THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME XV NOVEMBER, 1939 NUMBER 6

TOXOPLASMIC ENCEPHALOMYELITIS *

III. A NEW CASE OF GRANULOMATOUS ENCEPHALOMYELITIS DUE TO A PROTOZOON

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In 1937 Wolf and Cowen [67] reported a case of parasitic encephalomyelitis in an infant. The causative agent was found to be a protozoon which on morphological grounds was identified as an Encephalitozoon. At the time, however, the possibility that the parasite might be a Toxoplasma was considered. In this paper reports of similar infections in infants by Jankû [21] and Torres [59-61] were cited as instances of the same disease. Later, a case reported by Richter [49] was suspected, because of its pathological picture, of being the same disease, and reexamination of his histological sections revealed the presence of parasites similar to those observed in the first 3 cases cited.[68] In reviewing Richter's case the identity of the causative parasite was reconsidered and it was pointed out that the information available at that time was somewhat in favor of the microorganism being Toxoplasma, rather than Encephalitozoon. This decision again was reached on morphological grounds, but it was indicated that the final evidence as to the identity of the microorganism would be procured only if it could be recovered from a future case and studied experimentally.

* Investigation carried out under a grant from the Friedsam Foundation. Received for publication June 22, 1939.

A recent case, which came to autopsy at the Babies Hospital in New York City in June 1938, presented an opportunity for the transmission of the infection to experimental animals. A preliminary report [69] of the transmission experiments establishing the identity of the causative agent as a Toxoplasma has been made.

Toxoplasma is generally regarded as a protozoan parasite, the exact classification of which is as yet undetermined. The microorganism has been known since 1908 when it was reported independently by Splendore [55, 56] (Brazil) in the rabbit, and by Nicolle and Manceaux [41, 42] in the North African rodent, the gondi. In smears the parasites appear as well outlined, crescentic or curved masses of protoplasm 4–6μ in length and 2–3μ in width. The extremities are usually pointed, although one end may be rounded. In histological sections of fixed tissue, or under pressure, ovoid, rounded or fusiform types are more commonly seen. Each parasite contains a rounded chromatin mass situated centrally or nearer the blunter extremity. The chromatin body may appear granular or ring-like, possibly due to incomplete staining, or rod shaped or dumbbell shaped preparatory to cell division. Flagella are absent and motility has not been observed. Reproduction is by simple binary longitudinal division. In addition to the single parasites, large rounded masses of what appear to be aggregations of closely approximated parasites are also seen. Such masses are sometimes referred to as cysts although it is uncertain whether or not they possess a true cyst wall. In the cysts it is not always possible to distinguish clearly between the individual parasites which may appear to be differentiating out of a multinucleated mass of protoplasm. Such forms have been interpreted by some as indicative of reproduction by schizogenesis. It has not been possible to cultivate the parasites in artificial mediums although success has attended the use of those containing living cells.[28, 51]

In the past 30 years Toxoplasma has been described as a spontaneous infective agent in a variety of species of mammals and birds from many parts of the world. The strikingly wide geographic distribution of, and host susceptibility to these parasites is indicated by the following reports of naturally occurring toxoplasmosis: dog (Italy,[35] Brazil,[7] Germany,[72] France,[3, 39] Persia [30]);

rabbit (Brazil,[56] Senegal,[4] France,[28] Dutch East Indies,[5] Congo [52]); guinea pig (Brazil,[9] France,[37] United States [32, 51]); mouse (Italy,[53] France [38]); rat (Italy [54]); gondi, *Ctenodactylus gondi* (Tunisia [42, 43]); squirrel (England [13]); mole (Japan [48]); snake (London Zoological Garden [47]); lizard (France [14]); the fossa, *Cryptoprocta ferox* (London Zoological Garden [47]); wombat (Wellcome Bureau, London [15]); monkey, *Stentor senilicus* (Guiana [57]); baboon, *Cynocephalus* (France [29]); chimpanzee (France [22]); domestic pigeon (Brazil,[7] India [34*]); English sparrow, *Passer domesticus;* starling, *Sturnus vulgaris;* canary, *Serinus canarius* (United States [18, 19, 31, 70]); siskin (Germany [64]); and various other birds from the same and other lands.†

The morphology of the microorganisms and the histopathology of the disease produced in the animals are often very inadequately described. Some of the animals may not have had spontaneous toxoplasmosis since they were inoculated for other purposes and may have inadvertently received injections of tissues which were Toxoplasma-infected. Such biological characteristics as might be studied by transmission of the infection are lacking in many instances. Most of the reports however, are sufficiently docu-

* In these reports the parasites were not designated as Toxoplasmata by the author, but subsequent writers [23, 66] have generally so regarded them.

† These include the following: Brazil [25]: white-throated seed-eater (*Sporophila albogularis*), Andean white throat (*Brachyspiza capensis*), white-bellied swallow (*Atticora cyanoleucus*), yellow finch (*Sicalis flaveola*), palm tanager (*Tanagra palmarum*), Dominican cardinal (*Paroaria larvata*), red rump tanager (*Rhamphocelus brasilius*). Brazil [8]: rufous-bellied thrush (*Turdus rufiventris*), blue-black grassquit (*Volatinia jacarini*), (*Aaptus etiopi*), tyrant flycatcher (*Pitangus sulphuratus*), white-crested elaenia (*Elaenia albiceps*), king vulture (*Gypagus papa*). Brazil [46]: tanager (*Tanagra sayaca*). Gambia [52*]: African vulture (*Neophron monachus*). India [1*]: sparrow. France [23*, 25, 33]: Java sparrow (*Padda oryzivora*). waxbills (*Estrilda phoenicotis*), (*Lagonosticta senegala*), weaver bird (*Quelea erythrops*), fire finch (*Pyromelona francisca*), chaffinch (*Fringella coelebs*), yellow babbler (*Liothrix luteus*). London Zoological Garden [47]: fruit pigeon (*Carpophaga concinna*), pied bush chat (*Pratincola caprata*). United States [45*]: sparrow. United States [20]: catbird (*Dumatella carolinensis*), chipping sparrow (*Spizella passerina*), kingbird (*Tyrannus tyrannus*), red-eyed towhee (*Pipilo erythrophthalmus*), song sparrow (*Melospiza melodia*), swamp sparrow (*Melospiza georgiana*), Baltimore oriole (*Icterus galbula*), cowbird (*Molothrusater*), Savannah sparrow (*Passerculus savanna*). United States [71]: house finch (*Carpodacus mexicanus frontalis*). Argentina [50]: canary (*Serinus canarius*). Japan [62, 63]: white-eye (*Zosterops palpebrosa peguensis*), paddybirds (*Munia malaca, Munia maja, Munia atricapilla, Munia topela, Ploceus baya, Aidemosyne malabarica*), bamboo finch (*Erythrura prasina*), Java sparrow (*Oryzornis oryzivora*). Italy [17]: European tree sparrow (*Passer montanus*), Italian house sparrow (*Passer italiae*). Germany [44]: English sparrow (*Passer domesticus*), green finch (*Ligurinus chloris*), linnet (*Cannabina linota*).

mented and support the impression of the wide distribution of the infection.

Following the usage of Nicolle and Manceaux, who named their parasite *Toxoplasma gondii*, many subsequent observers have referred to each newly reported strain as *Toxoplasma cuniculi*, *T. musculi*, *T. columbae*, and so on, according to the host in which it was discovered. As a number of authors [12, 66] have pointed out, however, there is no morphological or other means of distinguishing between the various named forms of the parasite, and it may well be that they represent a single species capable of infecting many hosts. This low host specificity has been demonstrated experimentally on many occasions by inoculation of Toxoplasma-infected tissue into heterologous animal species. Thus, *T. gondii* [12, 24, 43] has been found pathogenic for the mouse, guinea pig, pigeon, rabbit, mole, shrew, dog, Java sparrow and cat; *T. cuniculi* [28] for the guinea pig, mouse, pigeon, chick, sparrow and other small birds; *T. canis* [39, 40] for the rabbit, guinea pig, mouse, sparrow and pigeon; *T. caviae* [9, 51] for the pigeon, mouse, rabbit, chick and chicken. Nothing is as yet known of the natural mode of transmission of the infection in animals or of the existence of intermediate vectors. In naturally infected animals the parasites have commonly been found free or in leukocytes in inflammatory parenchymal lesions and exudates in a variety of tissues, notably the brain, spinal cord, spleen, lung and liver. They have also been observed occasionally in the blood, bone marrow, intestinal mucosa, lymph nodes, heart, kidney, pancreas, omentum, mesentery and pleural exudate. The pathological changes in spontaneously infected animals have in most instances not been thoroughly described. The lesions most commonly encountered are small focal inflammatory nodules, with or without necrosis, in the spleen, lung and liver. The infiltrating cells are predominantly lymphocytes and large mononuclears. Comparable changes have been noted in the brain although there is little or no reaction to the presence of the parasites in this organ in some instances. The intestine may show ulceration. The kidney generally shows no pathological changes. The lesions in experimental toxoplasmosis, as described in the literature, and as we were able to observe them in rabbits and mice inoculated with a strain of Toxoplasma of animal origin [51] from the Rockefeller Institute of New York,

kindly furnished us by Drs. Sabin and Olitsky, may be briefly summarized. Intracerebral inoculation of rabbits results in chronic inflammatory foci in the leptomeninges, parenchyma, ventricular walls and choroid plexuses. The infection may spread down to the spinal cord. The lesions contain lymphocytes and mononuclear cells with fibrin and polymorphonuclear leukocytes when necrosis occurs. Plasma cells are common in the chronic lesions. Productive changes, such as multiplication of leptomeningeal cells, endothelial proliferation with production of new capillaries, formation of small granulomas of capillary origin, and proliferation of microglia and fibroblasts, are of frequent occurrence. The parasites occur free, in cysts, and intracellularly, in leptomeningeal cells, large mononuclear cells, endothelial cells of capillaries, epithelioid cells of the granulomas, phagocytes, ependymal and choroid epithelial elements, and rarely in nerve cells within the focal lesions. They are most numerous in the necrotic foci, although they may occur in considerable numbers about involved blood vessels, spreading into the parenchyma without much initial reaction. There are focal inflammatory and, at times, necrotizing and productive lesions in other organs. The lungs, liver and spleen, and less commonly the heart, adrenals, kidneys, intestines and lymph nodes are affected. Parasites are present in these lesions. Combined intracerebral and intraperitoneal inoculation of mice results in essentially the same picture with an associated peritonitis. Parasites may be found free and in large mononuclear cells in the peritoneal exudate. Infection also develops after inoculation by other routes with widespread dissemination and variations in the intensity and localization of the lesions in various organs.

The following is a description of the clinical and pathological changes observed in an infant from whom Toxoplasma was recovered. In view of the rarity of this condition a complete report of the case is presented.

Report of Case

Clinical History: C.D. (Babies Hospital, New York, No. 552107), a white male infant, was delivered at term by Cesarean section on May 23, 1938.

Both parents were in good health and had always resided in or near New York City. No history of contact of the parents with rabbits or other animals could be elicited. The mother had never eaten rabbit meat. The apartments

in which she had resided for several years before admission to the hospital were free of mice and rats. No pets, including birds, were kept in the home. The father was 32 years of age. The mother, a primipara 31 years of age, had been under continuous observation in the hospital for the last 3 months of her pregnancy as a suspected case of placenta praevia. During this period her temperature, pulse, respiration and blood pressure remained within normal limits. Her blood Wassermann test was negative, and the course of pregnancy was uneventful except for slight vaginal bleeding during the last months. Several days before the expected date of delivery there was spontaneous rupture of the membranes with a profuse discharge of yellowish fluid. During pelvic examination a large amount of thin meconium escaped. In view of the placenta praevia, it was decided to deliver the child by Cesarean section. This was performed under nitrous oxide-ether anesthesia. Recovery from the operation was uncomplicated. The placenta and membranes were unfortunately not kept for examination.

