YELLOW FEVER ENCEPHALITIS OF THE MONKEY (MACACUS RHESUS) *

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Since the discovery by the American Commission at Havana in 1900 that the etiological agent of yellow fever is filterable, this infection has generally been grouped tentatively with the virus diseases. In later years this classification has seemed more insecure because it has become apparent that certain bacteria, protozoa and spirochetes may pass through similar filters. The finding of leptospiras by Noguchi in a group of cases clinically diagnosed yellow fever made it seem for a while still less likely that the causative agent belongs to the virus group.

Recently, however, a mass of evidence has been gathered which seems to place the active agent of yellow fever not only among the filterable viruses, but also with the cytotropic group of these infectious agencies. The recent rapid accumulation of this evidence resulted directly from the discovery by Stokes, Bauer and Hudson [1] that yellow fever may be transmitted with regularity to the Indian monkey, *Macacus rhesus*. With this animal available for the experimental study of the disease many important facts have come to light.

Bearing upon the viral etiology of yellow fever was the absence of leptospiral infection in the West African cases, the reconfirmation of the filterability of the active agent in the blood stream, and the discovery by Torres [2] that intranuclear inclusions are to be found in the injured cells of the liver of experimentally infected monkeys. Shortly afterward similar inclusions were described by Cowdry and Kitchen [3] in liver cells of human cases of West African yellow fever.

In commenting upon these important discoveries I recently expressed doubt that the agent of yellow fever should be classified as a cytotropic virus, even though these two basic facts of filterability and specific cellular inclusions were available, for the reason that

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cytotropic filterable viruses should be known to reproduce themselves locally in association with the presence of cellular inclusions.[4] This evidence was lacking, inasmuch as the inclusions had been found only in the liver cells, and there seemed to be no evidence that virus was regenerated locally in the liver in association with them.

This essential condition seems now to have been satisfied through the extraordinary discovery by Theiler[5] that the virus of yellow fever appears to be infectious for the brain of mice; and his experiments indicate it may be successfully cultivated in series in this tissue, with the induction of a fatal encephalitis. Theiler's observations further show that the mouse encephalitic virus is essentially restricted in its distribution in fatal infections to nervous tissue and adrenal gland, which has a considerable nervous component in its medulla. The virus, according to his observations, also passes centrifugally from the spinal cord along peripheral nerves. These facts definitely relate the mouse strain of virus to other neurocytotropic viruses, namely those of rabies, poliomyelitis, enzoötic encephalomyelitis and herpex simplex.[6]

Furthermore, the recent investigations of Sellards[7] contribute the important information that the mouse virus passed serially through brains of mice becomes modified in its action upon monkeys (*M. rhesus*), in that it will then induce a fatal encephalitis in these animals when inoculated intracerebrally, without causing the usual symptoms and hepatic changes of the original yellow fever virus.

Theiler was rightly cautious in his attitude toward the question of the identity of the mouse encephalitic virus and that of yellow fever, notwithstanding the fact that inclusions quite similar to those found in the liver in the natural and experimental disease were to be observed in the central nervous system of the infected mice, and, what is more significant, that yellow fever immune serum from both monkey and man showed protective power for mice inoculated with the encephalitic virus.

Evidence of the identity of the mouse virus and that of yellow fever is further contributed by the investigations of Sellards, who showed that monkeys can be immunized against typical yellow fever virus by intraperitoneal injections of mouse virus, and that monkeys immunized to typical yellow fever virus manifest a well marked, though not entirely complete protection against intracerebral injection of virulent mouse virus. Sellards concludes that the results

of these cross-immunity tests are entirely consistent with the interpretation that the virus in mice is that of yellow fever, and there is no indication that it is contaminated by any secondary virus. He states however that the amount of data available at present is not overwhelming and there is no urgent need for drawing any altogether final conclusions. In regard to hepatic lesions in monkeys infected intracerebrally with mouse virus he states: "Of five normal monkeys injected into the brain with mouse virus, none showed lesions of the liver comparable to the changes which occur in man or in monkeys dying of typical yellow fever. In one of these monkeys, a moderate amount of necrosis of the liver was found, and in another, the liver was normal. In the remaining three monkeys the liver showed moderate degenerative changes consistent with the earlier changes seen in yellow fever but by no means diagnostic and quite unlike the extensive necrosis seen in monkeys dying in the usual manner."

For a more detailed study of the cytology and histology of mouse virus encephalitis in mice and monkeys, Dr. Sellards kindly sent to me stained sections and blocks of tissue from mice and monkeys infected with this virus, and in addition, for comparison, sections of human livers from West African cases of yellow fever, and of livers from monkeys experimentally infected with yellow fever virus. This report is based entirely upon a study of the material which Dr. Sellards made available to me for this purpose.

