozoite has the following characteristic features which are well observed in the life cycle of the Negri bodies: (1) It is characteristically ameboid in shape. (2) Spore formation commences early and continues throughout life. (3) Spores are produced endogenously, *i. e.*, within the protoplasm of the trophozoite. (4) The spores have one or more polar capsules. While it is true that the Cryptocysts are found more often inhabiting invertebrate hosts, several forms are known which make their home exclusively in the tissues of the vertebrates. As parasites they are more destructive in their growth to the host cells than any other group of the Sporozoa. They are in every detail essentially intracellular organisms differing from the Phænocysts which are the intercellular forms, and only exceptionally at the very early stages are they found within the tissue cells.

The group in the main has two modes of life, one within the body cavities of the host, and the other within the cells and tissues of the host. The latter is clearly the manner of life of the Negri bodies. While muscle and connective tissue are the ones usually selected as the seat of growth of the organism, some forms attack the nervous tissue alone, as is seen in the *Glugea lophii* which has a special affinity for the ganglion cells of the central nervous system of *Lophius piscatorius*. The Cryptocysts may restrict their ravages to a single organ or tract, or they may attack all parts of the body. Naturally the method of growth may be of two kinds; that in which the growth is confined to definite foci, and that in which there is a diffuse infiltration of the tissues. The latter method is peculiar to the Negri bodies in which the body of the parasite and the protoplasm of the cell become closely intermingled, spores are formed, and the specific tissue becomes actually filled with young forms.

Trophozoite Stage.—This is characterized by its ameboid form in which an uncertain division can be made out between the coarser outer region and an inner granular center. The endoplasm has various inclusions; in the Negri bodies have been observed only the

nucleus, chromatin granules, and possibly occasionally a vacuole or two. In the tissue-infecting forms, the pseudopodia are usually small, of ectoplasmal origin, and cannot be observed in the stained preparations. In the Negri bodies no pseudopodia have been recognized. Here perhaps we have, as in other well known cases, the protective function of the ectoplasm developed at the expense of the motility. The youngest trophozoites have but one nucleus, the endoplasm increases continually by division until there are many present in the full grown forms, often ten or more, while definite nucleoli or karyosomes have not been recognized except in a few instances.

Spore Stage.—Spores are seen to develop in a very early stage of the trophozoite and sometimes they continue to be formed until the whole endoplasm of the trophozoite is used up in its production. In other cases, however, there is a small amount of residual protoplasm. All the stages of spore development are commonly found at the same time in a given individual. The first sign of spore formation is the gathering of protoplasm around one of the nuclei in the endoplasm. This comes to form the sporoblasts and later the spherical corpuscles, or pansporoblasts. All nuclei may not be used up in this manner, but may remain as residual nuclei (plate 2, figures i to xiii).

Among the Cryptocysts the pansporoblasts always give rise to more than two spores, *i. e.*, four in *Gurleya*, eight in *Thelohania*, and to a large number in *Pleistophera* and *Glugea*. One or more pansporoblasts may be formed from each trophozoite, the Oligosporogenea under this order produce but one, however, and here the condition simulates greatly the development of the Coccidia except that with them we have an exogenous development instead of an endogenous one. In general we may say that the Myxosporidia represent an alternation of generations between trophic and reproductive individuals.

The spores of the Myxosporidia are rather variable in their external structural details. The spores of the Cryptocysts are for the most part minute, measuring 3 to 4 microns in *Glugea anomala*, and 1.5 to 2.5 microns in *Glugea ovidea*, and are usually pear shaped or oval. The Phænocysts have much larger spores, some 100 by 12 microns (in *Cestomyxa spærulosa*).

The capsule of the spore is usually situated at one end and when this is the case, that end is termed the anterior pole. In the Glugeidæ the spore capsule is invisible in the fresh condition. These spore capsules are a distinctive feature of the Myxosporidia and by some it is believed that they represent sporozoites that have become specialized in nature. The developmental period which intervenes between the ripe spore and the youngest trophic stages is the least known period in the life cycle of this group of organisms. The microscopic parasite often migrates a great distance in the body of the host before it gets to the organ or tissue which is its final field for growth. This is well illustrated in the rabic infecting agent which, from a cutaneous bite or abrasion, must travel until it reaches the central nervous system before it finds a suitable field for growth. This stage shows that undoubtedly at one time in its life the parasite is able to select, and, furthermore, to seek out its specific tissue which may, in some instances, be at a great distance from the original seat of infection.