At birth the infant was moderately asphyxiated but respiration was described as spontaneous. Crying was not vigorous. The infant weighed 3050 gm. and measured 50 cm. in length. The head measured 33.5 cm. in circumference, the chest 31 cm., and the abdomen 33 cm. On the 3rd day of life the infant had a right-sided convulsive seizure, lasting 3–4 minutes, with jerking of the hands, twisting of the mouth, and rolling of the eyes to the right. During the attack the respirations were shallow and rapid. There was no rigidity of the neck or bulging of the anterior fontanelle. The body temperature remained normal. Following the convulsion the infant was apathetic and respirations were irregular, shallow and rapid. A left-sided Horner's syndrome was observed. No gross hemorrhages were noted in the fundi. There was a normal withdrawal reaction to pin prick. The tendon reflexes were absent in the legs and hypoactive in the arms.

During the next few days of life the child's condition improved somewhat. There were repeated convulsive seizures but these gradually became less frequent. Feedings were taken fairly well, although in general the infant was drowsy and lethargic. By the 2nd week convulsions ceased, although weakness and a left enophthalmos persisted. A roentgenogram of the lumbosacral spine at this time showed no abnormalities. Lumbar puncture yielded bloody fluid but the relatively uncontaminated portions of the fluid appeared xanthochromic.

Physical examination on the 17th day of life showed retraction and turning of the head toward the right. The eyes deviated to the right and at times there was nystagmus toward the right. The upper extremities were spastic and the hands clenched, but the tendon reflexes were not increased. No thoracic breathing could be made out. The abdominal reflexes were absent, but sluggish cremasteric responses could be obtained. The lower extremities were withdrawn on painful stimulation. Babinski reflexes were not elicited. Response to pin prick was definitely less marked below the neck than on the face and scalp. The spleen was just palpable. The bladder was distended and there was dribbling of urine. The fontanelles were not tense nor was there any separation of the cranial sutures. It was felt that the clinical signs pointed to both spinal cord and cerebral injuries with the more severe injury in the spinal cord. The patient was discharged from the hospital at the age of 18 days.

At home there was at first no change in the infant's condition. On the 22nd day of life, however, the mother noticed a seizure in which the child's arms became stiff and remained straight and stiff by his sides. Following this episode he seemed weaker. On the 26th day vomiting began and although the mother diluted the formula and fed it in small amounts, the feedings were not retained. For this reason the infant was readmitted to the hospital after having been at home for 10 days.

As contrasted with examination several days previously, the infant's condition was poor. Respiration was quite irregular and labored, and appeared to be almost entirely diaphragmatic in type. There was moderate cyanosis and a grayish tint to the skin. No spontaneous movements below the neck were observed. The arms were pronated and held in extension at the elbows, and the fingers were kept flexed. Attempts to elicit the deep reflexes in the lower extremities resulted in flexion of the thighs and legs, and dorsiflexion of the feet. The abdominal reflexes were absent. There appeared to be insensitiveness to pain below the neck. Both liver and spleen were palpable but thought by the examiner to be of normal size.

Laboratory Data: Examination of the urine on June 20, 1938 showed a trace of albumin, no sugar, and microscopic examination showed 6–30 polymorphonuclears per high power field with occasional erythrocytes. A blood count on June 20th showed erythrocytes 5,970,000 per cmm., total leukocyte count 8000 per cmm.; polymorphonuclear leukocytes 61 per cent, lymphocytes 33 per cent, eosinophils 5 per cent, and monocytes 1 per cent. Examination of the spinal fluid on June 21st showed a pressure of 140 mm. of water. Respiratory oscillations were present but there was no response to compression of the jugular vein on either side. Three cc. of slightly cloudy, distinctly xanthochromic fluid were removed. This clotted promptly and gave a 4 plus Pandy reaction. The benzidine test was negative. Microscopic study of the fluid was not made. A blood Kahn test on June 23rd was negative.

Terminal Clinical Observations: In view of the suspected involvement of the cervical cord with subarachnoid 'block,' a cisternal puncture was attempted. About 3 drops of rather viscid, clear, slightly xanthochromic cerebrospinal fluid were obtained which gave a positive benzidine test and a 4 plus Pandy reaction. About 0.1 cc. of lipiodol was injected. Fluoroscopy and roentgenographic examination of the spine at intervals following this procedure showed all of the lipiodol to remain above the level of the second cervical vertebra, suggesting a 'block' at this point. During the last few days of life the infant's temperature fluctuated between 96° and 101.2° F. The cry was weak and respirations were of the Cheyne-Stokes type.

Examination of the fundi revealed an irregular reddish brown area in each macular region about 1 disc-diameter in size on the right, and somewhat smaller on the left. These changes were interpreted as resulting from hemorrhage.

On June 23, 1938, the infant became markedly cyanotic with rapid shallow respiration. At death the baby was 31 days of age. The clinical diagnosis was multiple injuries of the central nervous system with compression of the cervical spinal cord by hematoma.

Autopsy Report

Postmortem examination was performed 4½ hours after death and was limited to examination of the brain, spinal cord and posterior hemisphere of the right eye.

The surfaces of the cerebral hemispheres presented numerous focal lesions (Fig. 1) varying from a few mm. to approximately 2 cm. in diameter. In these areas the cortex was depressed, pitted and discolored yellow. This tissue was in most instances considerably softer than that of the surrounding unaffected gyri, and the overlying leptomeninges were thickened and grayish yellow in color. The most prominent lesions involved portions of the superior and middle frontal gyri, the frontal and temporal poles, the precentral and postcentral gyri, the superior parietal lobule and the lateral occipital gyri bilaterally. Most of the gyri on the medial and ventral surfaces showed similar focal lesions. The cerebellum and brain stem appeared normal externally. The leptomeninges about the basal cisterns were slightly grayish and opaque.

Coronal sections of the left cerebral hemisphere showed that the superficial lesions consisted of well demarcated zones of cortical softening (Fig. 2). The center of each was slightly sunken, finely cystic, and yellowish or grayish yellow in color, while its margin was sharply outlined, grayish and more prominent. The larger lesions extended from the cortex into the subcortical white matter, and at times into the centrum ovale. On incising some of the softened areas the knife passed through gritty material. A large cyst, 5 cm. in length anteroposteriorly, 1.5 cm. in diameter in its greatest cross section, and lined by necrotic discolored parenchyma, was present in the white matter inferomedial to the atrium and occipital horn of the left lateral ventricle.

Single and conglomerate foci of softening similar to those in the cortex involved portions of the island of Reil, and lenticular and caudate nuclei. The thalamus and hypothalamus appeared grossly unaffected.

The changes in the right cerebral hemisphere were much the same as those in the left, except for the absence of large cysts.

The lateral and third ventricles were slightly dilated. Their walls were smooth and glistening, except in the inferomedial

angles of the lateral ventricles where there were areas of yellowish discoloration denuded of ependyma.

Section of the cerebellum revealed no gross abnormalities, while the brain stem contained numerous lesions. There were numbers of soft, irregular, yellowish white areas in the midbrain, each bordered by a grayish translucent marginal band. The largest area was located in the right cerebral peduncle and measured 5 by 2 mm. in cross section. The others were present in the oculomotor nuclei and ventral portions of the red nuclei. The aqueduct of Sylvius was of normal size. In the cephalic portion of the pons, at the junction of the tegmentum and reticular area, was an ovoid, translucent grayish area 5 by 3 mm. in cross section, traversed by fine yellow, curving and interlacing lines (Fig. 7). Small, cream colored, sharply marginated lesions, pinpoint in size, were scattered through the reticular zone and in the regions of both fifth nerve nuclei. In the cephalic portion of the medulla two dull white areas with gray centers and scalloped edges were found in the restiform bodies and fifth nerve nuclei bilaterally, the right measuring 4 mm. and the left 2 mm. in diameter. At their margins white pin-point nodules were seen. The rest of this portion of the medulla was glassy in appearance and showed slight obscuration of its markings. In the midmedulla there were numerous lesions similar to those described in the midbrain. Many of those on the right side were softened centrally. The largest lesion was 10 by 5 mm. in cross section, oval, sharply marginated, grayish white in color, and involved almost the entire left side of the medulla at this level. At the junction of the middle and lower thirds of the medulla a syrinx measuring 4 mm. in length and 1 mm. in transverse diameter was present. It was lined by a narrow band of yellowish and gray translucent tissue, widest at the lateral border of the cavity. The right half of the lower medulla was soft to palpation and its architectural markings were obscured by gray and cream colored mottling.

The cervical segments of the spinal cord were markedly swollen, the greatest swelling occurring in the region of the cervical enlargement, which was firm and almost twice its normal size. The leptomeninges over its cephalic portion were slightly clouded. The first three segments of the thoracic cord were shrunken to about one-half of their normal diameter, and were softer than the ad-

jacent parenchyma. The leptomeninges over them were opaque and yellowish. There was a similar change in the seventh, eighth and ninth thoracic segments and overlying pia-arachnoid. The lowest thoracic segment was slightly swollen. The lumbosacral segments of the spinal cord, the nerve roots and the cauda equina appeared normal. Except in the regions where they were specifically noted as abnormal, the leptomeninges were thin and translucent. On section of the swollen cervical cord the parenchyma was observed to be translucent and gray, and the line of demarcation between gray and white matter was obliterated (Fig. 3). Section of the shrunken upper segments of the thoracic cord (Fig. 4) revealed that their normal markings were obscured. The tissue was gray and translucent and in it there were a number of punctate yellow and brownish nodules. In the seventh to ninth thoracic segments (Fig. 5) an area of grayish and light brown glistening tissue measuring 4 by 2 mm. in cross section was present in the central portion of the parenchyma obscuring all the gray horns. At the margins of this zone the tissue was studded by yellow punctate nodules 1–2 mm. in diameter. In the upper lumbar segments (Fig. 6) the outlines of the ventral horns were well preserved. The posterior horns, however, were obliterated by grayish tissue which passed into the posterior columns and parts of the lateral columns as well. Yellowish nodules, 1 mm. or less in diameter, were occasionally seen in the white matter.

Histological Examination

Leptomeninges of Cerebrum: Over the cortical lesions the leptomeninges were markedly edematous and congested. There was moderate or intense infiltration by lymphocytes, plasma cells, mononuclear leukocytes, lipoid laden phagocytes and eosinophils (Fig. 11). In some areas the last were almost as numerous as the plasma cells. Where the parenchymal changes were most severe the leptomeningeal exudate was directly continuous with that in the cortex, obliterating the line of demarcation between pia-arachnoid and brain. There was a multiplication of leptomeningeal cells. None of the leptomeningeal vessels was occluded, but there was endothelial hyperplasia in all the capillaries, many of the arterioles and venules, and some of the small arteries and veins.

Over the unaffected gyri the leptomeninges were somewhat edematous and occasionally infiltrated by small numbers of mononuclear leukocytes and lymphocytes.