In addition to the sections of human and monkey livers infected with yellow fever and sections and tissue from the brains of encephalitic mice, there was material from the following groups of experiments upon monkeys.

GROUP I: Included tissue from two monkeys which had received intracerebral injections of the typical monkey strain of yellow fever virus.

GROUP II: Included tissue from five normal monkeys inoculated intracerebrally with encephalitic virus from mouse brains.

GROUP III: Included tissue from four normal monkeys inoculated intracerebrally in series with virus originating from a monkey dead of mouse virus encephalitis.

In sections from the livers of one human and two monkeys, stained with methylene blue and eosin, intranuclear inclusions were found which correspond in all respects to the description of yellow fever

inclusions depicted by Torres and by Cowdry and Kitchen. The impressions gained from a study of these preparations served as a guide to the study of the encephalitic lesions.

Sections of brain from the two monkeys in Group I, which received typical yellow fever virus intracerebrally, show no evidence of encephalitis or of intranuclear inclusions. The livers of both animals contain the typical necrosis of yellow fever infection. As pointed out by Sellards, the typical yellow fever virus, even though introduced directly into the substance of the brain, brings about the usual appearance of yellow fever uncomplicated by a viral encephalitis.

Sections of the brains of mice dead of encephalitis show, as first described by Theiler, a perivascular mononuclear cellular exudate particularly marked in my preparations in the basal ganglia. In the brain of a young mouse, dead six days after inoculation, abundant nuclear inclusions were observed both in the ganglion cells of the cerebrum and those of the basal ganglia. It was noted that extensive necrosis of ganglion cells accompanied the presence of inclusions, and this without any evidence of cellular exudate. It seems evident from a study, both of the encephalitis of mice and of monkeys, that, as in other neurocytotropic virus lesions, the first change is in the ganglion cells, and inflammatory exudate is secondary, apparently to cellular necrosis. In an adult mouse brain perivascular infiltration and focal inflammatory exudate are prominent, but only a few inclusions were observed. This single observation suggests, on cytological grounds, that the brains of young mice are more susceptible to the virus.

The intranuclear inclusions observed in the brains of mice correspond in appearance in every way to the now well known descriptions of Torres and of Cowdry and Kitchen. Following is a description of lesions found in the brain of two mice, the first a baby mouse dead on the sixth day after inoculation, the second an adult mouse.

Baby Mouse — 6th Day

Cerebral Cortex and Basal Ganglia: (Stained with methylene blue and eosin.) Changes in ganglion cells throughout the sections are to be seen in great abundance. They are more numerous in the basal ganglia, but are also diffusely scattered through the cerebral cortex.

In the cortical cells the changes are largely nuclear, though occasionally shrunken, acidophilic necrotic cells are found. In the basal ganglia necrosis of cells is conspicuously in evidence. The necrotic cells occur in irregular groups.

The common and conspicuous nuclear change consists in the presence of masses of amorphous, finely granular, acidophilic material within the nucleus, associated with granules of basophilic material irregular in size. Sometimes, though less frequently, the acidophilic mass is single, occupies the center of the nucleus and is separated from the nuclear membrane by a clear zone.

More frequently, however, the acidophilic material is found in several masses, either almost filling the nucleus, or separated from the nuclear membrane by a clear zone. It is quite characteristic of these acidophilic inclusions that they incorporate amorphous granules of basophilic material. At times there is a large granule of basophilically-stained material which suggests a nucleolus. The central eosinophilic mass is not usually separated so clearly from the nuclear membrane by a clear zone, neither is the aggregation of chromatic particles upon the nuclear membrane so characteristic as in herpes. Quite commonly the rarefied zone about the inclusions is not distinctly clear. The acidophilic material seems finely granular in composition and only loosely adherent.

Occasionally one finds the entire nuclear content apparently coagulated into a coarsely granular clump in the center, separated from the nuclear membrane by a clear zone. These nuclear clumps stain basophilically and do not seem to be identical with the commoner acidophilic inclusion. I have observed similar clumping of basophilic nuclear material in sections of brains from apparently normal fowls. Only ganglion cells contain inclusions. No change is observed in neuroglia, ependyma, choroid plexus or endothelium.

Blood Vessels: These are generally congested, and punctate hemorrhages are found both in the cortex and basal ganglia, but more frequently in the latter.

Exudate: There is no diffuse cellular exudate. About some of the small distended veins of the basal ganglia there are collected a few mononuclear cells difficult to classify, and there is an occasional small group of mononuclear cells in a focus related to necrotic ganglion cells. In a superficial inspection of the section one would hardly detect any cellular exudate at all, notwithstanding the extensive

neuronic degeneration and necrosis. There is no exudate in the meninges. The cellular degeneration is diffuse, extensive and bilateral.

Cerebellum and Pons: Similar cellular changes are abundant in the pons. No definite changes are seen in the cerebellum. Purkinje cells contain much granular eosinophilic coagulum in the nucleus, but this appears to be normal.

