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BDRL ltr 29 Sep 1971





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In conducting the research described in this report, the investigator adhered to the "Guide tor Laboratory Animal Facilities and Care," as promolgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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#### ABSTRACT

The Arrican strain of chikongunya virus was used to inject newborn mice, and the central nervous system was examined in the electron microscope. Previously, it was shown that, with this virus strain, histological changes in suckling mice consisted primitily of necrosis of neurons in the cerebral cortex and spinal cord. In the present study, ultrastructural changes were tound only in the cerebral cortex and spinal cord. Electrondense particles were seen in the extracellular spaces of the neuropt1 and within axon tibers. A subtle change in the texture of the cytoplasmic substance and alterations of the endoplasmic reticulum were observed in neurons and glia! cells. As with tissue culture cells, the endoplasmic reticulum appeared to be the main organette involved in virus replication. The close association of electron-dense particles with this membranous structure and the presence of mature virus particles within the endoplasmic reticulum corroborated the findings in (issue culture. The viral core is apparently assembled at the endoplasmic reticulum, and the viral coat is formed from the cellular membrane, which is penetrated by the virus.

#### FLECTRON MICROSCOPY OF CHIKUNGUNYA VIRUS INFECTION IN THE NERVOUS SYSTEM OF SUCKLING MICE\*

Chikungunya virus is an arbovirus characterized antigenically as belongtug in group A. It is the etiologic agent of a dengue-like disease and has been implicated in epidemics of hemorrhagic tever.

Multiplication of the virus is possible in various tissue cultures. A lethal intection is produced in newborn mice but not in adult mice. Although a viremia develops after inoculation of other rodent species and subhuman primates, no signs of illness are seen. For this study, litters of newborn mice were injected intracutaneously with  $1 \ge 10^3$  SMICLD<sub>x</sub>, of the African strain of chikungunya virus. Inoculated and control mice were sacrificed daily for 7 days after injection of the virus, and tissues were prepared in the usual manner for examination with both light and electron microscopes.

Multiple cross sections of the suckling mouse were examined with the light microscope. Morphologic changes that could be observed with the light microscope were limited to the central nervous system. The most prominent changes observed were necrosis of neurons (Fig. 1) and a mild vasculitis (Fig. 2). The vasculitis, which consisted of endothelial proliferation with a mixed inflammatory infiltrate, appeared to precede the neuronal changes. These lesions were seen in the cerebral cortex, basal ganglia, and spinal cord. In the cord, motor neurons were more trequently involved.

The earliest changes observed with the electron microscope were in sections of tissues obtained on the 4th day after injection, 1 day later than changes seen by light microscopy. Some sections of the cortex and spinal cord contained neurons in which the cytoplasmic structure was altered. At low magnifications, the cytoplasm was dense and the endoplasmic reticulum very prominent (Fig. D. At a higher magnification, numerous spherical particles were seen surrounding portions of the endoplasmic reticulum. Some were scattered randomly, others were arranged in an orderly pattern throughout the cytoplasm (Fig. 4).

The perivascular changes noted in light microscopy were contirmed by electron microscopy (Fig. 5). Perivascular edem: is evident and one mononuclear lymphocyte is located in this space. The evtoplasm of this glial cell, shown in Figure 6, is morphologically quite similar in appearance to that of the intected neuron. Note the arrangement of the particles, their distribution, and the virus-like appearance of the particles, which is quite evident in the three vesicles in the center of the tigure. This

3 This report should not be used as a literature citation in material to be published in the open literature. Readers interested in referencing the information contained herein should contact the senior author to ascertain when and where it may appear in citable form. is consistent with the morphology of arboviruses; namely, a dense core surrounded successively by a light area and a darker-appearing structure, the membrane. The size of these particles (60 nm) and the cytoplasmic changes are identical to those seen in tissue cultures infected with chikungunya virus (Fig. 7).

All cells were not as extensively involved as those shown previously. In some neurons, there were just a few clusters of particles (Fig. 8), and in others the only evidence of virus multiplication was the presence of mature virus in vehicles (Fig. 9). Occasionally, structures compatible with mature virus were seen in axon tibers (Fig. 10).

The nature of the neuronal alteration was the same in the cerebral cortex and the spinal cord. Myelinated fibers were found in sections of cord from mice sacrificed later than 5 days. In a few instances, lesions involving these myelinated fibers were seen. The nature of this type of lesion is seen in Figure 11. The continuity of the myelin sheath of this fiber has been destroyed, the cytoplasm of the Schwann cell contains various large inclusions, the cytoplasmic integrity of the surrounding glial cells is altered, an inflammatory infiltrate consisting of neutrophils and monocytes is present, and mature virus can be seen (Fig. 12).

These data show that the in culation of newborn mice with chikungunya virus produces an encephalitis that primarily affects the cerebral cortex and spinal cord. The virus multiplies within the neurons and glial cells of these areas in a manner identical to that seen in L cells maintained in culture. Mature virus was seen within cells of the central nervous system as well as extracellularly.



FIGURE 1. Section of Cerebral Cortex Showing Neuronal Necrosis. Hematoxylin and cosin. ca. 875X.



FIGURE 2. Section of Cerebral Cortex Illustrating Vasculitis. Hematoxylin and eosin. ca. 875X.



FIGURE 3. Non-op in Corebral Cortex. Note granularity of the extopless is the exopilarea. cr. 5,800%.



FIGURE was Hardon Manager (1999) of the Granular Portion of the Neuropell Classifier a Compress electron-dense particles surrout (the superblashes better home. Some mature virus is in the endoples of performance, i.e., 16, 200X.



FIGURE 5. Cross Section of Small Blood Vessel in Cerebral Cortex. The perivascular space contains a histiocyte. Note granularity of the glial cell in lower center of the photomicrograph. ca. 5,800X.



FIGURE 5. Higher Manification of Glial Cell Shown in Previous Figure. ca. 38,800%.



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FIGURE 7. Tissue Culture (Mouse L Cell) Cell Infected with Chikungupya Virus. The appearance, size, and location of the virus are identical to those seen in glial cells and neurons. ca. In.200X.



FIGURE S. COLAR COLE Spinit Cord. ca. 23,000%.

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FIGURE 4. Matter Version Extracell for Spaces of Spinal Conductors, 25, 1955



200 V. ..



FIGURE 11. Myelinited Fiber in Spinal Cord. The continuity of the myelinihal been destroyed. A neutrophil and some lymphocytes are shown, ea. 3,800%.



FIGURE 12. Matsie Views are shown in the Cytoplasm of the Schwann Cell Above and the Sentrophfl Below. ca. 20,000%.

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