Cerebral Cortex: There was a complete loss of cortical architecture and a total destruction of all neural and glial elements in the large zones of necrosis (Fig. 8). These were occupied by a mass of eosinophilic and nuclear débris in which only a few vessels were still partially preserved. Their walls were permeated and surrounded by fibrin. Toward the margins of these areas of total degeneration, polymorphonuclear leukocytes, lymphocytes, plasma cells, lipoid laden phagocytes and eosinophils were present in moderate numbers. Frequently they were concentrated in the walls and perivascular spaces of blood vessels The parenchyma was intensely edematous and showed a considerable loss of neural and glial elements, moderate hyperplasia of capillaries, and considerable astrocytosis. The majority of the astrocytes showed intense clasmatodendrosis. Beyond the marginal zone of reaction the parenchyma was edematous and studded by numerous miliary granulomas (to be described in detail below). Between the granulomas in the gray matter there was a moderate diffuse loss of ganglion cells, and many of the remaining cells were either swollen and vacuolated or pyknotic. The oligodendroglia were swollen and the astrocytes hypertrophied and fibrillary.

In some of the severely necrotic areas cyst formation occurred. Within the cavities lipoid laden phagocytes lay in a meshwork of hyperplastic capillaries, the walls of which were infiltrated by small numbers of plasma cells, lymphocytes and mononuclear leukocytes. Fibroblasts derived from the capillary walls were present. There was multiplication of microglia cells at the margins of the cavities and of the necrotic zones. They gave rise to numerous rod cells and transition forms of lipoid laden phagocytes. In relation to the cysts, astrocytosis was usually more prominent, the cells consisting of plump astrocytes, some of which were binucleated or multinucleated.

A striking feature of the process was the marked calcification of necrotic material in some areas (Fig. 9). This involved either the majority of the cortical layers, resulting in a broad band of calcification, or consisted of scattered calcific material, such as

was seen at the margins of the cysts. The bands of calcification often stopped abruptly. The calcium occurring in coarse granules was deposited in clusters or diffusely. Considerable numbers of calcified cells (Fig. 15), the majority of which appeared to be nerve cells, were identified. The margins of these were sharp and the nuclei remained unencrusted. Short undulating bands of calcium of varying thickness had the appearance of encrusted dendrites or axones.

The cortex adjacent to these foci of severe cortical necrosis, inflammation and calcification was often surprisingly well preserved. Single granulomas were occasionally encountered in these areas, most frequently in the zonal or pyramidal layers (Fig. 10). The cortical architecture was normal but there was a diffuse edema and a slight diffuse loss of ganglion cells. The remaining neural elements had undergone complete chromatolysis, and some were swollen, vacuolated or pyknotic. No myelin sheaths were present in the gray matter, but moderate numbers of unchanged axones were observed. There was a mild generalized astrocytosis with thickening of the external glial membrane near the focal lesions.

Cerebral White Matter: Where the cortical lesions were most severe, inflammation and necrosis extended into the subcortical white matter and in places into the centrum ovale. Here amorphous débris was found in place of normal structures, and at its margin was a band of intensely edematous, partially degenerated white matter, moderately infiltrated by cells similar to those seen in the cortex. The capillaries in this zone were hyperplastic and there was a considerable astrocytosis, many of the astrocytes being partially degenerated. Numerous miliary granulomas were present at the margins of the zones of infiltration and in the relatively intact white matter subjacent to purely cortical lesions. The oligodendroglia were markedly swollen. Small numbers of myelin sheaths were seen in the subcortical white matter and centrum ovale. They were widely separated, but they, as well as the axones, appeared normal. The subependymal tissue about the lateral ventricles showed a marked astrocytosis. This broadened subependymal glial mat was mildly infiltrated by plasma cells and lymphocytes. The infiltration varied in intensity and where it was greatest granulomas were present. Small deposits of calcium

were occasionally seen. The walls of the lateral ventricles were denuded of ependyma at some points.

Corpus Striatum: There were large areas of necrosis involving the globus pallidus, putamen and caudate nucleus. Centrally these were filled with eosinophilic débris and degenerating lymphocytes, mononuclear leukocytes and polymorphonuclear leukocytes. Focal collections of such cells clustered about persisting capillaries. The degeneration passed into the adjacent internal capsule and centrum ovale. Where it reached the surface of the caudate nucleus the wall of the lateral ventricle was completely denuded of ependyma except in the lateral angle (Fig. 13). In the superficial periventricular necrotic material there were small numbers of degenerating mononuclear leukocytes and occasional clusters of calcium granules. At the margins of the totally degenerated areas the inflammatory, glial and vascular changes were similar to those described in the cortex. Granulomas in moderate numbers were scattered through the rest of this region. The nerve cells in the preserved areas showed complete chromatolysis and occasional vacuolization. Most of the myelin sheaths, not directly in the zones of necrosis, were well preserved.

Thalamus and Hypothalamus: The nerve cells in the thalamus were well preserved and contained a normal amount of Nissl substance. Numerous granulomas were scattered through the parenchyma, and some were present in the thickened subependymal glial mat in the wall of the third ventricle. The ependyma lining the latter was well preserved, although there were numerous ependymal granulations.

Cerebellum: The leptomeninges over the folia were slightly congested and contained occasional lymphocytes and monocytes. There were no abnormal changes observed within the folia proper. Occasional granulomas were found in the central white matter of the cerebellum and subependymal tissue of the wall of the fourth ventricle.

Midbrain: The leptomeninges were congested and contained small numbers of mononuclear leukocytes. The aqueduct of Sylvius was slightly reduced in size due to the presence of many flat ependymal granulations. Numerous granulomas similar to those in the cerebrum were scattered in the substantia nigra, cerebral peduncles, colliculi and periaqueductal region. A group

of large nerve cells in one colliculus was partially calcified. The rest of the nerve cells in the nuclei at this level showed no abnormal changes, and the axones were well preserved. The myelin sheaths appeared normal. There was a slight astrocytosis about the granulomas.

Pons: There were many more granulomas in this portion of the brain stem than in the midbrain, and they occurred in both the reticular and the tegmental regions, as well as in the middle cerebellar peduncles. A large area of diffuse infiltration was encountered in the midline of the dorsal half of the reticular zone. Here the tissue was quite edematous, showed mild astrocytosis, and was moderately infiltrated by lymphocytes, plasma cells, mononuclear leukocytes and occasional eosinophils. Some of the vessels showed mild endothelial hyperplasia and infiltration of their walls. The nerve cells were fairly well preserved. In foci within the zone of inflammation the process was more intense. Here there was a concentration of infiltrating cells with satellitosis and varying degrees of degeneration in some of the ganglion cells. In these foci capillary hyperplasia and microglial proliferation were also seen. Granulomas were concentrated near the margins of the infiltrated zone and involved the nearby pyramidal tracts. There were small numbers of ependymal granulations in the floor of the fourth ventricle and the subependymal glial mat was thickened and contained granulomas. The leptomeningeal changes were similar to those about the midbrain.

Medulla: In the cephalic portion of the medulla there were disseminated miliary granulomas. In the ventral half of the midmedulla diffuse infiltration and partial degeneration were present. In addition to infiltrating cells similar to those described elsewhere, there were small numbers of lipoid laden phagocytes. The exudate showed focal and perivascular concentration. All of the neural and glial elements had disappeared. At the margins of the necrotic and inflammatory zone were vascular hyperplasia and a concentration of granulomas. Degeneration and inflammation were even more extensive in the caudal portion of the medulla where only a narrow band of relatively well preserved tissue containing numerous granulomas was present at the periphery. A large central cavity was present in the necrotic zone. Most of the neural elements had disappeared in the degenerated area and only

a few were preserved in the nuclei at its edges. Axones and myelin sheaths were well preserved in the marginal tissue but had disappeared elsewhere.

Choroid Plexus: Especially in the lateral ventricles near the glomus, there was a moderate amount of exudate between the villi of the choroid plexus. This was composed of mononuclear leukocytes, lymphocytes, and occasional polymorphonuclear leukocytes and strands of fibrin. The choroid tufts were hyperemic and their central connective tissue cores edematous. Eosinophils, scattered in small numbers beneath the choroid epithelium, were present in nearly every villus. There were fewer lymphocytes and polymorphonuclear leukocytes and these were usually found deeper in the core of the tuft. Occasionally there was a more cellular inflammatory focus, and over this area the choroid epithelium had disappeared in places.

Spinal Cord: Upper Cervical Region: The spinal roots showed no abnormal changes. The leptomeninges were mildly infiltrated by lymphocytes, mononuclear leukocytes, polymorphonuclear leukocytes and eosinophils. This mild infiltration passed into the dorsal medial septum and showed focal concentration over the more severe parenchymal lesions where it was associated with hyperplasia of leptomeningeal cells. The leptomeningeal vessels were patent although some of the smaller ones showed endothelial and adventitial hyperplasia. The most marked parenchymal changes occurred in the columns of Goll and were similar to those in the lower medulla, except for the absence of a syrinx. There was marginal astrocytosis and granulomas were present in the columns of Burdach. A small number of granulomas was scattered through the remainder of the white matter. There was generalized edema, most marked in the anterior horns where the nerve cells were pale staining and a few partially degenerated. Polymorphonuclear leukocytes and lymphocytes in moderate numbers were present here (Fig. 14). The central canal was distended by amorphous material in which polymorphonuclear leukocytes, lymphocytes and mononuclear leukocytes were seen. There was a total loss of myelin sheaths and axones in the posterior columns. At the margins of the degenerated zones swollen fragmented myelin sheaths were seen and phagocytosis of myelin fragments by large mononuclear cells occurred.

Cervical Enlargement: The spinal cord was considerably swollen at this level due to intense edema. The posterior columns showed even greater degeneration than in the preceding level with extension of necrosis and inflammation into the posterior horns and parts of each lateral column. Most of the nerve cells in the posterior horns and the medial portions of the anterior horns had either disappeared or showed marked degeneration. The remainder of the nerve cells had undergone complete chromatolysis. Granulomas were present, not only in the white matter at this level but also in the anterior horns. There was a loss of myelin sheaths in the posterior and lateral columns and a mild diffuse loss in the anterior columns. The other changes were similar to those at the preceding level.

Upper and Lower Thoracic Levels: These corresponded to the macroscopically shrunken regions. There was almost complete necrosis of the parenchyma which was collapsed and devoid of architectural markings. The leptomeningeal infiltration in these areas contained a greater number of plasma cells. In places the exudate passed directly into the parenchyma so that the line of demarcation between pia-arachnoid and cord proper was often lost. Granulation tissue invaded the posterior columns from the leptomeninges. Almost all of the remaining tissue consisted of cellular débris and occasional hyperplastic capillaries. All the neural and neuroglial elements had disappeared. In a few strips of partially preserved marginal white matter, mild inflammatory and productive changes, fragments of degenerated myelin, and large clusters of lipoid laden phagocytes were seen.

Lumbar Cord: In the upper lumbar segments there was widespread necrosis of the posterior columns, dorsal portions of the lateral columns, posterior horns, parts of the anterior horns, and central gray matter and commissures (Fig. 18). The changes in these areas were similar to, but less intense than, those in the severely degenerated areas of the thoracic cord. In the lower lumbar segments and in the sacral cord there was a mild leptomeningitis. Numerous miliary granulomas were scattered throughout the parenchyma, especially in the white matter (Fig. 17). The majority of the nerve cells were normal. The descending tracts showed degeneration, while the ascending tracts were well preserved.