Adult Mouse Brain

Section Through Cerebral Cortex, Basal Ganglia and Ammon's Horn: One can easily recognize under low magnification that there is a diffuse encephalitis throughout the midcerebrum. This is indicated by an abundant perivascular cellular infiltration, very marked in the basal ganglia, and inconspicuous in the cortex. There is moderate round-cell infiltration in the meninges at the base of the brain. The inflammatory lesions are bilateral in distribution.

Blood Vessels: The blood vessels, including capillaries, are congested and occasional punctate hemorrhages are seen in the basal ganglia.

There is an abundant perivascular cellular infiltration about the larger veins. The cells are all mononuclears, some of them are lymphocytes, but most are wandering cells. No polymorphonuclear leucocytes are seen. In addition to the perivascular exudate there is also a diffuse invasion of parenchyma by mononuclear wandering cells. This is most abundant about the mantled veins and capillaries. An occasional polymorphonuclear leucocyte is seen in the parenchymal exudate. Now and then a mitotic figure is found in a neuroglial cell.

Cellular Changes: Despite the abundant perivascular and diffuse cellular exudation, neuronic alterations are difficult to find. There are occasional necrotic cells, but very careful search is necessary to discover a nuclear inclusion. They are almost negligible in number in the cerebral cortex and midbrain where perivascular infiltration is most marked, but are fairly numerous and typical in Ammon's horn, where there is no inflammatory exudation.

Encephalitis of Monkeys

No distinct differences could be noted between the severity, extent or general characteristics of the lesions in the brains of monkeys, whether they received directly the virus from infected mouse brains, or serial inoculations of brain from other monkeys infected with the mouse virus. Each of the brains of Groups II and III shows an extensive, severe, bilateral acute encephalitis which affects especially the gray matter, and in general seems most intense in the basal ganglia and pons. Altogether there were nine monkeys in these two groups. In addition to sections of the brain there was also tissue from the spinal cord from five of the nine monkeys. In four of these there is a severe, destructive, acute myelitis affecting the entire gray matter of the cord, but particularly involving the motor ganglion cells of the anterior horns. In one spinal cord no inflammatory changes were observed. The sections, however, were taken from one level only.

An illustrative protocol of the encephalomyelitis in monkeys follows:

Rh–282. Mouse Brain to Monkey Brain

Cerebral Cortex: In the plane of inoculation there is an extensive degeneration and necrosis of ganglion cells. The nuclei of many of these cells contain rather coarse acidophilic clumps or inclusions. It is difficult or impossible to recognize in these inclusions anything characteristic of yellow fever. Certainly one would hesitate to make a tentative diagnosis of yellow fever encephalitis on that basis.

There is a diffuse, though moderate polynuclear leucocytic infiltration of the cortical tissue, and to a less extent a mononuclear wandering cell exudate. About many blood vessels there is a thin perivascular mantle of mononuclear cells. The vessels generally are greatly dilated and distended. Petechial hemorrhages are numerous. Edema is evident. There is no meningitis.

Cerebellum and Pons: The cells of the cerebellum show no recognizable changes. The pyramidal cells of the normal monkey's cerebellum contain relatively conspicuous eosin-staining clumps and granules about the nucleolus. There is no inflammatory exudate in the cerebellar cortex.

The gray matter of the pons beneath the cerebellum shows, particularly within and about groups of large ganglion cells, an ex-

tensive degeneration, necrosis and inflammatory exudate. In the nuclei of relatively intact ganglion cells showing chromatolysis occasional distinct acidophilic inclusions were observed. These sometimes correspond in appearance to the yellow fever inclusion in general. Other nuclei, perhaps more commonly, contain in addition to the nucleolus one or more compact, spherical or oblong, pink-staining, homogeneous masses somewhat larger than nucleoli, situated in the center of the nucleus and separated from the nuclear membrane by a clear zone. Upon the nuclear membrane lie particles of basophilic material. These inclusions are not typical of yellow fever.

Many ganglion cells are shrunken and necrotic, and apparently they may reach the stage of necrosis without exhibiting the change characterized by inclusions. Early in the degenerative stage mononuclear phagocytic cells appear about the periphery of the cell, and soon entirely replace it. Occasionally a mitotic figure is seen which seems to be in a neuroglial cell. Of especial interest is the observation that not infrequently an acidophilic inclusion is to be found within the nucleus of one or more of the mononuclear inflammatory cells which are phagocyting a ganglion cell. These structures are round or elongated, and are about the size of a nucleolus, but distinct from it. They appear more dense, concrete, and refractive than the acidophilic inclusions generally seen in the ganglion cells, but are no more so than others that are occasionally found.

Polymorphonuclear leucocytes are rarely found in this section. There is a diffuse infiltration of the affected gray matter by mononuclear wandering cells with pale irregular nuclei, and a slight perivascular accumulation of similar mononuclears and lymphocytes. Veins are conspicuously distended.

