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Cerebral Form of Generalized Cytomegaly of Early Infancy

Light and Electron Microscopic Findings

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Summary. A 9-day-old baby boy developed Escherichia coli meningitis and died 10 weeks later despite antibiotic and corticosteroid therapy. Generalized cytomegaly was found at autopsy with unusually severe cerebrospinal involvement. The CNS showed two different types of findings: acute inflammatory changes with innumerable inclusion-bearing giant cells in the circumlittoral tissues, and burned-out necrotic lesions irregularly scattered in the cerebrum. The electron microscopic demonstration of cytomegalovirus (CMV) particles in the nucleus and cytoplasm of typical owl-eyed cells lent confirmatory support to the histologic diagnosis of cytomegaly. The case was thought to represent postnatal CMV disease arising in the course of Escher. coli meningitis. The preceding bacterial meningitis may have precipitated and/or promoted the spread of virus in the cerebrospinal fluid and the subsequent viral colonization of the littoral tissue of the CNS. The intrathecal corticosteroid administration patently failed to stop the cytomegalic infection and possibly contributed to the luxuriant viral replication. No satisfactory explanation could be found for the regions of old necrosis and scarring within the brain. The necrotizing phlebitis accompanying the acute inflammatory lesions could probably account for the hemorrhagic quality of the latter.

Zusammenfassung. Ein 9 Tage alter Knabe erkrankte an einer bakteriologisch gesicherten Coli-Meningitis und kam, obwohl eine intensive Therapie mit Antibiotica und Corticosteroiden durchgeführt worden war, 10 Wochen später ad exitum. Autoptisch wurde eine generalisierte Cytomegalie mit ungewöhnlich schwerer Beteiligung des Gehirns und Rückenmarks festgestellt. Die am ZNS erhobenen Befunde waren von zweierlei Art: Einerseits fanden sich akute entzündliche Veränderungen mit zahllosen einschlußkörperchenhaltigen Riesenzellen, die weitgehend auf die subependymalen und subpialen Gewebszonen beschränkt blieben, andererseits aber auch ältere Nekroseherde und gliöse Narben, die unregelmäßig über das ganze Großhirn verstreut waren. Durch den elektronenmikroskopischen Nachweis von Cytomegalieviruskörperchen im Kern und Cytoplasma typischer Eulenaugenzellen konnte die histologische Diagnose einer Cytomegalie erhärtet werden. Bei dem hier beschriebenen Fall dürfte sich die Speicheldrüsenviruskrankheit erst postnatal entwickelt haben. Die vorausgegangene bakterielle Meningitis hat die Aussaat der Cytomegalieviren in den Liquor und den nachfolgenden Virusbefall der Randzonen des ZNS wahrscheinlich erleichtert bzw. beschleunigt. Die intrathekale Corticosteroidapplikation konnte die Ausbreitung des viralen Infektionsprozesses offensichtlich nicht aufhalten und hat möglicherweise sogar zu der reichlichen Virusvermehrung beigetragen. Für die älteren Nekroseherde und gliösen Narben im Gehirn ließ sich keine befriedigende pathogenetische Erklärung finden. Die nekrotisierende Phlebitis, welche häufig im Bereich der entzündlichen Infiltrate beobachtet wurde, dürfte für den hämorrhagischen Charakter der letzteren verantwortlich zu machen sein.

We report the case of a 12-week-old infant with generalized cytomegaly, the salient feature of which was a very severe form of meningo-encephalitis teeming with innumerable inclusion-bearing cells in all affected areas of the CNS. While the findings conform, on the whole, to the heretofore recorded descriptions of

CMV disease of the brain, the severity, type, and distribution of the tissue changes go well beyond the limits of the average case of CMV disease likely to be encountered. Furthermore, the electron microscopic demonstration of the CMV particles in the affected nervous tissue has never been recorded. Finally, some of the questions raised by this observation and touched upon in the discussion appended to the case report, have a bearing on the general problem of CMV infection of man.