Granulomas: Each of the granulomas referred to above was composed of large polygonal, round, stellate or irregularly shaped cells (Fig. 12). These had abundant eosinophilic, homogeneous or coarsely granular cytoplasm. Their nuclei were spherical, oval or irregular, stained deeply and contained a moderate amount of coarsely granular chromatin. In some granulomas few, if any, infiltrating cells were seen. In others, lymphocytes, mononuclear leukocytes and occasional eosinophils or plasma cells were distributed among the outer epithelioid cells. Hyperplastic capillaries were often seen at the margins of these lesions or embedded in them. Their plump endothelial cells seemed to be the precursors of the epithelioid cells of the granulomas. No giant cells or any central necrosis of the lesions were encountered. In the gray matter, well preserved nerve cells were frequently found at the margins of the granulomas. Myelin sheaths were deflected at their margins or often passed directly through the granulomas unchanged. Small numbers of axones were similarly affected. There was a moderate astrocytosis at the margins of the lesions in some areas (Fig. 16), and occasionally persisting astrocytes mingled with the outer epithelioid cells.

Right Eye: One portion of the retina (Fig. 19) showed edema of all its layers and distortion of the stratum opticum, ganglionic, and inner molecular layers. The capillaries in this zone had undergone endothelial hyperplasia. Many nerve cells in the ganglionic layer were partially degenerated. The layer of rods and cones was markedly necrotic. The pigmented layer was partially disrupted and the destruction of its cells gave rise to much extracellular pigment. The choroid was congested, showed capillary hyperplasia, and was infiltrated by plasma cells, lymphocytes and eosinophils. The leptomeningeal sheath of the optic nerve showed a similar mild infiltration.

Microorganisms: Parasites (Figs. 20–27) were present in the lesions of the central nervous system and eyes, and occurred in two forms. They were commonly seen as single bodies, ovoid, oval, pyriform or rounded in shape, either free in the tissue or within the cytoplasm of cells. In material fixed in 10 per cent formalin, refixed in Zenker's solution, and embedded and cut in paraffin, in sections 4–5μ in thickness, the majority of the organisms measured 2–3μ in length, and 1.5–2μ in width. More fell below this

range than rose above it. Each of the parasites was distinctly outlined and had a more deeply staining margin. A round, oval or band-like chromatin mass, the largest of which was one-third the size of the corpuscle, was present at or near one pole. Rarely the microorganisms were quite slender and lunate or scimitar-like in shape, and in these, lunate or comma shaped as well as band-like chromatin masses were more frequent. Two chromatin masses were occasionally encountered. One might be smaller and situated at the opposite pole of the cell. More often they were equal in size, symmetrically placed with their long axes parallel, and the parasites containing them probably represented dividing forms. The edges of the chromatin bodies were sharp and usually stained more deeply than their central portions. The cytoplasm at their margins was often lighter staining. No rod-like chromatin body (kinetoplast) was present, nor could a polar capsule or filament be identified. No budding was seen. The staining reactions were similar to those of the microorganism described in our 1st case.[67]

The intracellular parasites were present either singly or in considerable numbers, usually in mononuclear cells, often in epithelioid cells of the granulomas, less frequently in polymorphonuclear leukocytes and rarely in the endothelial cells of capillaries. None was found in nerve cells or eosinophils. The intracellular microorganisms lay in the cytoplasm of the parasitized cell, sometimes within a vacuole. Such cells frequently showed degeneration varying from swelling and vacuolization of the cytoplasm to extrusion of the nucleus, disruption of the cytoplasm and liberation of the microorganisms. Often the parasitized cells were surprisingly well preserved. The extracellular parasites showed varying degrees of pallor and degeneration in the necrotic areas of the parenchyma, but were well preserved elsewhere. In the areas of calcification some of the single calcific granules and a few of the clusters suggested encrusted microorganisms. The shape of the granule and an unstained area corresponding to the chromatin body were the identifying features.

The parasites were also found in compact, round or oval clusters which varied in size from 8 by 8.5μ to 16 by 19.5μ. The organisms in these masses were closely packed, often smaller than the free corpuscles, and on close inspection their individual outlines were

easily discernible in thin sections. In some clusters, however, the cytoplasm seemed to form a continuous syncytial mass, although this was not common. Such compact groups of parasites had the appearance of cysts, but they may simply have represented cells which had lost their nuclei and were completely occupied by microorganisms. Rarely a flattened nucleus was present at the margin of the cluster. At the margins of the cysts a matrix less dense than the cytoplasm of the parasites was present in the spaces between them. An outer membrane appeared to envelop the cluster. This was sharply outlined, refractile, but not doubly contoured, and as was noted in the description of our 1st case, may represent the denser appearing edge of the matrix. The majority of the cysts lay free in the tissue. Cysts were more often encountered in comparatively normal marginal tissue at the edges of the parenchymal lesions, particularly in the retina.

The cysts and individual organisms were never present in normal tissue distant from the lesions. They were found in small numbers in the leptomeningeal exudate, and in great numbers in the parenchymal lesions of the brain and spinal cord. They were occasionally seen in the ventricular exudate and in that of the spinal canal. Only a few were encountered in the choroid plexus, walls of the blood vessels and between ependymal cells. They were seen once within the lumen of a spinal leptomeningeal arteriole.

No other organisms were detected in any of the sections stained by a variety of methods.

Summary of Case

A white male infant, delivered at full term by Cesarean section, became ill at 3 days of age and developed convulsive seizures, disturbances in respiration, and symptoms of involvement of the spinal cord with subarachnoid 'block' in the cervical region. Terminally, irregular reddish brown areas were observed ophthalmoscopically in each macular region. The infant died at the age of 31 days. Autopsy revealed a widespread encephalomyelitis characterized by multiple focal areas of inflammation and necrosis, and disseminated miliary granulomas. There was localized leptomeningitis in relation to the superficial parenchymal areas of inflammation. Cystic degeneration occurred in some of the lesions while others, especially those in the cerebral cortex, showed a dis-

tinct tendency to become calcified. The inflammation and degeneration in the spinal cord resulted in a marked swelling of the lower cervical segments, sufficient to account for the subarachnoid 'block' observed during life. The right eye contained a localized zone of chorioretinitis. A protozoan parasite was present, often in great numbers, in the leptomeningeal and parenchymal exudates, in the granulomas and in the lesions of the choroid and retina.

Discussion

The case reported above is the 5th recorded instance of a new disease entity, a form of granulomatous encephalomyelitis of infants. The clinical history resembles that of our 1st case in the occurrence of symptoms soon after birth, the manifestations of diffuse involvement of the central nervous system, the evidence of focal chorioretinitis, the short course and the fatal outcome. That the 2 cases are instances of a single disease is further indicated by the similar pathological changes: a widespread encephalomyelitis characterized by inflammation, necrosis and miliary granulomas, focal leptomeningitis and localized chorioretinitis. As has been pointed out elsewhere,[67,68] the resemblance of the pathological changes described in 3 infants by Jankû,[21] Torres,[59] and Richter [49] to those in our 1st patient makes it evident that these cases are instances of the same disease.

The lesions in each of the 5 affected infants contain a protozoan parasite showing the same morphological characteristics. In sections the microorganisms are oval, ovoid or pyriform, 2–3μ long and 1–2μ wide, and contain deeply staining chromatin bodies which are usually spherical and polar in position. This microorganism, as seen in our 1st case, was considered to be an Encephalitozoon because of its resemblance to that parasite in sections and because the characteristic lesion that the latter produces in the central nervous system is a miliary granuloma similar to that found in this human disease. Encephalitozoon corresponds in size and shape to the causative parasite of this disease, is frequently intracellular, and occurs regularly in the form of similar cysts. Although Torres [59,60,61] favored the identification of his microorganism as an Encephalitozoon and named it *Encephalitozoon chagasi*, he also entertained the possibility that it might be a Toxoplasma. Later, Levaditi,[26] in discussing the identity of

the parasites in the cases of Jankû and Torres, pointed out their similarity to Encephalitozoon and to *Toxoplasma cuniculi*. He referred to resemblances in the pathology of these cases to experimental toxoplasmic infection in rabbits, and favored the identification of the microorganisms in the human cases with Toxoplasma. It was noted in our first report that the lesions in the central nervous system show a resemblance to those in experimental toxoplasmosis in the rabbit: diffuse necrotizing and inflammatory lesions of the cortex and basal ganglia at times associated with miliary granulomas which do not become necrotic centrally and which are disseminated widely throughout the brain and spinal cord. This was discounted, however, for two reasons: (1) the microorganism of the human disease, as seen in sections, did not have the morphological characteristics commonly described for Toxoplasma — lunate shape, larger size, 4–6μ by 2–3μ, and central chromatin body; and (2) since the human infection was not transmitted to animals, an experimental infection produced by it could not be directly compared with experimental toxoplasmosis. During a restudy [68] of Richter's case in which a protozoon similar to that in our 1st case was identified, an opportunity arose to make some observations on the morphology and biological characteristics of a strain of Toxoplasma recovered from a guinea pig at the Rockefeller Institute. It was found that in sections of lesions of the brain and other organs in the rabbit and mouse, this Toxoplasma was almost identical in appearance with the parasite in our 1st case and in Richter's case. In smears, however, it had the more commonly described appearance of Toxoplasma given above. It became clear that apparent morphological differences between Toxoplasma and Encephalitozoon were insufficient to distinguish between them in sections and certainly could not serve as a basis for identifying an unknown parasite as one or the other. In retrospect the staining properties of the microorganisms might have furnished a minor clue to the identity of the protozoon of the human disease. It is stained easily with all the common stains and this is true of Toxoplasma of animal origin. Encephalitozoon, on the other hand, is stained by the carbol fuchsin stain and is less readily brought out by other common stains. Further, some features of the pathological lesions in the human disease, as noted above, are more like those

encountered in experimental toxoplasmosis in the rabbit than spontaneous Encephalitozoon infection in that animal. The granulomas in the central nervous system in Encephalitozoon infection often show central necrosis, while in this human disease and animal toxoplasmosis they do not. No diffuse inflammatory and necrotizing lesions are present in the brain in Encephalitozoon infection, whereas they are prominent in the human disease and occur in experimental toxoplasmosis. Spontaneous Encephalitozoon * infection is chronic, and in the majority of instances non-lethal, while the human disease and experimental toxoplasmosis, as a rule, are subacute and fatal. In the 1 case of the human disease in which other organs were involved, the heart showed lesions and the kidneys did not. This is more like toxoplasmosis than Encephalitozoon infection. Some of these points were discussed in the report of new observations in Richter's case, and it was pointed out there that the possibility that the human infection was toxoplasmosis rather than Encephalitozoon infection would have to be seriously considered. It was obvious, however, that until the human infection could be transmitted to animals and the microorganism and the experimental infection produced by it studied and compared with toxoplasmosis, no decision could be made.

The transmission of the infection from the infant (present case) to animals and the experimental studies [69] which followed yielded definite evidence that the causative microorganism in this case is a Toxoplasma. (1) The morphology of the microorganism isolated from the human case corresponded to that of Toxoplasma of animal origin. (2) The course of the disease and the lesions produced in the animals inoculated with it were similar to those noted in the same species by inoculation of a Toxoplasma of animal origin. (3) The susceptibility of the rabbit, mouse, guinea pig and chick to this microorganism corresponded to the wide host range of Toxoplasma of animal origin. (4) Convincing evidence

* The meager knowledge of Encephalitozoon is due to the fact that so few have been able to transmit the infection experimentally (and then with equivocal results [27]), and that it has not been possible to cultivate the microorganism. The resemblances between it and Toxoplasma make one wonder whether there may not be some close relationship between the two microorganisms. Our failure to transmit an Encephalitozoon infection has prevented us from directly comparing the biological characteristics of this parasite with those of Toxoplasma. It is remarkable that others who have worked with one or both of these organisms have not troubled to make any exact and clarifying comparison between them.

of the nature of the microorganism was obtained by cross-immunity experiments. Rabbits and mice immune to the human strain proved to be immune to the Rockefeller Institute guinea pig strain of Toxoplasma and *vice versa*. This experimental material will be described in detail in a forthcoming report. Although experimental evidence is lacking to establish the identity of the protozoa in the other 4 cases (our Case 1, and those of Jankû, Torres and Richter), their morphological resemblance to this proved Toxoplasma and the similarity of the lesions produced make it extremely probable that they, too, are Toxoplasmata. The disease represented by these 5 cases might, therefore, be designated toxoplasmic encephalomyelitis and the causative microorganism, *Toxoplasma hominis*.