Right Hemisphere and Brain Stem: One-half the brain, including the pons and medulla, was available in formalin, to study the distribution of lesions on the side opposite that receiving the inoculation.

Transverse sections including the entire half brain were cut through the frontal, parietal and occipital lobes, and through the cerebellopontine portion and through Ammon's horn. A diffuse encephalitis with lesions similar to those described, though varying in extent, was found in the gray matter from the frontal region through the pons. In some areas, such as Ammon's horn, the inflammatory exudate consists almost entirely of polymorphonuclear leucocytes.

Spinal Cord: There is ganglionic necrosis in both ventral horns. Several of these cells are being phagocyted by mononuclear phagocytes. There is a diffuse inflammatory exudate consisting of both polynuclear and mononuclear leucocytes. Edema and petechial hemorrhages are found.

Comment: An examination of these nine monkey brains shows that the strain of virus derived by inoculating mice intracerebrally with yellow fever virus and passed serially through these animals is an exceedingly destructive infectious agent for the central nervous system of normal monkeys, whether the virus is introduced directly from the mouse or passed serially through the brains of monkeys. One is led to judge that the virus rapidly traverses the central nervous system from the site of inoculation, causing an intense encephalomyelitis. The meninges do not seem to be involved in the inflammatory process.

The infectious agent attacks primarily, if not exclusively, the neurons (both sensory and motor), resulting in rapid degeneration and necrosis of these cells before inflammatory exudate appears. Associated with the injury to ganglion cells there is congestion of capillaries and veins, an inflammatory edema, and focal hemorrhages.

In what seem to be unusually severe acute lesions polymorphonuclear leucocytes make their appearance early and in considerable numbers before mononuclear phagocytes are to be found. Not only may there be a diffuse distribution of polynuclears in the inflamed area, but not infrequently they localize about dead ganglion cells. More commonly, however, there is an admixture of large mononuclears or the cellular exudate is composed of them entirely. Ordinarily phagocytosis of dead ganglion cells is accomplished by the mononuclears entirely. It is in these inflammatory cells collected about or replacing dead ganglion cells that one occasionally sees an acidophilic intranuclear inclusion, the significance of which is not apparent. If the lesion is of sufficient duration the veins become mantled by an accumulation of mononuclear cells, for the most part lymphocytes.

It seems evident in these preparations that ganglionic injury and necrosis is the first manifestation of the destructive effect of the virus in the nervous system, and inflammatory reaction, including cellular infiltration, is secondary.

In comparison with other neurocytotropic virus lesions, the mouse virus encephalitis resembles that of herpes in the rabbit and polio-

myelitis in man and monkey, rather than that of rabies and Borna disease. Like herpes and poliomyelitis the mouse virus causes a very acute fulminating disease, acutely destructive of ganglion cells. Unlike poliomyelitis, however, the injury is not so restricted in its distribution and affects both sensory and motor cells. In its distribution and its action upon both sensory and motor neurons it is more like the herpetic encephalitis, as seen in fulminating infections of rabbits. Unlike herpes, however, the mouse virus does not seem to affect the meninges, and its lesions are not so focal.

Nuclear Inclusions in Mouse Virus Encephalitis of Monkeys

Of especial interest in this study is the cytology of the neurons affected by the virus, with particular reference to the occurrence of intranuclear inclusions in the brains of monkeys. The observation by Theiler that intranuclear inclusions similar to those described in yellow fever occur in the brains of infected mice, and the presence of such inclusions in the mouse brains sent to me by Dr. Sellards, led to the expectancy that the mouse virus encephalitis of monkeys would be easily distinguishable from other forms of acute encephalitis by the presence of specific inclusions in ganglion cells. This, however, did not prove to be the case. It is true that intranuclear inclusions have been found in my preparations, but they are usually detected with difficulty, are few in number, and are often distinctly different morphologically from the typical intranuclear inclusions of yellow fever livers and mouse brains infected with the yellow fever virus. All of the inclusions observed were intranuclear and they were found in only five of nine cases of encephalitis in monkeys. My search was not exhaustive, however, and an investigation of more slides from different blocks of tissue possibly would have revealed a higher incidence. The inclusions found impress one as being of viral origin and occasionally they appear typical of yellow fever. The variations from type were found particularly in large multipolar ganglion cells, in one case the motor ganglion cells of the anterior horns of the spinal cord. In such cells there is chromatolysis and an eosinophilic staining of the cytoplasm. The nucleus is perhaps slightly enlarged. The nucleolus is partially or completely preserved, staining with methylene blue. About the nuclear mem-

brane are aggregated amorphous basophilic particles. The remainder of the nucleus appears empty except for one or more spherical or oblong, homogeneous, hyaline, pink-staining masses, usually larger than the nucleolus. Sometimes there are in addition to these structures smaller aggregations of minute pink particles resembling the material which constitutes the typical yellow fever inclusions. This description is based upon sections fixed in Zenker's solution and stained with methylene blue and eosin. In smaller ganglion cells the central area of the nucleus is sometimes found to be filled with pink-staining granular material, with chromatin particles collected upon the nuclear membrane. In these cells no nucleolus could be detected. Usually necrotic cells show no evidence of inclusions.