Clinical Summary

This 9-day-old infant boy was taken to the hospital with a history of poor eating and irritability of about 24 hours duration. The mother and the infant had been discharged from a maternity clinic 2 days previously, both apparently in satisfactory condition. The pregnancy was supposed to have run an uneventful course. The membranes had ruptured 4 days prior to delivery. This was said to have occurred spontaneously 2 weeks before the EDC. The parents were simple people and showed in general poor cooperation. Once the anatomical diagnosis became known, permission to draw some blood for a complement fixation test on the mother's serum was not granted. On admission the baby weighed 3.320 gm and measured 53 cm. Head circumference was 35 cm. Temperature was 38.2 degrees C. Anterior fontanelle was neither bulging nor sunken. Nuchal rigidity was not present. The spleen was not palpable and the liver was felt at the costal margin. Nothing was said about the presence or absence of inguinal herniations. Petechiae were not mentioned. Hemoglobin was 18.25 gm; hematocrit 57 per cent; white-cell count 16800 with 66 per cent neutrophils. A lumbar puncture carried out on admission yielded purulent CSF from which Escherichia coli was grown. Other findings were the following: total protein 528 mg and glucose 20 mg per 100 ml. Most of the cells were polymorphonuclear leucocytes. On the first hospital day the patient received 25 mg of prednisone, 20 mg of colistin, 1.4 gm of ampicillin and 2 million units of penicillin G. Subsequently, specific therapy was modified as follows: 10 mg daily of ampicillin given intrathecally, together with 1 gm of ampicillin and 10 mg of prednisone administered daily by continuous intravenous drip. The patient's condition improved steadily and a spinal tap carried out on the 13th hospital day gave the following results: total protein 72 mg, glucose 27 mg per 100 ml, cells 18 per cubic millimeter with 84 per cent lymphocytes. Intrathecal therapy was discontinued after one week. Intravenous treatment was terminated on the 16th hospital day. Three days later, the temperature rose to 40 degrees C and the baby's condition suddenly worsened. The liquor became purulent once more. Escherichia coli was again cultured from the CSF on the 19th, the 20th and then, for the last time, on the 22nd hospital day. The previously outlined therapeutic regimen was reinstituted. In addition, 200 mg/day of chloramphenicol were given intravenously and 15 mg/day of prednisone were administered intrathecally. No lasting favorable response to the therapy was ever observed. It was a stormy declivitous course, highlighted by periods of fever, seizures, unresponsiveness, opisthotonus, twitching of the extremities, alternating with brief intervals of mild clinical improvement. The CSF findings varied accordingly, at times approaching but never reaching the normal values. The last period of life was further complicated by a serous subdural effusion and a massive pyuria. At no time were jaundice or petechiae observed. X-ray films of the skull taken 4 days prior to death failed to reveal any calcification. Death ensued in coma on the 74th hospital day. The clinical diagnosis was leptomeningitis. Except for minor upward variations of the daily corticosteroid dosage during the most critical periods, the specific therapeutic management of the case was continued unchanged till the very end.

Autopsy Findings

The thoracic organs, including the thymus, were of normal weight and appearance. The liver and spleen were grossly unremarkable. The kidneys were swollen and had a mottled cut surface. The weight of the brain was not given, and the cranial dura was not examined. The fixed brain was of normal size and configuration. A grayish cloudiness of the meninges was noticed over the ventral aspects of the brain and around the upper segments of the spinal

cord, the only ones which had been submitted for examination. The available section of the optic nerves showed a peripheral dirty grayish discoloration mottled with brown spots. The olfactory bulbs and tracts had been torn away and were not identified on the fixed specimen. Coronal sections of the cerebral hemispheres showed a mild symmetrical dilatation of the lateral ventricles with artifactual disruption of the corpus callosum and septal structures. The ventricular walls were coarsely rugose, covered with small and large, irregularly shaped patches of brownish slough. A dirty grayish discoloration was seen subependymally all along the shores of the ventricular system as well as focally over the superficial layers of the orbital and basal temporal cortex. In addition, the cortical ribbon, the cerebral white matter, and the basal ganglia were sprinkled with small and medium-sized foci, which had a whitish, at times yellowish colour and a granular, occasionally gritty cut surface. Areas of porencephaly or microgyria were not seen. The cerebellum was normal. Sections of the brainstem revealed a muddy staining of the subependymal tissues bordering on the 4th ventricle. The subpial layers along the outer contour of the brainstem and upper cord were hazy brown in colour and friable in consistency.

Light Microscopic Findings

Only lungs, heart, spleen, kidneys and CNS were examined. The heart and the spleen were unremarkable. The lungs showed a diffuse interstitital pneumonitis and the kidneys a severe pyelonephritis. A few typical owl-eyed cells were found among the desquamated alveolar cells of the lungs and within the epithelial lining of the distal convoluted tubules of the kidneys. In the CNS, focal areas of old necrosis stood side by side with widespread areas of acute inflammation. The brunt of the inflammatory changes was born by a narrow band of subependymal and subpial tissue. Subependymally, the lesions extended in a discontinuous fashion from the anterior horn of the lateral ventricles all through the aqueduct down to the 4th ventricle. Subpially, the inflammatory changes spread almost uninterruptedly from the midbrain down to the upper segments of the spinal cord. A heavy inflammatory involvement was noted on the outer rim of the optic nerves and tracts and in the cortical layers of the adjacent orbital and temporal regions. A few foci of subpial inflammation lay further afield over the cerebral and cerebellar hemispheres. The hallmark of the inflammatory process was the extreme profusion of large inclusion-bearing cells (Fig. 1). The typical owl-eyed cell was encountered just as frequently as an almost endless series of variation of this classical cell type. Side by side with slightly enlarged cell bodies there were huge multinucleated cells. The cytoplasm contained a swarm of minute inclusions or a cluster of relatively large inclusions with variable staining properties. Not infrequently the cell body was occupied by a round, eosinophilic, glassy mass surrounded by a rim of residual cytoplasm. The PAS stain revealed cells which were entirely PAS negative as well as a few cells which had an intensely red coloured cytoplasm, while the majority of them contained a variable amount of faintly PAS positive material. Comparable results were obtained with the ORO stain for fat. The nucleus always appeared somewhat enlarged. A typical Cowdry's type A inclusion was occasionally missing; whenever present, its outline varied from round to crescent-shaped or even barlike, and the colour ranged from deep blue to purplish blue. In the acridine orange preparations (pH 3.8), some intranuclear inclusions had a feeble but distinct greenish fluorescence. The tissue reaction accompanying the infected cells ranged from practically nought to a severe degree of necrotizing inflammation with numerous polymorphonuclear leucocytes. Between these two extremes, there were