Three cases of obscure human infections which have at times been cited as possible instances of toxoplasmosis do not withstand critical analysis. The 1st case was reported by Castellani [10] (1914) from Ceylon in a boy of 14 who had a prolonged fever, splenomegaly and severe anemia, and was markedly emaciated at death. The organs were described as normal grossly except for the spleen which was greatly enlarged. The nervous system was apparently not examined. No histological examination was reported. Smears of the blood and spleen revealed bodies that Castellani decided were Toxoplasmata and named *Toxoplasma pyrogenes*. There were two types, the larger of which measured 7–12μ in maximum diameter. They were rounded or pear shaped and contained several large masses of chromatin. The smaller measured 2.5–6μ in maximum diameter, were round, oval or crescentic in shape, and had one large rounded mass of chromatin at one pole or centrally placed. Wenyon [65] in discussing this case voiced a justifiable doubt as to the nature of the structures described. The larger forms he believed are portions of degenerated cells and the smaller forms probably vegetable organisms, like yeasts. The lack of any description of lesions in the organs which might be compared with those in animal toxoplasmosis renders any decision as to whether this was a toxoplasma infection or not even more difficult.

Fedorovitch [16] (1916) described a case of chronic fever in a boy of 10 years from the Black Sea district. This child also had anemia and a markedly enlarged spleen. Blood smears revealed

an organism which the author considered to be very much like the bodies described by Castellani. These were not present in material from a puncture of the spleen. The fate of the patient is not known and there is, therefore, no clue as to what pathological lesions may have been present. Wenyon [65] was of the opinion that the bodies were vegetable organisms like large cocci or yeasts.

Chalmers and Kamar [11] (1920) observed soldiers in the Sudan with chronic fever, headache, slight cough and diarrhea, and terminal severe anemia and gingivitis. The pathological lesions in an autopsy performed on 1 individual were not recorded except for a photograph of a splenic film. This illustrates bodies which the authors do not describe but state are similar to those Castellani considered to be Toxoplasmata. Wenyon [65] believed these bodies to have been altered Leishmania.

It is clearly impossible to determine whether or not these are cases of human toxoplasmosis. The pathological lesions are not described so that a comparison cannot be made with the lesions in animal toxoplasmosis, and transmission to animals was not attempted for the purpose of identifying the organisms. Although the morphology of some of the single bodies may suggest Toxoplasma, cysts are not described and some of the structures illustrated are quite unlike Toxoplasma.

That there may be forms of human toxoplasmosis other than granulomatous encephalomyelitis of infants is possible. One cannot, however, accept these 3 cases as instances of another type of toxoplasmosis in the face of the inadequacy of the data concerning them.

From a review of the 5 cases of toxoplasmic encephalomyelitis, the disease is found to have the following characteristics:

Clinical Features: Although the records are not always complete, the clinical data in this series of patients are sufficiently alike to furnish at least the outlines of a syndrome (Table I). The patients were all infants, 4 of whom died before the age of 2 months. The youngest of these was 2 days of age and the oldest 7 weeks, the duration of the illness having varied from 2 to 28 days. The age at death in the 5th case, that of Jankû, was not clear from the record, but appears to have been the 11th or 16th month, and the duration of the illness was not exactly stated, but

TABLE I

Summary of Clinical Data in Five Cases of Toxoplasmic Encephalomyelitis

Case	Location	Sex	Age at death	Duration of illness	Symptoms and signs	Ophthalmoscopic examination	Spinal fluid
Authors' 1st case J. S.[57]	New York City	F	30 days	28 days	Convulsions, diarrhea, vomiting, labile body temperature, slight enlargement of head (?), disturbances in respiration	Yellowish white focal area of chorioretinitis, bilateral	Xanthochromia, high protein content, pleocytosis (largely mononuclears), 2 eosinophils in smears
Jankû [21]	Prague, Czechoslovakia	M	11–16 mos. (?)	8–11 mos. (?)	Marked hydrocephalus, blindness, convulsions, anorexia, vomiting	Yellowish white focal areas of chorioretinitis bordered by pigment in macular region bilaterally	
Torres [59, 60, 61]	Rio de Janeiro	F	2 days	2 days (?)	Convulsions		
Richter [49]	Chicago, Ill.	F	7 weeks	1 week (?)	Convulsions, opisthotonos, fever, "cold"		Xanthochromia, high protein content, pleocytosis (mild, cell type not stated)
Authors' 2nd case C. D.	New York City	M	31 days	28 days	Convulsions, vomiting, sensory and motor signs of cervical cord lesions with subarachnoid block, labile body temperature, disturbances in respiration	Reddish brown areas of chorioretinitis in macular regions bilaterally	Cloudy xanthochromic fluid, high protein content, clotted spontaneously (no microscopic examination)

seems to have been at least 8 months. Two of the infants were males and 3 were females.* All suffered convulsions at some time or other during their illness. Two had enlargement of the head due to internal hydrocephalus. In 3 of the infants there was a labile body temperature with occasional mild fever or subnormal temperature. In 3, vomiting occurred at intervals. The spinal fluid from 3 of the patients was examined and showed xanthochromia and a high protein content, and in 2 there was pleocytosis. The spinal fluid smear in 1 case revealed occasional eosinophils in addition to mononuclear cells. In this case parasites were identified in paraffin sections of precipitated ventricular fluid. An ophthalmoscopic examination was made of 3 of the infants and in all a focal chorioretinal lesion was found in each eye. The disease, then, appears to affect young infants, produces manifestations of involvement of the nervous system, may give rise to ophthalmoscopically identifiable focal lesions in the eyegrounds, and terminates fatally after an acute or subacute course.

Gross Pathology: The pathological picture of the disease is distinctive. The central nervous system is the site of the most severe and widespread changes. Macroscopically depressed, softened, yellowish focal lesions varying in size from a few millimeters to 3 cm. in diameter are seen on the surface of the cerebrum. In these areas the convolutional markings are obliterated and the overlying leptomeninges are thickened and rendered opaque by a grayish yellow exudate. There may be swelling of the gyri at the margins of these lesions while the intervening gyri and their overlying leptomeninges appear normal, except for a varying amount of congestion. The spinal cord may show similar focal areas of softening and collapse, or considerable localized swelling with an accompanying leptomeningeal reaction limited to such regions.

The cerebral lesions are often confined to the cortex but may involve the subcortical white matter and centrum ovale and reach the wall of the lateral ventricle. They are well demarcated and range in size from minute nodules to patches several cm. in diameter. The center of such lesions is yellowish, soft, and sometimes cheesy, while the edges may be grayish and glassy. In some

* Torres' patient, whose sex is not given in the author's report, was a female (personal communication).

of the cerebral foci gritty material may be palpable. Others may contain cysts which occasionally reach a diameter of several cm. Focal changes similar to those in the cortex and white matter are encountered in the corpus striatum, thalamus and hypothalamus, and may occur in the midbrain, pons and medulla as well. The cerebellum shows minor lesions in 1 case. There may be a varying degree of enlargement of the lateral and third ventricles due in part to stenosis of the aqueduct of Sylvius, and partly to degeneration of the ventricular walls. The latter may be a prominent gross lesion and is seen as a well demarcated broad band of yellowish, soft, friable periventricular necrotic tissue. It is associated with extensive denudation of the ependymal lining. Coarse ependymal granulations may be present in the better preserved portions of the ventricular walls. The lesions in the spinal cord may also vary from minute yellow foci to large confluent softenings involving the entire diameter of the cord in a number of segments, obliterating all the normal architectural markings, and leaving only yellow pultaceous material.

A complete autopsy was performed in 3 of the 5 cases: Torres', Richter's, and our 1st case. The last 2 cases showed no pertinent gross changes in any of the viscera, bones or muscles. Torres gave no gross description of his material except for a brief reference to the brain, although microscopic changes were referred to in some of the other organs, as will be noted below.

Microscopic Examination: The histological changes are characteristic. There is a widely disseminated encephalomyelitis in which the severest lesions are associated with necrosis. There is a total destruction of neural and neuroglial elements in the areas of degeneration leaving amorphous débris. In the marginal necrotic material, lipoid laden phagocytes and often polymorphonuclear leukocytes are present. There is a bordering zone of reaction containing hyperplastic capillaries, plasma cells, lymphocytes, mononuclear leukocytes, neutrophils and eosinophils. Fibroblasts derived from hyperplastic capillaries and from the contiguous leptomeninges often mingle with these cells, and in places where the capillary proliferation is intense, give rise to a rich granulation tissue in which many collagen and reticulum fibers may occur. Beyond the zone of cellular infiltration there is a moderate astrocytosis as well as hypertrophy and multiplication of microglial cells

with production of rod cells and transitional phagocyte forms. Cavities may occur in the necrotic zones and contain persisting hyperplastic capillaries and varying numbers of lipoid laden phagocytes. Degenerated tissue may become partially or completely calcified and give rise to broad bands of calcific material in the cortex or periventricular zone. Incrustation of nerve cells and other elements occurs in these areas.

Miliary granulomas constitute a prominent feature of the pathological process in the nervous system. They are found scattered through the brain and spinal cord and often cluster near the focal necrotic and inflammatory lesions. Each granuloma is composed of a circumscribed group of closely approximated epithelioid cells, evidently of capillary endothelial origin. Mingled with these, usually in the outer portion of the granuloma, are varying numbers of plasma cells, lymphocytes, mononuclear leukocytes and eosinophils.

The leptomeninges overlying the parenchymal lesions show a moderate hyperplasia of their cells with the production of fibroblasts, and they are infiltrated by cells similar to those seen in the parenchymal exudate. Here again plasma cells and eosinophils are a characteristic feature of the inflammation. Often the exudate is continuous from pia-arachnoid to parenchyma, obliterating the line of demarcation between them. Many of the leptomeningeal capillaries in these areas of inflammation and some of the larger vessels show endothelial hyperplasia. There is no occlusion of leptomeningeal or parenchymal vessels to account for the areas of necrosis, although secondary thrombosis is encountered. Infiltration of the connective tissue core of the choroid tufts and tela choroidea may be present. The walls of the lateral and third ventricles are frequently denuded of ependyma and may be covered by exudate. Where the ependyma is intact there are at times numerous ependymal granulations and subependymal gliosis. This may lead to stenosis of the aqueduct of Sylvius.

The focal lesions in the eyes consist of patches of severe chorioretinitis. The involved retina is swollen and shows varying degrees of degeneration. Total necrosis may occur in some areas and involve many of the layers. The internal limiting membrane is at times disrupted. At the margins of completely necrotic areas the cells of the ganglionic layer are degenerated or disappear.