In this investigation only the staining reaction of inclusions with eosin, and their morphology, have been considered, partially because of the limited possibilities of the material at my disposal. In an exhaustive and detailed investigation of the yellow fever inclusions of human and monkey livers Cowdry and Kitchen were unable to detect any microchemical differential characteristics of these structures, and they finally relied largely, as did Torres, upon morphological configuration for evidences of specificity.

Discussion

The discovery by Theiler that the encephalitic brains of mice inoculated with the virus of yellow fever contain intranuclear bodies similar in every way to the inclusions previously described by Torres, and by Cowdry and Kitchen in the livers of monkeys and human beings dead of this disease, is very strong evidence that this cellular change is a characteristic effect of yellow fever virus upon cells. Especially significant is the fact that similar changes are brought about in two tissues so different as those of the liver and the brain. This cytological characteristic of the lesion, together with the immunological data supplied by the experiments of Theiler and of Sellards, makes it seem very probable that the virus of mouse encephalitis induced by the inoculation of typical yellow fever virus is in reality a modified form of the active agent of yellow fever.

It seems to be a unique phenomenon that a virus can become so distinctly and rigidly changed in its tropism or cellular relationship, although experience affords several instances of the variability of

viruses induced by experimental procedures, such as the modification of smallpox virus by passage through the calf. Such changes, however, represent apparently only variations in virulence, not of cytotropism. The virus of herpes simplex affords an instance of a profound divergence in cytotropic affinity of a virus in different species, as manifested by strains which possess a predilection for the skin in human beings and nervous tissue in the rabbit. The herpes virus, passed serially through the brains of rabbits, according to the experiments of Teissier, Gastinel and Reilly,[8] tends to lose its infectiousness for the human skin, but there is no indication that herpes virus becomes thereby more neurotropic in the human.

There is no reasonable doubt that Theiler's mouse virus is a neurocytotropic virus. It corresponds in its pathological activity and tissue affinity to the viruses of rabies, poliomyelitis, Borna disease and herpes. It is rather unexpected therefore that the mouse virus inoculated into the brains of the monkey (*M. rhesus*) does not induce more characteristically the cellular changes found in the brains of mice infected with the virus of yellow fever. However, there is a variation in the observed incidence of the yellow fever inclusions in the livers of human beings and of monkeys. The most distinctive difference between the effect of the mouse virus in the brains of mice and in the brains of monkeys is in the morphology of the intranuclear inclusions. Although one occasionally finds inclusions in encephalitic monkey brains which may be interpreted to be similar to those of mouse encephalitis, it is more common to find intranuclear inclusions, apparently of viral origin, which differ from them. An intranuclear inclusion in the monkey encephalitis atypical of yellow fever is a more compact, homogeneous, and discrete acidophilic mass somewhat suggestive of that found in Borna disease, though usually larger.

It should be borne in mind, however, that there is considerable morphological variation in most inclusions, though similar variations occur in each tissue regardless of the species of the host. The yellow fever inclusions are especially difficult to diagnose with certainty in their finely granular form as observed in fixed tissue, because they resemble so closely the granular precipitate from nucleoplasm which may be observed in many normal nuclei. They may be recognized with certainty, as is true also with the herpetic inclusions, only in their well developed forms, and when they occur in numbers.

The difference in structure of the typical intranuclear inclusions of the encephalitis of monkeys inoculated with mouse virus may represent, therefore, another variation in the activity of this virus not commonly seen in viral diseases.

In consideration of the protection experiments of Theiler and of Sellards, and of the fact that intranuclear inclusions quite like those of yellow fever are demonstrable in the cells of mouse brains inoculated with yellow fever virus, and finally that a fatal viral encephalitis may be induced in monkeys by the intracerebral injection of virulent mouse brains, characterized by the presence of intranuclear inclusions (some of which may resemble those of yellow fever) one feels that the evidence, both immunological and cytological, favors the view that the mouse virus represents a modified strain of yellow fever virus.

It is felt, however, that monkey encephalitis induced by mouse virus should be much more carefully studied from the viewpoints of its cytology, and of the cellular relationship and distribution of the virus.

Summary

1. A histological and cytological study has been made of an encephalitis of monkeys (*M. rhesus*) inoculated intracerebrally with the mouse strain of yellow fever virus.