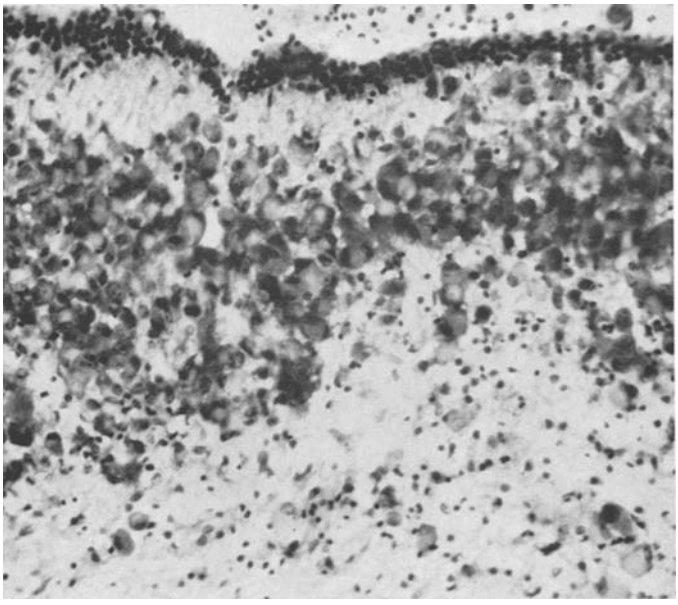

Fig. 1. Wall of the anterior horn from the right lateral ventricle. The ependymal lining is at the top of the picture. A broad, solid band of owl-eyed cells runs through the subependymal tissue. A scanty mononuclear cell infiltration is also present. Celloidin, H & E. ×224

extensive areas showing a moderate cellular infiltration made up of mononuclear cells. Perivascular cuffings were neither numerous nor thick; they were limited to the inflamed areas. Some of the small veins cought in the midst of the most severely affected regions showed a fibrinoid type of vascular wall necrosis. Thrombosed vessels were never seen. Inclusion-bearing cells were often closely apposed to the outer coat of the vessels. Rarely, they lay on the inner lining projecting into the lumen. Interstitial hemorrhages were strewn throughout the inflamed tissues. Images of neuronophagia were not encountered. Cell nodules of a mixed mesenchymal and microglial type, occasionally centered around an inclusion body, were not rare, particularly in the brainstem. They often strayed beyond the confines of the circumlittoral regions. The subarachnoid space contained many small and large round cells, a sprinkling of leucocytes, collections of red blood cells, rare hemosiderin-laden macrophages and an occasional inclusion cell. Bacteria could not be demonstrated. A frankly meningitic cellular reaction became evident only in relation to underlying parenchymal lesions. In these areas, fibrin deposits dotted occasionally the cellular exudate and the latter tended to be more pronounced around the blood vessels. The choroid plexuses, which had been stripped off and examined serially, failed to reveal any inclusion cell. The ependymal lining was partially missing; when still in place, it was coated with a hemorrhagic slough in which inflammatory cells and rare inclusion cells lay embedded. Inclusion bearing cells were often regularly aligned together with the normal appearing ependymal cells, at times overlying areas of undisturbed brain

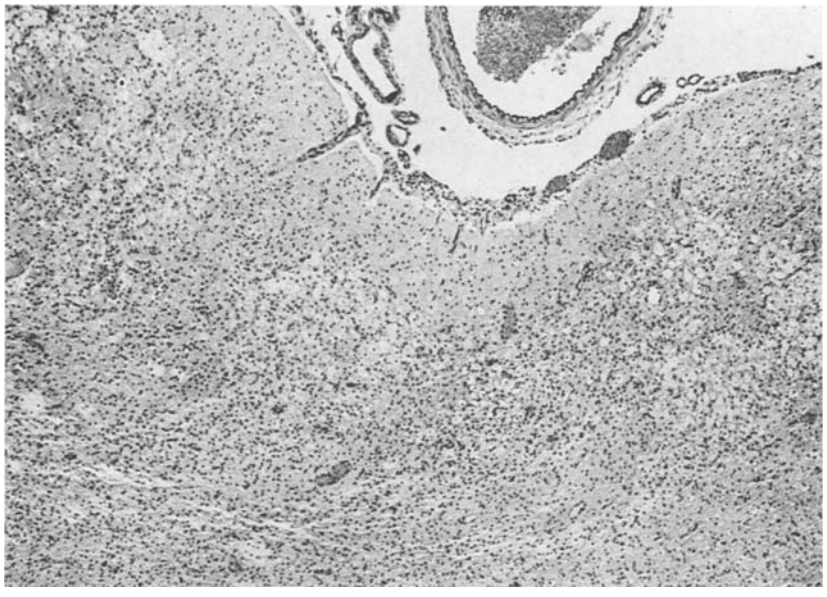

Fig. 2. Section of the left parietal cortex. The normal cytoarchitecture is totally obliterated and replaced by focal collections of foamy appearing scavenger cells in a framework of glial elements. Paraffin, H & E. ×56

parenchyma. This finding had a counterpart at the brain surface, where some parasitized cells stood singly or in short rows right at the junction between brain parenchyma and meningeal coverings. The changes described up till now were clearly inflammatory, selectively confined to certain regions facing the liquoral compartments of the CNS. In addition, we found several focal lesions irregularly distributed in the basal ganglia, the cerebral white matter and cortex. In these regions, the nerve cells had disappeared and there remained a spongy, at times, more compact glial network containing a variable number of lipid-laden macrophages (Fig. 2). Some of these foci had become secondarily impregnated with a basophilic mineral matrix. Heavy calcific deposits were not seen. Occasionally, cytomegalic inclusion bodies were found near or even in the middle of these focal lesions. On the other hand, an isolated inclusion-bearing cell could be discovered in areas of normal brain parenchyma and even within the roots of the cranial nerves. In the tissue examined foci of early ischemia or acute "rarefaction necrosis" were not encountered. Microscopic evidence of CNS malformation was not found.