The deeper layers, although edematous, are better preserved except for the layer of rods and cones and the pigmented layer, which are often necrotic and disrupted. Free pigment granules as well as dislocated pigmented cells are often extruded into the internal retinal layers. There may be scattered plasma cells and lymphocytes in the necrotic areas with moderate infiltration by similar cells as well as occasional eosinophils, neutrophils, mononuclear leukocytes and lipoid laden phagocytes in the marginal zone. In the more severely affected layers of the retina there is an increase in glial tissue and formation of granulation tissue. The latter may invade the posterior chamber. An exudate similar to that described above may be present on the internal surface of the retina. The choroid is congested, hyperplastic, and infiltrated chiefly by plasma cells and lymphocytes. A mild similar infiltration may occur in the sheath of the optic nerve. The sclera remains unchanged.

Inflammatory lesions may occur in other organs, as reported in Torres' case. This author mentions the presence of "disseminated foci of myositis" in the striated muscles, and "acute diffuse myocarditis" in which the predominant cells are mononuclear in type with an admixture of numerous eosinophils. Complete autopsies in 2 other cases revealed no lesions in the other organs except for a terminal bronchopneumonia in 1.

Microorganisms: A comparison of the morphology of the parasites in the 5 cases referred to in this paper makes it seem probable that we are dealing with the same organism, or at least closely related forms in each instance. The parasites seen in sections of fixed tissue, using any of the common stains, are usually ovoid corpuscles with a spherical polar chromatin body. They may be oval, pyriform, rounded or occasionally lunate, and the chromatin body may rarely be centrally placed and band-like. They also occur less frequently in clusters which have been described as cysts. The cysts are composed of varying numbers of closely packed organisms which for the most part are clearly outlined but sometimes seem to form a syncytial mass. A cyst wall appears to be present but this may be the margin of a matrix in which the parasites are embedded. The apparent cyst wall, on the other hand, may be the remains of the cytoplasm of a parasitized cell.

Parasites are present in small numbers in the leptomeningeal exudate. Large numbers are found in the inflammatory tissue at the margins of the necrotic parenchymal lesions, and numerous degenerated forms are present in the central débris. Moderate numbers of parasites occur in the granulomas. They are abundant in the focal chorioretinal lesions. In the 1 case (Torres) in which other organs were involved, namely the heart and striated muscles, parasites were seen in the lesions and microorganisms were also described in the subcutaneous tissue.

The parasites may be free or intracellular. The intracellular forms occur in large mononuclear cells and epithelioid cells of granulomas, less frequently in polymorphonuclear leukocytes, and rarely in the endothelial cells of the capillary walls, eosinophils or nerve cells. It is probable that they occur in other cells such as ependymal, choroidal and leptomeningeal elements, but as yet they have not been found parasitizing such cells.

Some minor differences in the size and morphology of the parasites in the 5 cases do not appear to be significant. The majority of the single organisms as described above in paraffin sections of formalin and Zenker-fixed tissue measure $2–3\mu$ in length and $1.5–2\mu$ in width. Torres finds the length of the individual organisms to be slightly greater (3.5μ), some of those in the muscles reaching a length of 6μ. In Richter's material the parasites measured $2–2.5\mu$ in length and $1.5–2\mu$ in width, figures slightly smaller than those given in our cases. All of these measurements are average figures and do not indicate the overlapping which occurs when the extremes are included. In any case the differences in fixation and in preparation of the tissues may well account for the slight dissimilarities noted. The variation in the size of the cysts, particularly the larger average sizes given by Jankû, probably depend on similar factors and do not appear to be important. The apparent differences between the appearance of the microorganisms in these human cases and that of Toxoplasma, as generally described in the literature, would seem to depend on differences in histological technic. As has been demonstrated, Toxoplasmata from an animal source, when seen in sections of embedded tissue, are exactly like those in the human cases, while the microorganisms in smears assume the larger lunate form commonly described for Toxoplasma.

Mode and Source of Infection: In considering the mode of infection in 3 of these cases, in a previous paper it was pointed out that the onset of the clinical manifestations of the disease soon after birth in 2 cases, and the advanced nature of the lesions, suggested that the infection had begun during intrauterine life. This is supported by the evidence derived from the case reported here in which symptoms began on the 3rd day of life. Although blindness was first noted in Jankû's patient at 3 months of age, Jankû considered the infection congenital since a maldevelopment of one eye was present which he thought ascribable to infection during fetal life. In Richter's case the infant was said to have become ill at the age of 6 weeks, but the incompleteness of the clinical data permits a doubt as to whether the onset was not at an earlier age. It was Richter's opinion that the infection was congenital in view of the apparently advanced age of some of the pathological changes. As in the case described here, there was marked calcification of many of the focal lesions.

That the mothers of the 5 infants were apparently in good health does not preclude the possibility of the infection having occurred *in utero*. It is conceivable that they were carriers of a clinically inapparent Toxoplasma infection to which the fetus was more susceptible. Toxoplasma have often been found in animals which showed no clinical symptoms, although the virulence of the parasites has been demonstrated by their ability to produce active infection when inoculated into other animals. If the infection was transmitted *in utero*, it might be expected that the placenta would show specific pathological changes. Unfortunately the placentas were not examined in any of these cases. It is to be hoped that in the future such an examination will be made. How the mothers might have been infected, or the children, if they acquired the infection independently after birth, is not clear.

As mentioned above, Toxoplasma has a widespread geographic distribution, and pathogenicity for a wide variety of hosts, but its natural mode of transmission is as yet unknown. Experimentally toxoplasmosis has been successfully transmitted by inoculation of infected material by many routes.[28] Infection has followed cannibalization [51] of animals recently dead of the disease. Instillation of infected peritoneal fluid into various cavities lined by mucous

membrane, including the vagina and conjunctival sac, has resulted in a generalized infection in some instances.[36]

As has been noted previously, Jankû, apparently unaware of the occurrence of spontaneous Toxoplasma infection in rabbits, alluded to the fact that the mother of the infant he described had been resident during her pregnancy on a farm where rabbits were raised, and that she had eaten much rabbit meat during the period of gestation. In Torres' and Richter's reports no reference was made to contact of the mother with animals. It is of interest in relation to Torres' case that Brazilian rabbits and birds are known to be infected with Toxoplasma. In our 1st case the home was so overrun with mice that the mother changed her residence in the midst of her pregnancy. Although spontaneous toxoplasmosis has not been described in mice in North America, its occurrence in that species is known in other parts of the world. There was also a canary in the home during the pregnancy in our 1st case. These birds have been found to be subject to toxoplasma infection. In the case reported here there was no history of contact with animals.

In the 2 instances in which there was contact of the mother with animal species which may harbor Toxoplasma there is a possibility that transmission occurred by ingestion of infected material, *i.e.*, rabbit meat in Jankû's case, and food contaminated by mouse excreta in our 1st case. The existence of an insect or other vector as an intermediate host between a possible animal carrier and man cannot be excluded. The portal of entry of Toxoplasma in the mother and its localization prior to infection of the infant remain undetermined in the light of our present knowledge. In view of the report of experimental vaginal infection with Toxoplasma one must consider the possibility of vaginal infection in the mothers with direct extension of the infection to the uterine contents. This hypothesis seems unlikely.

The possibility that a maternal vaginal infection was transmitted to the infant in its passage through the birth canal is excluded in our 2nd case in view of the fact that delivery was by Cesarean section, and by analogy is unlikely in the other instances.

If the infection be congenital it is probable that it occurs late in fetal life since developmental anomalies were absent except in 1 instance (malformation of the eye in Jankû's case). It is clear that

no absolute evidence exists that the infants became infected before birth. This problem has yet to be attacked experimentally in animals and evidence sought in future human cases.

Pathogenesis: The description of the probable mode of spread of the infection, the susceptibility of various organs and tissues, and the development of the lesions, as summarized in the discussion of our 1st case, apply to the case reported here as well. No new facts as to the pathogenesis of the disease have been added by a study of the pathological material from the present case. Study of the characteristics of the infection in animals has afforded an opportunity to test these hypotheses of the pathogenesis of the human disease and they will be discussed in the presentation of the experimental material.

Diagnosis: Although it may be premature to attempt to establish criteria for the clinical diagnosis of toxoplasmic encephalomyelitis, it is useful to summarize the facts available to date which may lead to a recognition of the disease during life. Young infants of either sex become ill soon after birth. They are subject to repeated convulsions and may show symptoms and signs of widespread involvement of the central nervous system. Ophthalmoscopically, focal areas of chorioretinitis are seen in each eye. These appear as yellowish white or brownish red, round or oval patches which may show irregular black, often marginal pigmentation. The intense calcification of the cerebral lesions in some of these cases suggests that stereoroentgenograms of the skull may reveal the presence of such changes. The cerebrospinal fluid is xanthochromic, contains a large amount of protein, and shows a pleocytosis chiefly of round cells. Eosinophils have been found in ventricular fluid. Toxoplasmata have been identified in fluid from the same source and it seems probable that intracerebral inoculation of such fluid into rabbits or mice will demonstrate the presence of the parasite by the production of a specific infection.

Summary and Conclusions

1. A 5th case of a new disease, granulomatous encephalomyelitis due to a protozoon, occurring in an infant is described.

2. The clinical and pathological observations in this case are shown to be similar to those in the first 4 cases. This group forms a distinct disease entity. The disease affects young infants, pro-

duces manifestations of generalized involvement of the nervous system, may give rise to ophthalmoscopically identifiable focal lesions in the eyegrounds, and terminates fatally after an acute or subacute course. The spinal fluid shows xanthochromia, a high protein content and pleocytosis. The central nervous system is the site of focal inflammatory and degenerative lesions which are widely disseminated. Similar changes are found in the retina and choroid. Miliary granulomas are a characteristic feature of the process in the nervous system. Focal inflammatory lesions were present in the heart and striated muscle in 1 case.

3. A protozoan parasite is present in all the lesions.

4. The results of transmission of the infection to animals from the case reported here indicate that the causative protozoon is a Toxoplasma. The designation *Toxoplasma hominis* is suggested for the microorganism and the term toxoplasmic encephalomyelitis for the disease.

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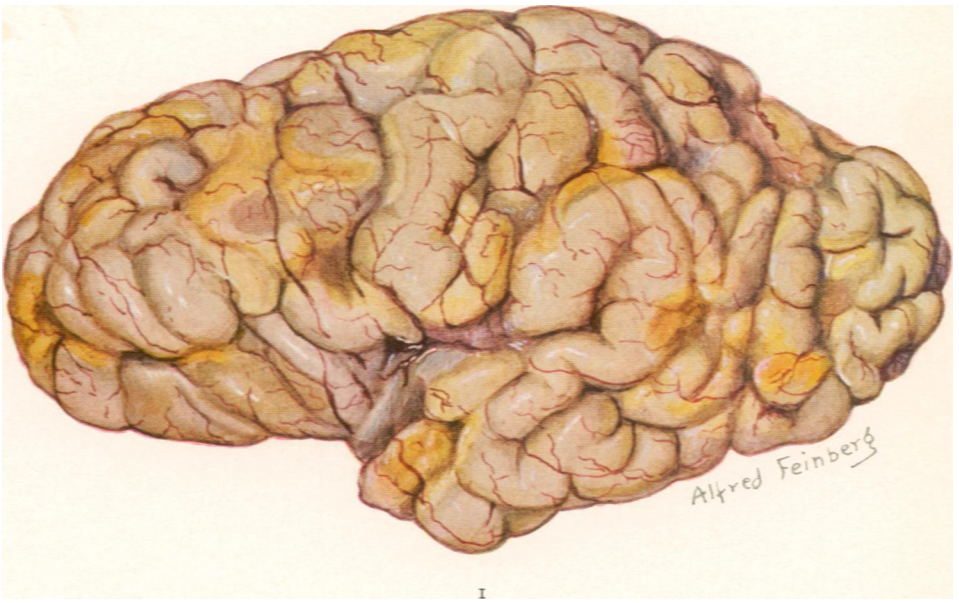
DESCRIPTION OF PLATES

PLATE 99

FIG. 1. Left cerebral hemisphere showing depressed, yellowish and softened cortical lesions.