Schizogony, or Multiplicative Process.—When the amebula reaches its special tissue it can grow endogenously with great rapidity. The two processes of growth are called multiplicative, like schizogony, and reproductive, like sporogony. Multiplicative growth has always been attributed to the Negri bodies on account of the vast numbers of parasites that may be present in a given host, and the difficulty of supposing that each parasite could have originated from a separate and distinct spore infection. The multiplicative reproduction in the full grown trophozoite takes place in one of two ways, by simple fission, or by budding. This plasmatomous division has been termed, in the first case, simple, and in the latter, multiple amitosis (plate 2, figures 1 to 18).

The youngest forms divide by nuclear fragmentation and multiple amitosis following a breaking up of the protoplasm into minute uninucleate swarm spores, and in this way the tissue becomes diffusely infected.

CONCLUSION.

1. The Negri bodies, as the etiological agent in rabies, present two general types or phases in morphology, in growth, and in reproduction.

2. These two phases are constantly cyclic in their development and correspond (1) to a multiplicative, or schizogonous, and (2) to a reproductive, or sporogonous, life cycle.

3. By the detailed study of these forms and their succeeding stages we are inclined to believe that the Negri bodies are definite protozoan parasites, and from a study of their life history we are led to place them in the suborder of Cryptocysts, or Microsporidia, of the Sporozoa, and more definitely among the Oligosporogenea of the Glugeidæ family, which forms produce but one pansporoblast.

With the recent advances in the growth of tissues outside the body, particularly the work of Carrel, Burrows, Harrison, Lewis and Lewis, and Rous upon the infectiousness of tumor extracts, with the results of Noguchi in cultivating pathogenic *Treponema pallidum*, important discoveries concerning the Negri bodies will undoubtedly be made in the near future.

I wish to extend my thanks to Dr. Charles V. Chapin, Superintendent of Health of the City of Providence, for the material used in this work, and to Prof. F. P. Gorham, of Brown University, for his valuable suggestions.

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EXPLANATION OF PLATES.

PLATE I.

- FIG. 1. Two nerve cells from hippocampus major in a smear preparation.
- A. Deeper staining nuclei of the two nerve cells.
 - B. A large Negri body of the sexual type and pansporoblast stage, without a surrounding membrane and containing many individual spores.
 - C. Spores of the sexual type lying free in the protoplasm of the nerve cell.
 - D. A Negri body of the asexual type or multiplicative stage, containing the characteristic chromatin granules.
 - E. A small sexual pansporoblast containing several spores.
 - F. A small sexual pansporoblast surrounded by a membrane and containing several spores.
- FIG. 2. Two nerve cells in a smear preparation.
- A and B. Asexual type of Negri bodies with chromatin granules.
 - C and D. Nucleus of one of the nerve cells.
 - E. Sexual type of Negri body containing spores.
 - F. Smaller sexual type of a Negri body containing spores.
 - G. Proliferating endothelial cell.
 - H. A small sexual type of a Negri body containing spores.
 - I. A large pansporoblast containing many spores which have begun to leave the center of the Negri body preparatory to being disseminated through the protoplasm of the nerve cell. The membrane is lacking.
 - J. Small sexual type of a Negri body with membrane and spores.
- FIG. 3. A. A small asexual trophozoite with chromatin granules.
- B. Nucleus of the nerve cell.
 - C. A small asexual type of body.
 - D. A large pansporoblast pressed out of the nerve cell, showing absence of the membrane and the characteristic arrangement of the spores about the periphery.
- FIG. 4. A. Spores liberated from the pansporoblast and lying free in the protoplasm of the nerve cell.
- B. Nucleus of the cell.

PLATE 2.

Sexual and asexual life cycle.

- FIGS. I to 18. Asexual or multiplicative cycle of the Negri body, showing the development from the spore and trophozoite through the various division forms, all containing the characteristic chromatin granules.
- FIGS. i to xiii. Sexual or sporogonous cycle, showing the development from the original spore to the pansporoblast with the surrounding membrane and endogenous spores; later, without the membrane and with the peripheral arrangement of the contained spores; and finally, the disseminated spores throughout the protoplasm of the nerve cell.