Electron Microscopic Findings

Fragments from the superficial white matter of the cervical cord were rinsed in a phosphate buffered saccharose solution, postfixed with osmium tetroxide (Palade, 1952), dehydrated in graded ethanols and embedded in Epon 812 (Luft, 1961). Semithin sections were prepared from all available blocks, stained with paraphenylenediamine (Estable-Puig *et al.*, 1965) and examined with a phase

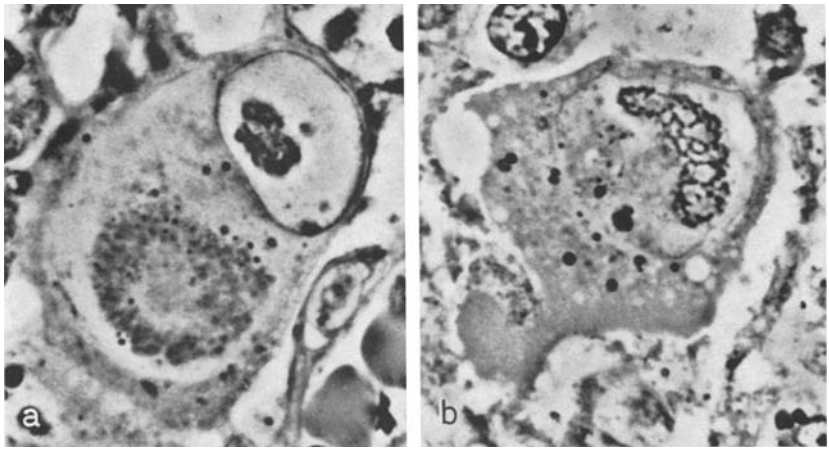

Fig. 3a and b. Phase-contrast images of semithin sections showing typical owl-eyed cells. a This giant element exhibits a small but conspicuous intranuclear inclusion which is surrounded by a clear halo extending to the nuclear envelope. In the cytoplasm there can be seen a ring-shaped granulated inclusion. b In this cytomegalic cell the reticulated structure of the intranuclear inclusion is clearly visible. Epon 812, paraphenylenediamine stain. ×1800

microscope. Ultrathin sections from selected blocks were stained with uranyl acetate (Huxley and Zubay, 1961) and Reynolds' lead citrate (1963). The specimens were examined with a Zeiss EM 9A electron microscope at initial magnifications of from 1900 to 41000×. Cellular ultrastructure was relatively well preserved, considering the long fixation in acid formalin. While finer cytological details were largely lost, cytoplasmic organelles, such as for instance mitochondria, were still recognizable in a number of cells. In general, however, it proved impossible to identify the different types of cells found within the severely inflamed spinal cord parenchyma. One could only say that the cell population seemed to consist chiefly of mesenchymal elements including lymphocytes and macrophages. Among these cells, one saw very often rather giant elements obviously corresponding to the inclusion-bearing cells seen in the light and phase microscopic examinations. These large cells had usually a round-shaped configuration and a diameter up to 5 times that of the neighboring cells. The nucleus was oval or somewhat elongated; as a rule, it was eccentrically situated within the cell body. The nuclear envelope was often uneven on account of multiple indentations and infoldings. The normal marginal clumping of the chromatin was largely missing. In contrast to the smoothness and compactness of the light microscopic picture, the phase microscope revealed frequently an irregular outline and a reticulated structure of the intranuclear inclusions (Fig. 3). On the electron microscopic screen, these inclusions appeared as a netlike mass of finely granular, fairly dense chromatin-like material. A more or less clear halo of variable width extended from the jagged edges of the central mass to the inner nuclear membrane (Fig. 4). Embedded within this reticulated chromatin-like matrix and, to a lesser degree, free in the pale zone around it, lay numerous corpuscles the viral