2. The lesion in the monkey's brain is an acute, disseminated encephalomyelitis, extending apparently throughout the central nervous system, affecting the cellular tissues and causing necrosis of ganglion cells, both sensory and motor.

3. Intranuclear inclusions sometimes resembling, but more often differing from, those characteristic of yellow fever have been demonstrated in ganglion cells of the encephalitic monkey's brain.

4. On immunological and histological grounds it is judged that the virus of mouse and monkey encephalitis represents a biologically modified strain of yellow fever virus.

5. Cytologically the evidence of morphologically characteristic yellow fever intranuclear inclusions in the brains of encephalitic monkeys inoculated with the mouse virus is inconclusive.

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DESCRIPTION OF PLATES

Magnification 2300, except Fig. 3, which is 60 diameters.

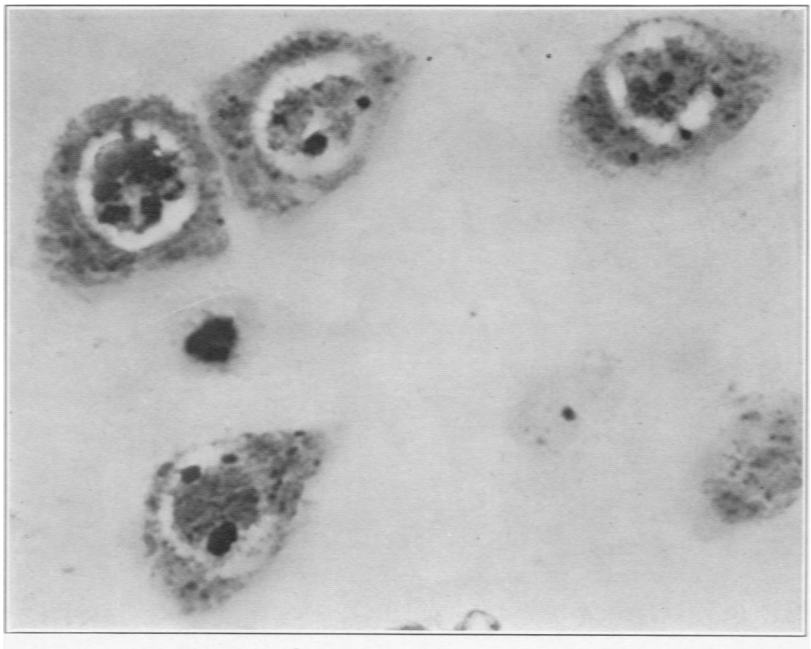
PLATE 24

FIG. 1. Ganglion cells from baby mouse's brain. Intranuclear granular acidophilic inclusions interspersed with basophilic granules. The larger ones may be nucleoli. These inclusions are like those of yellow fever livers.

FIG. 2. Ganglion cell from baby mouse's brain. Intranuclear mass largely composed of basophilic granular material. Atypical of yellow fever.

FIG. 3. Monkey encephalitis, to show perivascular and diffuse cellular infiltration.

FIG. 4. Ganglion cell from monkey encephalitis showing nucleolus (dark sphere) and acidophilic granular material rather loosely arranged, resembling yellow fever inclusions.



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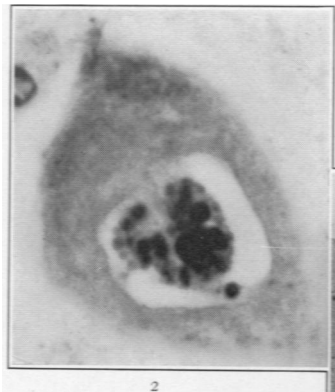

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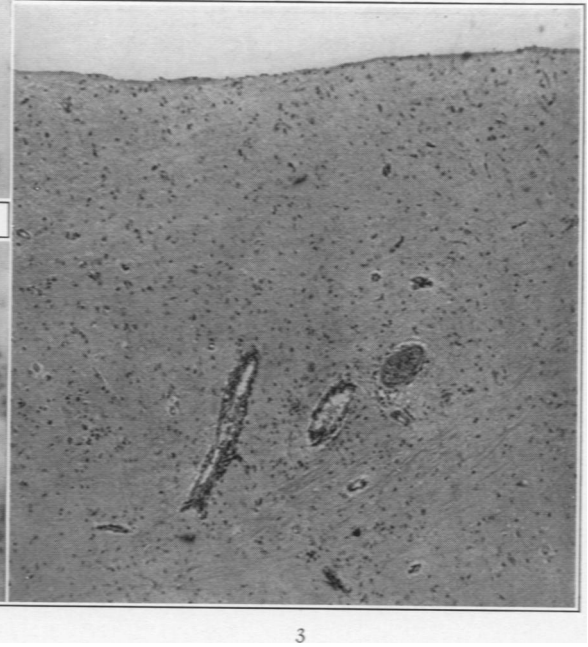