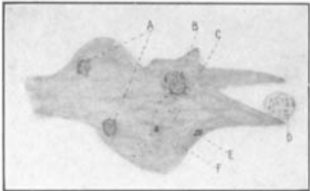


FIG. 1.

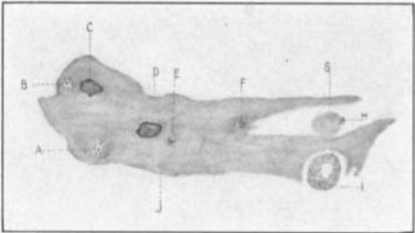


FIG. 2.

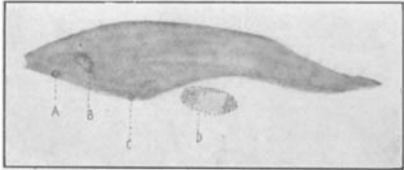
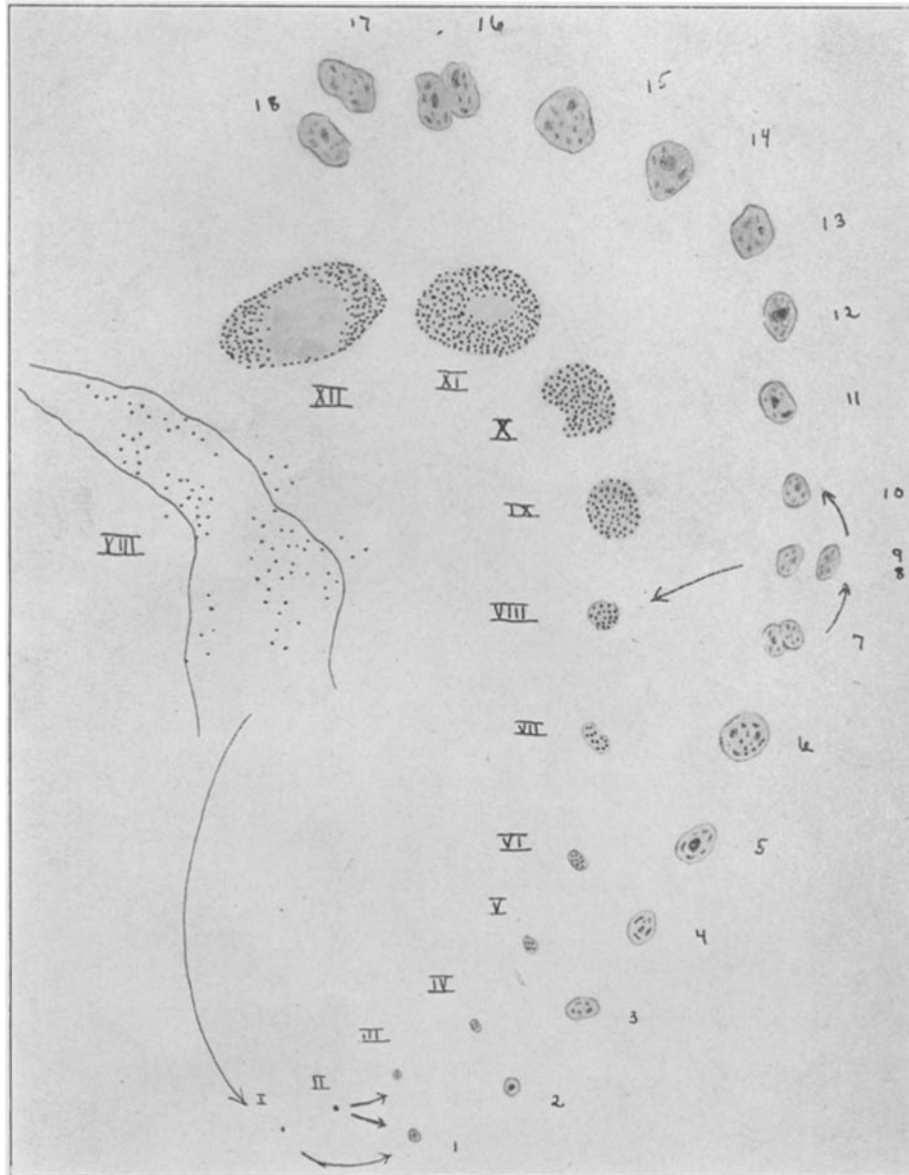


FIG. 3.



FIG. 4.

(WATSON: The Negri Bodies in Rabies.)



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