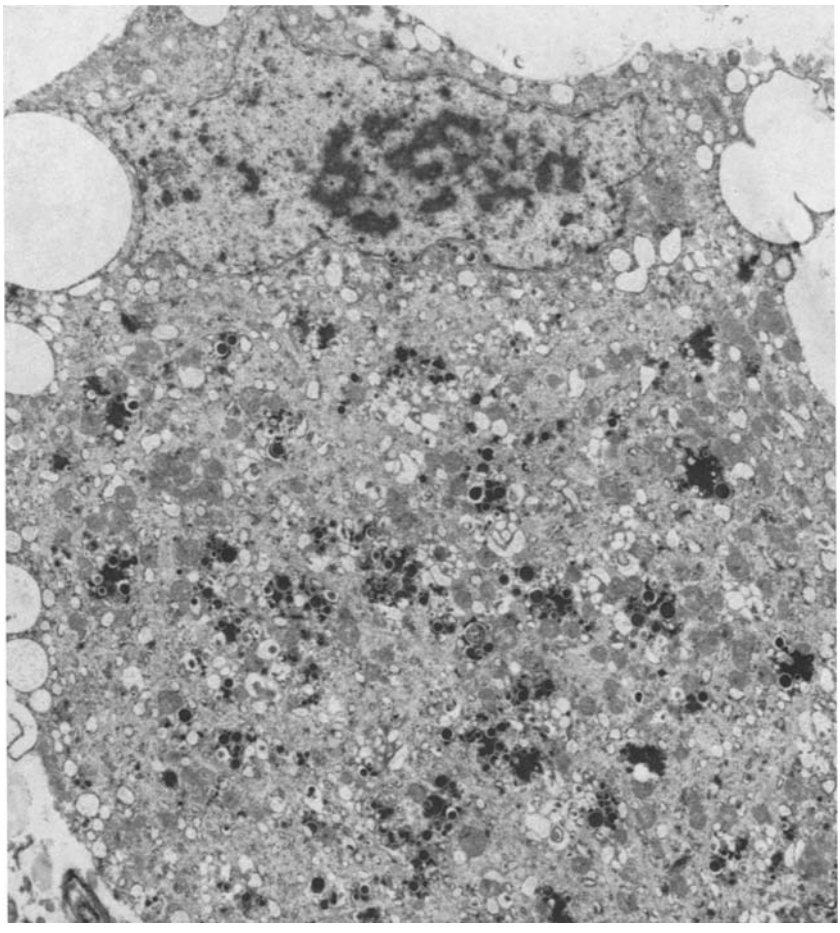

Fig. 4. Survey electron micrograph of an owl-eyed cell. The nucleus is at the top of the picture. Note the reticulated appearance of the intranuclear inclusion. In the cytoplasm there are scattered accumulations of rather opaque lysosome-like bodies. Numerous mitochondria are still recognizable between the latter. The large marginal vacuoles are probably artifacts due to inadequate fixation. ×5700

nature of which was apparent from the following ultrastructural features. These virus particles were greatly uniform in size averaging about 93 mμ in total diameter. They consisted of a central, spherical, sometimes roughly hexagonal or pentagonal core with a diameter of approximately 55 mμ and a single, membrane-like, 9 to 10 mμ thick envelope, from which the former was separated by a circular, lucent interspace measuring 9 to 10 mμ in width. The vast majority of the particles had an obviously incomplete central core. This appeared as a ring-like structure which was either totally empty or contained only a homogenously distributed, slightly opaque material (Figs. 5 and 6a). Rarely, the viral core was entirely filled up with an electron dense substance, thus appearing as a compact

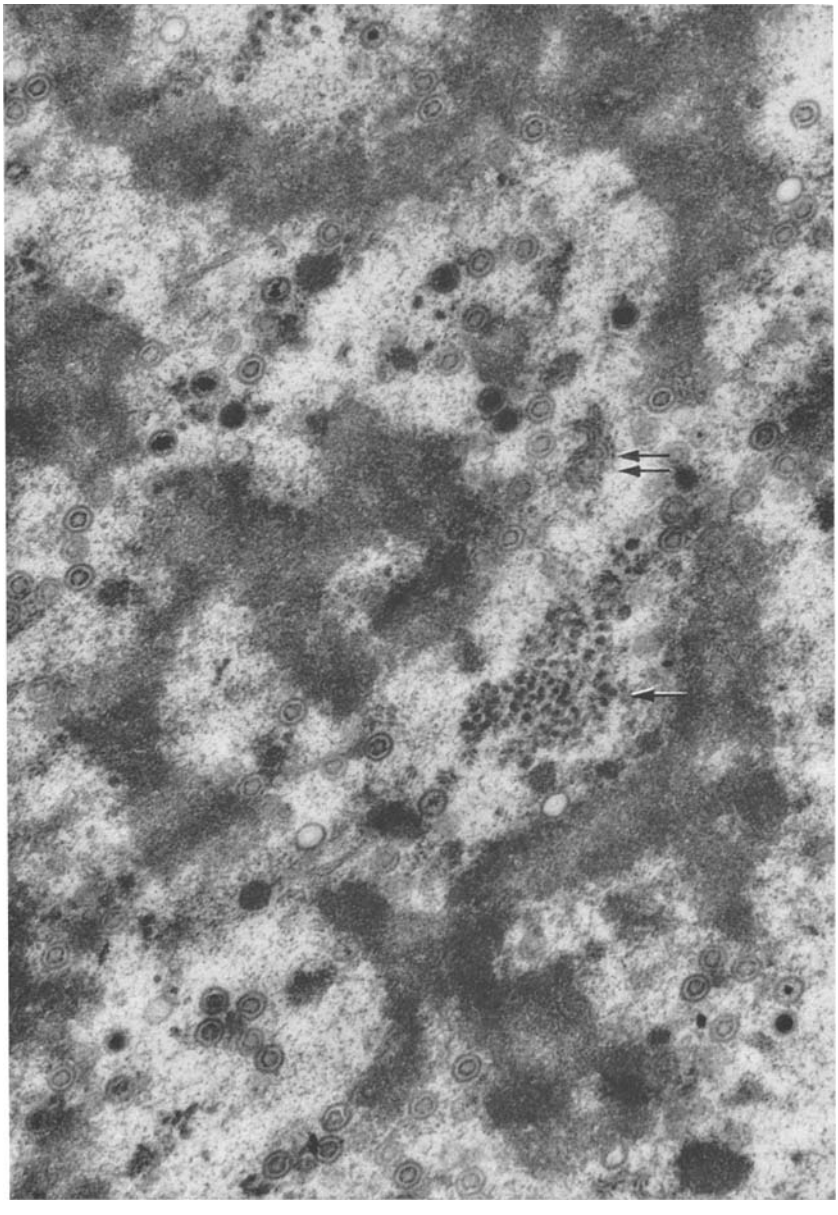

Fig. 5. Detail of a cytomegalic intranuclear inclusion. This is formed of anastomosing trabeculae of a finely granular chromatin-like material. Scattered in its interstices are numerous CMV particles in different developmental stages (coreless capsids, nucleocapsids with both empty and compact dense cores). An area of tiny granules (arrow) and a small conglomerate of ruptured virions (double arrow) can also be observed. ×40000

globule. Empty viral capsids, i.e., annular envelopes devoid of any central structure, could also be observed occasionally (Fig. 5). In contrast to this, naked