I

Wolf, Cowen and Paige Toxoplasmic Encephalomyelitis

PLATE 100

FIG. 2. Left cerebral hemisphere, coronal section. Focal necrotizing lesions are present in the cortex and in the subcortical white matter.

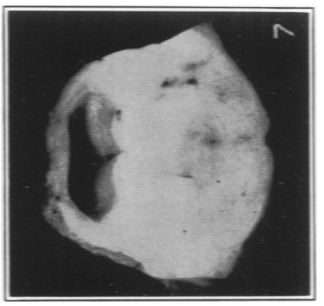
FIG. 3. Cervical spinal cord showing swelling of cord and obliteration of normal architectural markings.

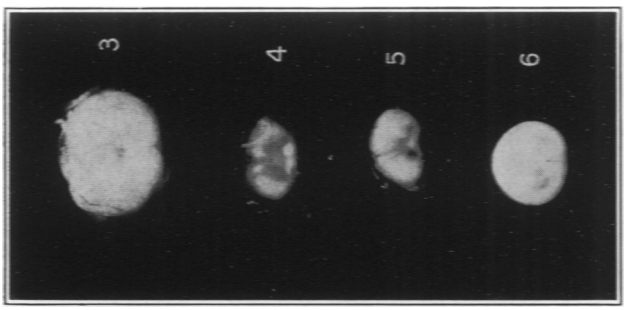
FIG. 4. Upper thoracic spinal cord showing discoloration with obscuration of normal markings.

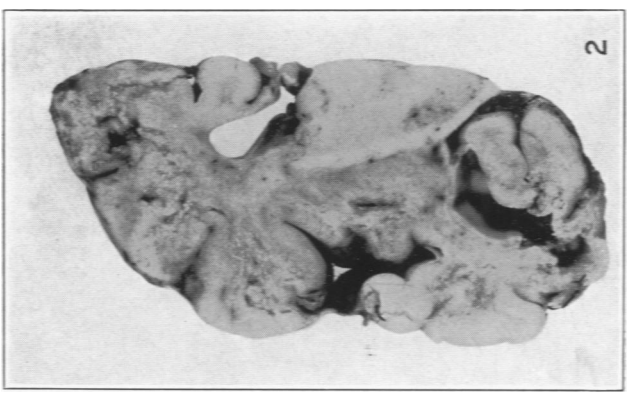
FIG. 5. Lower thoracic spinal cord showing changes similar to those present in Fig. 4.

FIG. 6. Lumbar spinal cord showing obliteration of posterior columns and horns by grayish tissue.

FIG. 7. Pons. A sharply demarcated focal lesion is present at the junction of the tegmentum and the reticular zone.





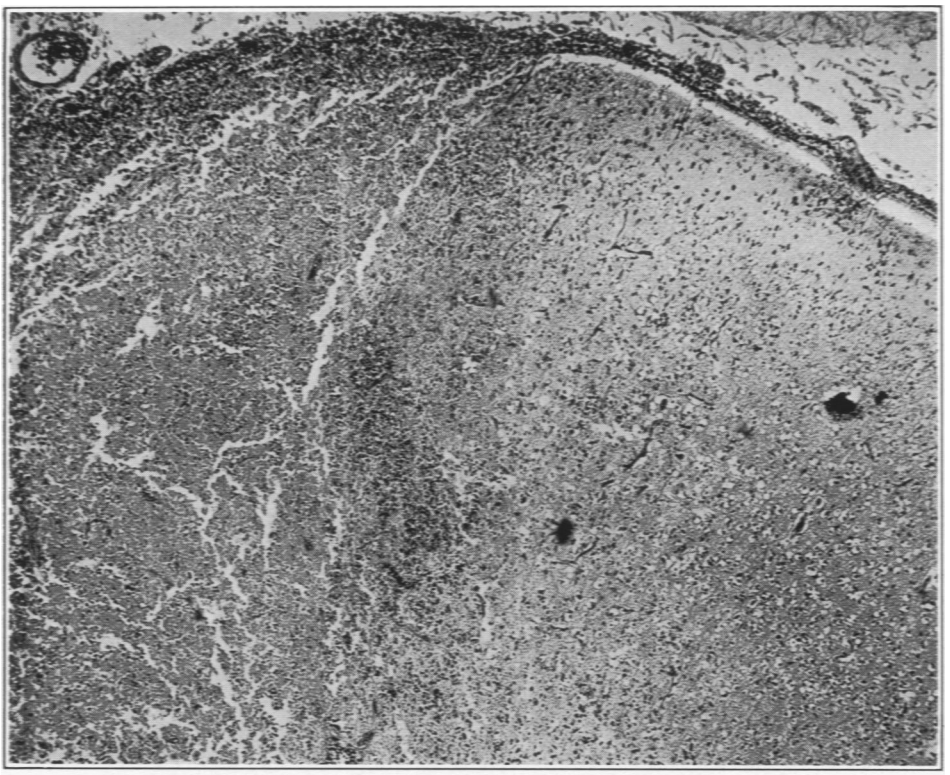


Wolf. Cowen and Paige Toxoplasmic Encephalomyelitis

PLATE 101

FIG. 8. Cerebral cortex. A focal inflammatory and necrotizing lesion is present in the cortex. Note the comparatively sharp margin and accompanying focal leptomeningitis. The adjacent cortex on the right is relatively well preserved. Hematoxylin-eosin stain. × 80.

FIG. 9. Cerebral cortex. Note the marked calcification of a necrotizing cortical lesion. Hematoxylin-eosin stain. × 80.



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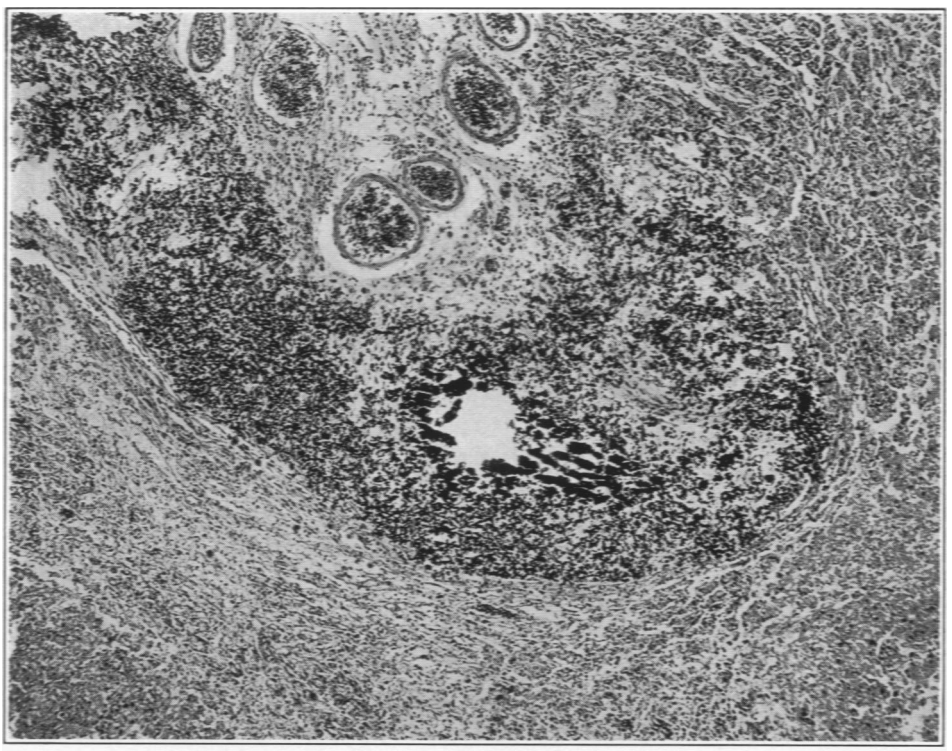

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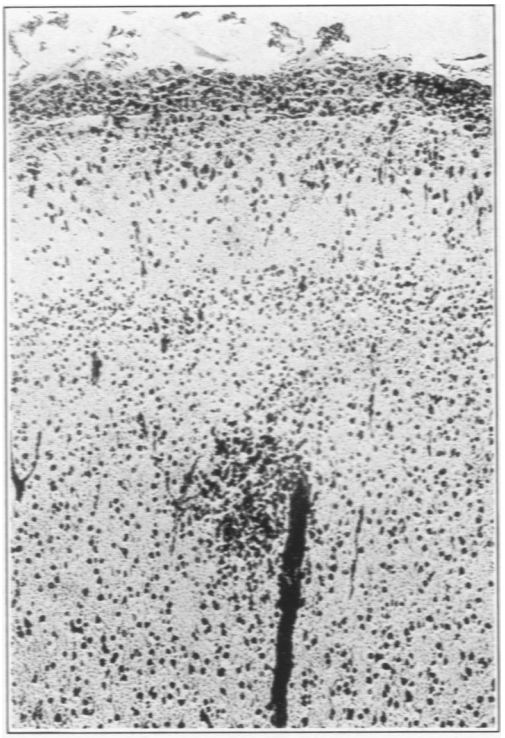
PLATE 102

FIG. 10. Cerebral cortex. A granuloma is present in the third cortical layer adjacent to a blood vessel. Focal leptomeningitis. Hematoxylin-eosin stain. × 150.

FIG. 11. Cerebral leptomeninges. Focal leptomeningitis. Lymphocytes, plasma cells and large mononuclear leukocytes are present in the exudate. Lipoid laden phagocytes, lymphocytes and plasma cells are seen in the underlying degenerated cortex. Hematoxylin-eosin stain. × 300.

FIG. 12. Lumbar spinal cord. White matter showing a granuloma composed of epithelioid cells and a few lymphocytes. Hematoxylin-eosin stain. × 300.

FIG. 13. Wall of the lateral ventricle. Inflammation, necrosis and loss of the ependymal lining are present. Hematoxylin-eosin stain. × 150.