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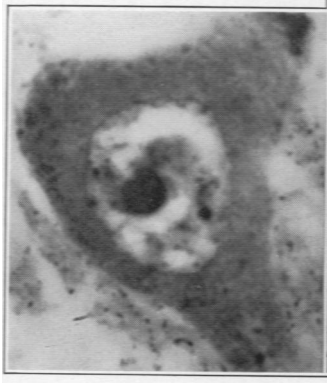

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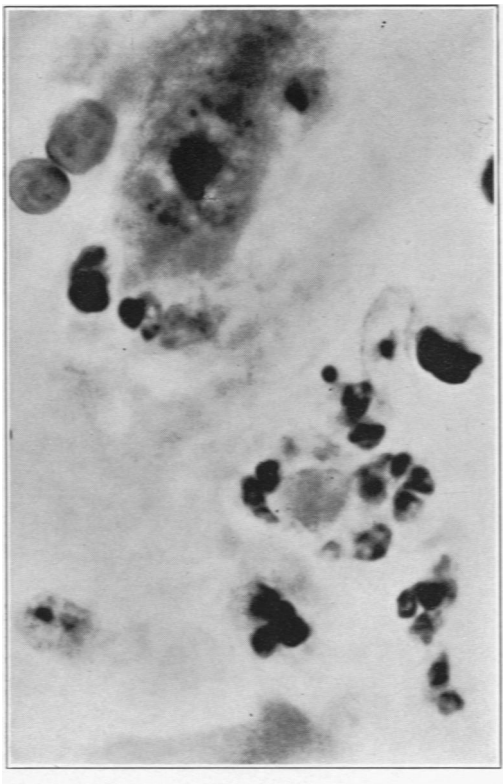
PLATE 25

FIG. 5. Monkey encephalitis to show phagocytosis of dead ganglion cell by polynuclear leucocytes.

FIG. 6. Same showing diffuse polynuclear exudate.

FIG. 7. Ganglion cell from monkey encephalitis showing oblong compact acidophilic intranuclear inclusions, at one end of which is a nucleolus. Note clear intranuclear space and aggregation about nuclear membrane of basophilic particles. Atypical of yellow fever.

FIG. 8. Ganglion cell from monkey encephalitis showing nucleolus and acidophilic masses or inclusions, atypical of yellow fever.



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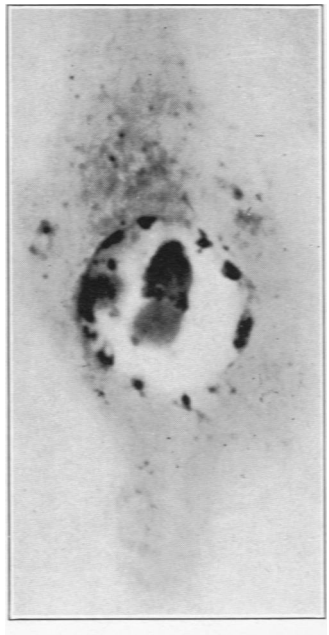

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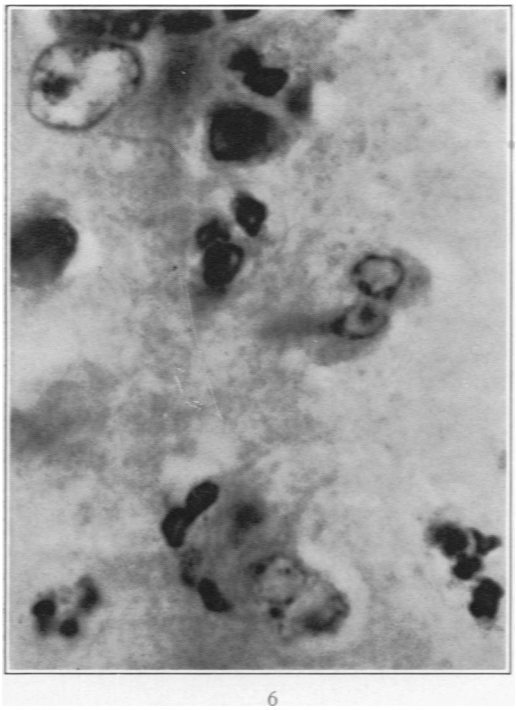

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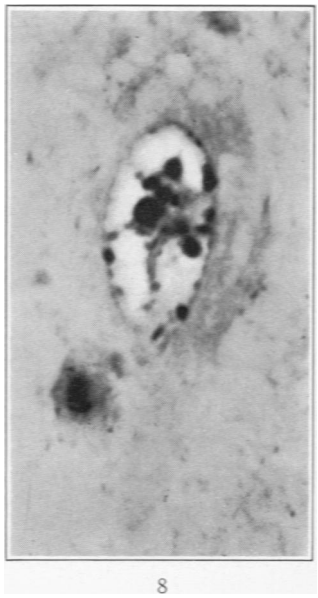