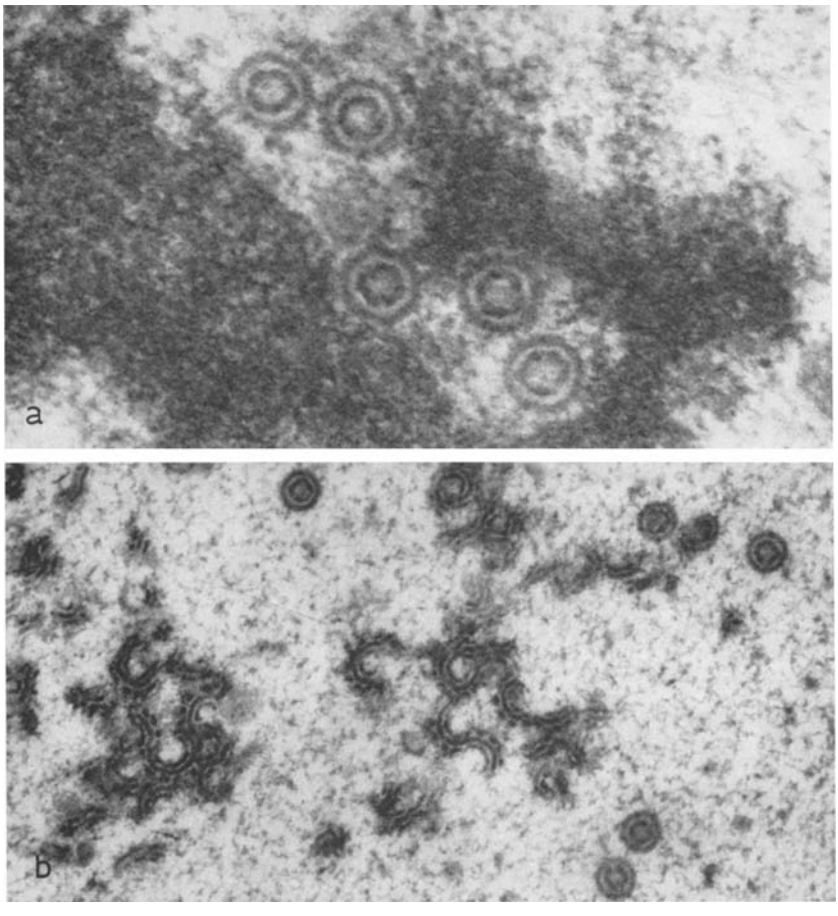

Fig. 6. a High resolution electron micrograph revealing that the cores of the nuclear CMV particles tend to be pentagonal or hexagonal rather than circular. ×108000. b Electron microscopic image showing several clusters of disrupted nuclear virions. ×54000

viral nucleoids, i.e., central cores devoid of any membranous envelope, were never seen. The virus particles were either diffusely scattered or joined together into several loose groups; however, they never showed any tendency to be arranged in a crystalloid pattern. Clusters of partially or totally disrupted virions were also seen (Figs. 5 and 6b). In addition, in the nuclei of several inclusion-bearing cells we came across more or less loosely knit arrays of poligonally shaped, variably dense granules with a mean diameter of about 20 to 30 mμ. These granular aggregates, which could occur either isolatedly or repeatedly within a given nucleus, were frequently situated in close proximity to the intranuclear virus particles (Fig. 5). Virions were observed not only inside the nuclei of the owl-eyed cells, but also, though less numerous, within the perikarya. These intracytoplasmic virus particles, unlike the intranuclear ones, displayed a very pleomorphic ultra-