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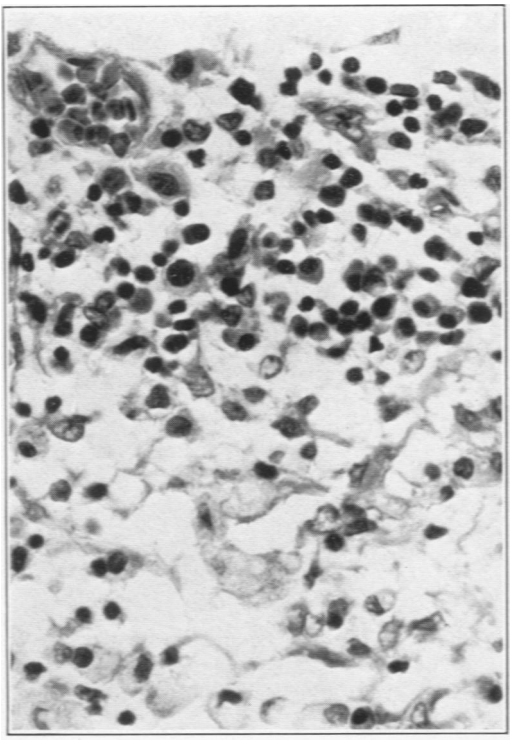

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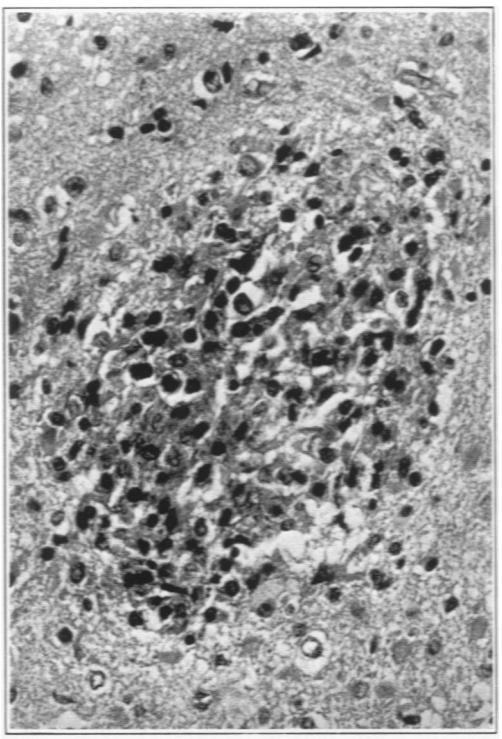

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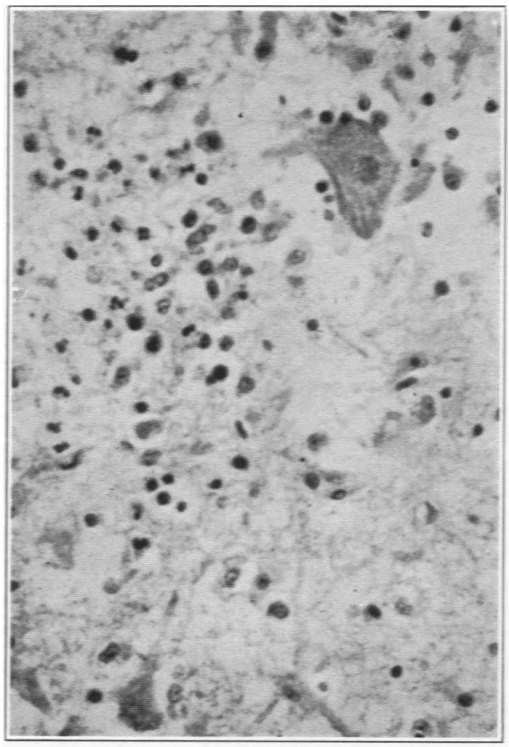
PLATE 103

FIG. 14. Cervical cord. Section of anterior horn showing an acute inflammatory and necrotizing lesion with infiltration by polymorphonuclear leukocytes, lymphocytes and large mononuclear cells. Hematoxylin-eosin stain. × 250.

FIG. 15. Cerebral cortex. Calcification is seen in a degenerated focal lesion in the cortex. Note the encrusted nerve cells. Hematoxylin-eosin stain. × 200.

FIG. 16. Granuloma with surrounding astrocytosis. The epithelioid cells in the granuloma are obviously unrelated to astrocytes. Cajal's gold sublimate stain. × 300.

FIG. 17. Lumbar spinal cord. Miliary granulomas in the lateral and the anterior white columns. Giemsa's stain. × 150.



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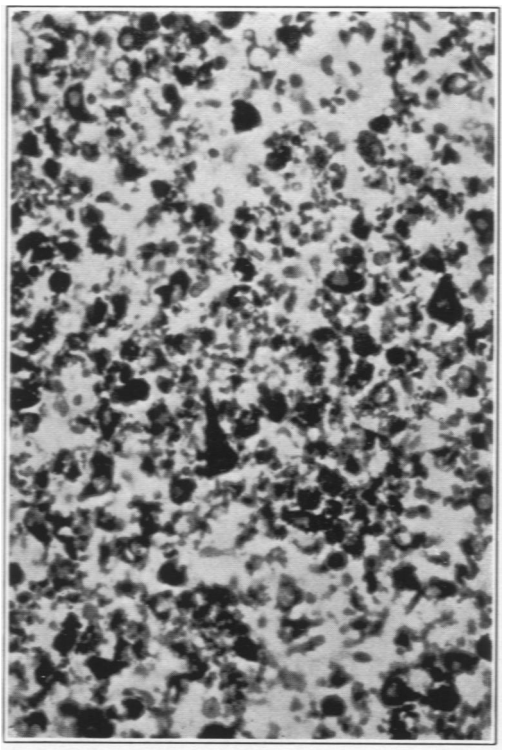

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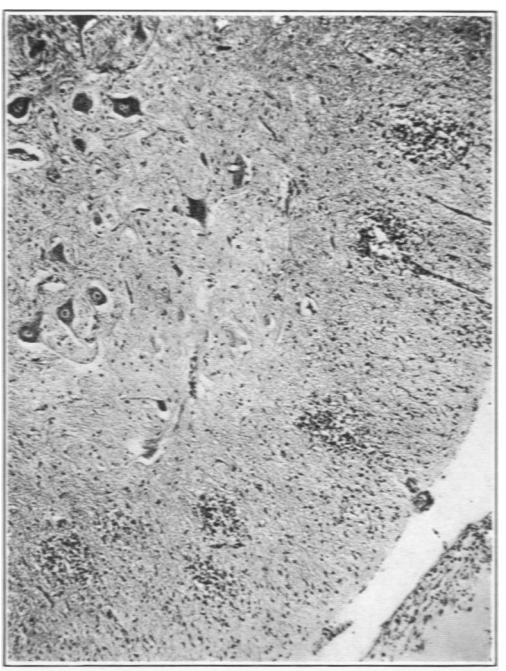

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PLATE 104

FIG. 18. Lumbar cord. Note the intense necrosis of the posterior and portions of the lateral columns, the posterior and parts of the anterior horns and the central gray matter and commissures. Pal-Weigert stain. × 20.

FIG. 19. Retina of the right eye. Note the edema and degeneration of the retina and infiltration of the choroid. Hematoxylin-eosin stain. × 40.

FIGS. 20–27. Show parasites in lesions in the cervical cord and pons. × 1050.

FIG. 20. Single oval intracellular parasite with polar chromatin body. Phloxine-hematoxylin stain.

FIG. 21. Two free ovoid parasites. Hematoxylin-eosin stain.

FIG. 22. Four free oval parasites. Hematoxylin-eosin stain.

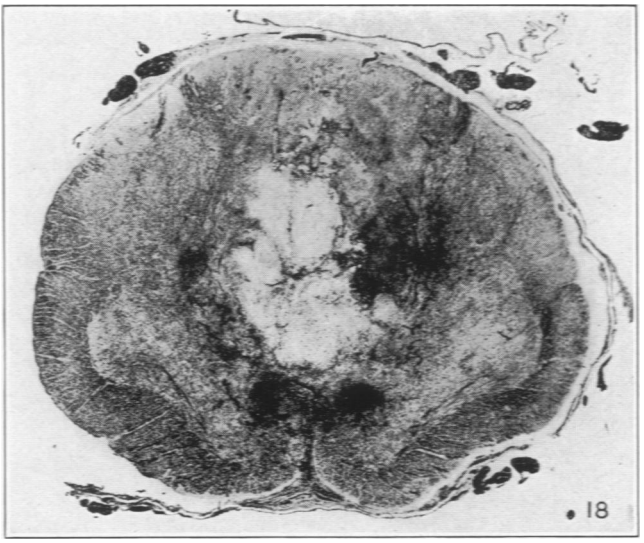
FIG. 23. Three intracellular round and oval parasites. Hematoxylin-eosin stain.

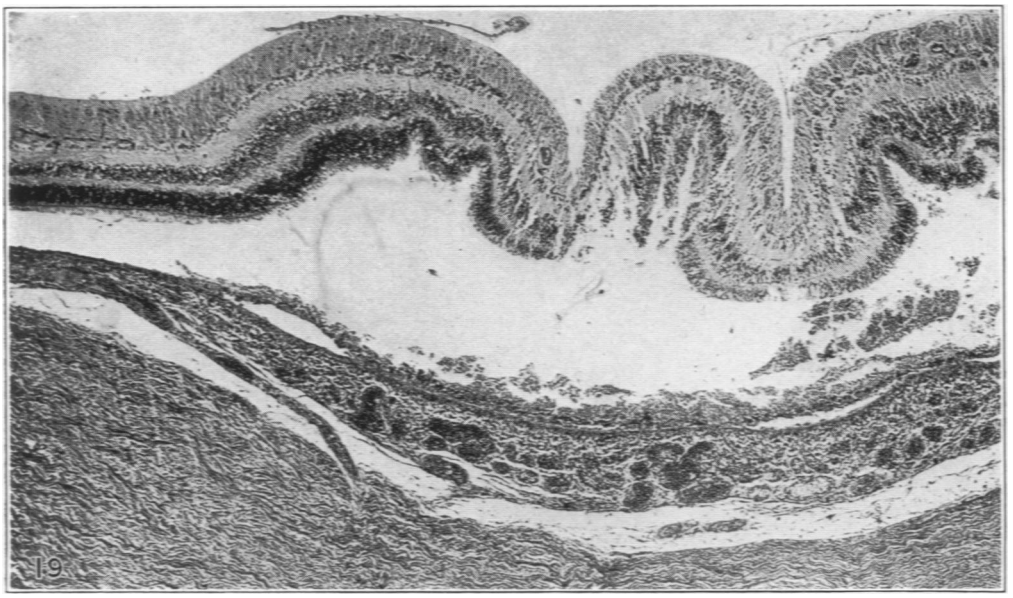
FIG. 24. One round intracellular parasite showing division of its chromatin body. Hematoxylin-eosin stain.

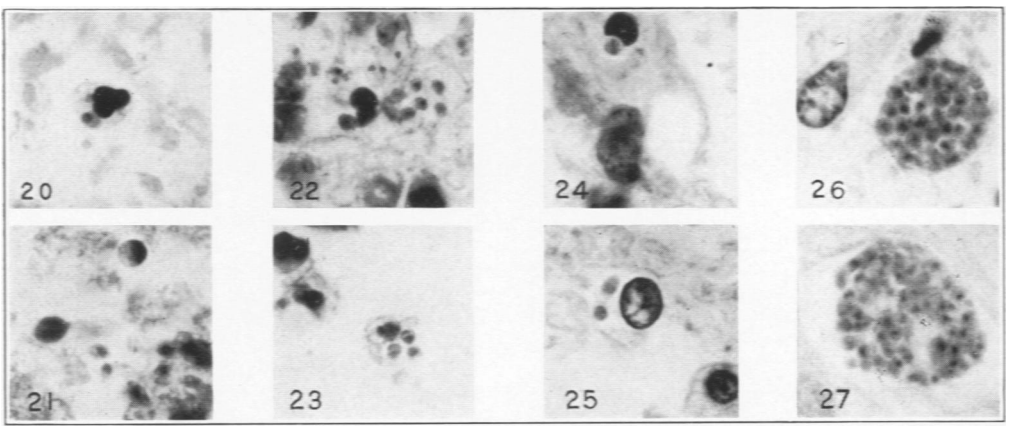
FIG. 25. Two intracellular parasites, one binucleated, apparently dividing. Hematoxylin-eosin stain.

FIG. 26. Parasitic cyst. Hematoxylin-eosin stain.

FIG. 27. Parasitic cyst rupturing and liberating parasites. Hematoxylin-eosin stain.







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