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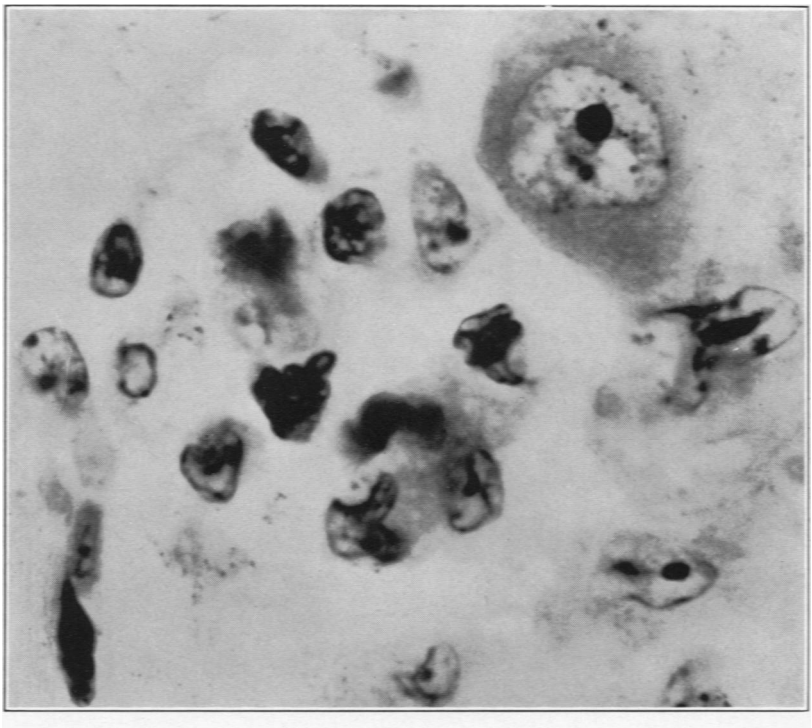
PLATE 26

FIG. 9. Monkey encephalitis. Phagocytosis of dead ganglion cell by mononuclear leucocytes.

FIG. 10. Necrotic ganglion cells of monkey encephalitis. Central eosinophilic material filling nuclear space. Basophilic particles upon nuclear membrane. Atypical of yellow fever.

FIG. 11. Large ganglion cell from monkey encephalitis showing large eosinophilic masses. The basophilic nucleolus is incorporated in the mass to the left. Atypical of yellow fever.



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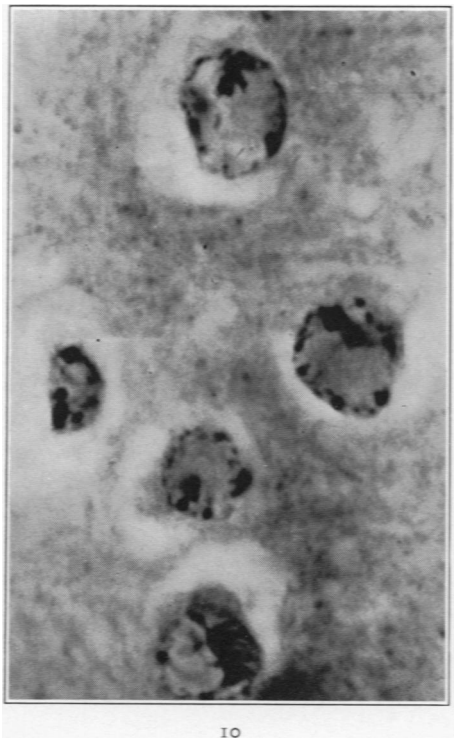

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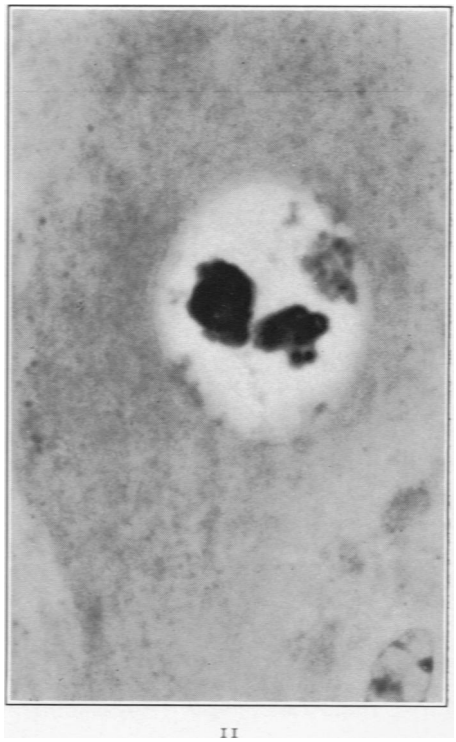

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