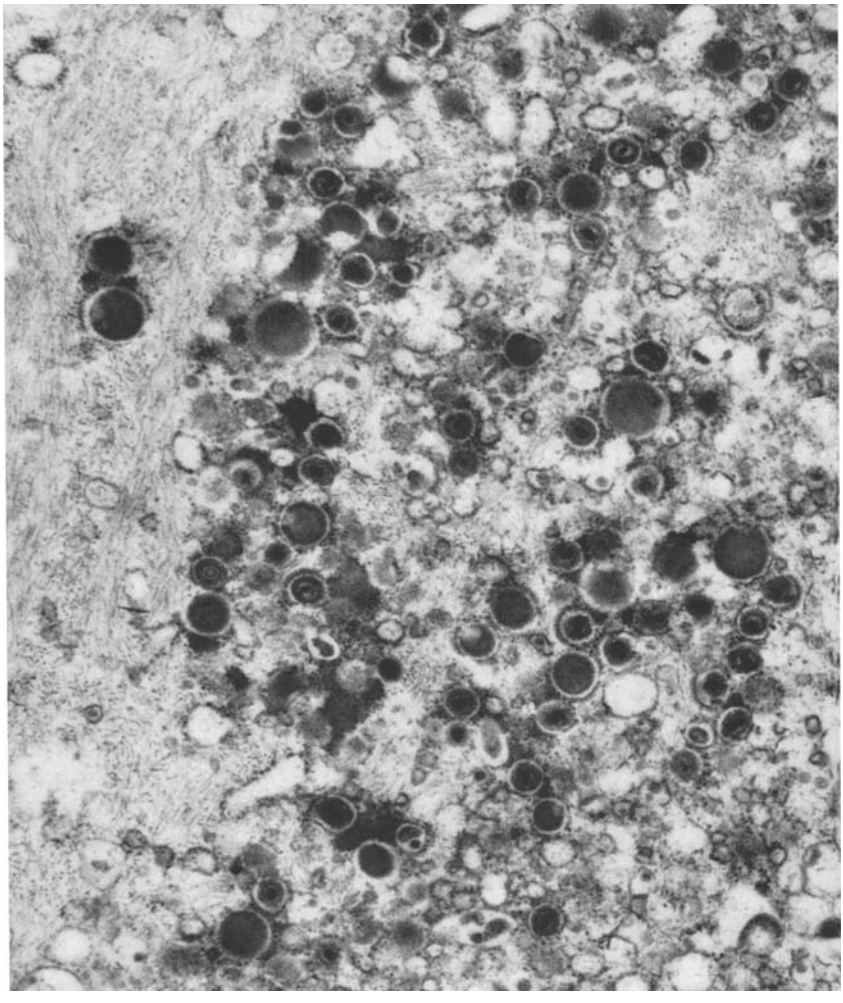

Fig. 7. Cytoplasmic area of an inclusion-bearing giant cell. Many CMV particles can be observed to lie in close association with lysosome-like organelles. Note that the cytoplasmic virions possess always a solid opaque core and an envelope which is considerably thicker than that of the nuclear ones. Masses of thin filaments are prominent in the left third of the picture. ×24000

structure and a great dimensional variability. Most of the cytoplasmic nucleocapsids possessed a very dense, tightly packed, central core, the diameter of which varied between 40 and 70 mμ. The annular capsids appeared always thicker than the corresponding structures found intranuclearly. In some virions they were up to 40 mμ in width. Hence, the total diameter of the cytoplasmic virus particles exceeded considerably that of the nuclear particles and measured, in some instances, up to 170 mμ. Some intracytoplasmic virions exhibited two separate concentric envelopes, which, together with the dense core, gave them a

target-like appearance. On the other hand, there were also several virus particles in which no clear distinction could be made between the central nucleoid and the surrounding capsid, for a radiolucent interspace between them was lacking. Such virions appeared then as solid spherules of homogeneous opacity. A detailed description of all variants observed amongst the intracytoplasmic virus particles would be neither possible, nor perhaps justified in view of the inadequate fixation of our material. It is probably more relevant to emphasize that, very often the cytoplasmic nucleocapsids lay closely associated with, or even embedded in lysosome-like bodies. Furthermore, in some instances single intracytoplasmic virions were seen to be enclosed within membrane-bound vacuoles of variable width. And finally, several of the owl-eyed cells contained thin cytoplasmic filaments resembling those usually seen in fibrous astrocytes (Fig. 7).

Discussion

To dismiss as a contaminant the Esch. coli which was isolated 5 times from the CSF would probably simplify matters, but it would hardly correspond to the real state of affairs. Indeed, the bacterial species involved, the premature rupture of the membranes, the onset of the meningitis in the first 10 days of life, plus the repeated cultural isolations, are all arguments in favour of a genuine case of Esch. coli meningitis of the neonatal period (Ziai and Haggerty, 1958). On the other hand, at the end of the fatal clinical evolution, we found overwhelming evidence of an altogether different type of agent, which alone should be held responsible for the entire pathological picture disclosed by the postmortem examination. We are forced to conclude that this patient contracted a bacterial meningitis from which he completely recovered and upon which a CMV disease was subsequently grafted. This is well in keeping with the known proclivities of the CMV to set up full blown infectious processes in individuals whose natural defenses are diminished because of age, impaired by reason of an intercurrent systemic disease or modified through therapeutic handling. However, previous reports of generalized cytomegaly developing in the course of an Esch. coli meningitis are unknown to us. The proposed sequence of events leaves unanswered the questions concerning the portal of entry and the time at which the CMV may have gained entrance into the body of the host. The normal birth weight, the lack of clinical manifestations in the first week of life, as well as the lack of cerebral and visceral malformations, are all arguments against a prenatal CMV disease. The possibility remains, though, that the CMV may have entered the host during the terminal weeks of fetal life only to produce a generalized disease at a later more appropriate time. Be that as it may, we should like to view our case as a case of postnatal CMV disease. At the same time, we should like to leave in abeyance the question whether the infection had been vertically transmitted or acquired postnatally. With regard to the clinical picture complicated terminally by a subdural effusion, we may recall that such an effusion constitutes a common complication of bacterial meningitis of infancy (Smith, 1954). However, we are not aware of a previous report of a subdural effusion in the course of CMV meningo-encephalitis. It would then appear that, under appropriate circumstances, a viral meningo-encephalitis is apt to develop

this type of complication just like any other ordinary bacterial meningits of the young infant. As for the therapy, despite a few isolated claims to the contrary (Thalhammer, 1967), the general consensus is that no effective treatment of CMV disease is as yet available. To be sure, the specific therapy of cytomegaly may still elude us for a while. However, clinical improvement has been recently observed in cases of CMV pneumonitis treated with floxuridine (Cangir *et al.*, 1967). In addition, idoxuridine has been shown in vitro to inhibit the murine CMV synthesis (Henson *et al.*, 1966), and clinically to be effective in cases of Herpesvirus encephalitis (Nolan *et al.*, 1970). In view of these reports it would seem to us that, future cases of severe CMV disease of the brain should warrant a serious trial with anyone of these two compounds rather than further tampering with corticosteroids. The truly unmitigated growth of the virus in the nervous tissue of our patient, raises the question whether steroids, aside from failing to check the infectious process, may in fact have contributed to support the viral replication. Experimental studies exist which would indeed substantiate such a view (Medearis, 1964; Henson *et al.*, 1967). One wonders further what may have been the role, if any, of the bacterial meningitis in initiating and/or sustaining the CMV meningo-encephalitis. Since cytomegalic viremia is at least partially cell-bound (Foster and Jack, 1968; Long and Noren, 1968), it seems reasonable to assume that a great number of viral units may have been able to negotiate the blood-cerebrospinal fluid barrier with the cellular exudate of the early bacterial meningitis. This would help to explain the striking cerebral localization of this case of generalized cytomegaly. This, however, is only a supposition. The fact remains, though, that the inflammatory changes were extremely severe and, for all intents and purposes, selectively limited to the littoral tissues of the CNS. It appeared as though the infectious process, once having gained entrance into the CSF spaces, spread along the tissues bordering on these spaces, regardless of their meningeal or ventricular situation, in a manner much like the infectious processes do in the serous cavities of the body, i.e., by contiguity. In the past, much emphasis has been placed on the supposedly selective periventricular localization of CMV disease of the brain (Haymaker *et al.*, 1954). Our case, with its array of subependymal and subpial lesions, seems to indicate that the littoral localization is probably a function of the route of entry into the CNS more than of a hypothetical specific vulnerability of certain regions of the neuraxis. Incidentally, the recently recognized nodular form of encephalitis associated with CMV disease (Schneck, 1965; Vortel and Plackỳ, 1968) can be much better explained in terms of multiple primary parenchymal foci arising in the wake of a viremic spread than on the basis of minute target areas, each possessed of a supposedly unique susceptibility. Turning to the necrotic foci found in our case side by side with the inflammatory lesions, it might be remembered that several cases of CMV disease of the brain show predominantly old burned-out lesions with only a handful of inclusion-bearing cells. The pathogenesis of these changes, their relationship to the acute inflammatory lesion, and, in general, their place in the overall process of CMV disease of the brain, are obscure, and the students of the subject have done little to clarify these points by lumping together all sorts of findings without regard for particulars or details. On the other hand, necrotic lesions are not unique to CMV encephalitis. In fact, they occur in a wide variety of

viral encephalitis and their pathogenesis, regardless of their specific viral etiology, remains evermore obscure (Peters, 1970). Bednař (1966) attributed the foci of encephalomalacia to the venous thromboses he had repeatedly demonstrated in his own cases of CMV disease. We have not seen such thromboses, nor have we demonstrated a cerebral analogue of the necrotizing arteritis of the coronaries reported in a few cases of generalized cytomegaly (Vortel and Fingerland, 1966; Koten and Harinck, 1969). The necrotizing phlebitis which we did see in areas of acute inflammation, could probably explain the hemorrhagic quality of the imflammatory changes, but it could hardly account for the foci of necrosis and scarring. Limiting ourselves to the present observation, we should like to submit that some of the smallest necrotic lesions may indeed represent early foci of inflammation which have run the full gamut of tissue changes up to the cicatricial stage and in the process have cast off their initial distinguighing features. As for the larger necrotic lesions, we would rather favour an ischemic and/or hypoxic origin, only indirectly and secondarily related to the main inflammatory pathology of CMV disease of the CNS. It was the unusual severity of the latter which actually enabled us to study the case electron microscopically. Up till now we know only of one other author who succeeded in demonstrating the CMV particles in the brain tissues of an infant with generalized cytomegaly (Oda, 1969). Our electron microscopic findings are in substantial agreements with the results of previous electron microscopic studies performed on CMV infected cultures of human fibroblasts (Luse and Smith, 1958; Stern and Friedmann, 1960; Patrizi *et al.*, 1965; McGavran and Smith, 1965; Becker *et al.*, 1965; Ruebner *et al.*, 1965, 1966) and on biopsy (Donnellan *et al.*, 1966) or autopsy material (Timmel, 1964; Seifert and Gieseking, 1965; Seifert and Oehme, 1967) from patients with generalized cytomegaly. Aside from the general ultrastructural features, the demonstrated close association of cytoplasmic virions and lysosome-like bodies seems to be both characteristic of this viral agent (Ruebner *et al.*, 1966) and unknown amongst other essential members of the Herpesvirus group. Therefore electron microscopy of formalin-fixed necropsy material has once again proven to be a useful adjunct in securing or completing the histologic diagnosis of a viral encephalitis. Conversely, electron microscopy has failed anew to clarify the histogenetic origin of the cell or cells supporting the viral replication in the brain tissues. Classically and often quite arbitrarily, CMV inclusion bodies have been described in all possible cell types found within the CNS. The thin filaments which we have seen in the cytoplasm of many parasitized cells might bespeak the astrocytic nature of these cellular elements. We would not dare say that the foregoing is more than a plain suggestion, for filament formation may well represent a simple accompaniment of the viral infection.

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