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Rabiesvirus Neuronitis

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Neuronitis is produced by extraneural inoculation of rabiesvirus into suckling mice. Temporal quantitative studies suggest that rabiesvirus (fixed, attenuated strain) spreads centripetally along peripheral nerves, reaching the level of the ganglion cells within 24 hr after infection (2). By immunofluorescence, the first evidence of viral replication within the cytoplasm of ganglion cells occurs 3 days after inoculation. Encephalitis soon follows the development of neuronitis. Although murine rabies encephalitis has been studied by electron microscopy, the ultrastructural features of rabiesvirus neuronitis have not been previously reported.

In this study, two litters of newborn Swiss mice were inoculated intranasally with a virulent street strain of rabiesvirus previously described (1). A blunt needle was placed in the nasal cavity, and about 0.02 ml of virus suspension was injected. Animals were then sacrificed at 15, 24, 38, 48, and 60 hr and at 3, 6, and 8 days after inoculation. The trigeminal nerve and its ganglion were dissected and then processed for electron microscopy as previously reported (1).

Rabiesvirus was not seen in any part of the trigeminal nerve in the first 3 days after inoculation. Rabies virions were observed, however, in the trigeminal nerve and its ganglion 6 and 8 days after inoculation. Viral matrices or "factories" filled the perikaryon of some ganglion cells (Fig. 1). Many virus particles 65 nm in diameter were seen within dilated cisternae associated with reticulo-granular viral matrices (Fig. 2). Adjacent myelinated (Fig. 3) and nonmyelinated (Fig. 1) axons also contained characteristic viral matrices with abundant reticulogranular material; rabiesvirus particles were numerous. Developing virus particles and matrices were frequently seen at nodes of Ranvier (Fig. 4). Rabies virions were also noted in the endoplasmic reticulum of axons, discrete from viral matrices (Fig. 1 and 3). Virus particles were not seen, however, in the supporting structures of the trigeminal nerve or in the extracellular spaces.

A companion electron-microscopic study of herpesvirus trigeminal neuritis showed that this deoxyribonucleic acid-containing virus spreads centripetally along axonal cylinders by infecting primarily Schwann cells (4). However, in our study, no evidence was obtained that Schwann and endoneural cells supported viral growth after intranasal inoculation of the ribonucleic acid-containing rabiesvirus. The neurotropism of rabiesvirus was evident from the discovery of developing virus particles in the perikaryon of the trigeminal ganglion cells (Fig. 1) as well as within adjacent axons (Fig. 1, 3, and 4). The mechanism of centripetal spread of rabiesvirus en route to the trigeminal ganglion is uncertain; virions may have been in too few numbers to be detected. In this regard, Johnson (2) suggested tissue interspaces as the most likely route of neural spread of attenuated fixed rabiesvirus.

The development cycle of rabiesvirus in the trigeminal nerve and ganglion is identical to that previously reported for rabiesvirus in the brain (1, 3). In addition, rabies virions, either singly or in small groups, were occasionally noted within the endoplasmic reticulum of axons, sometimes discrete from viral matrices (Fig. 1 and 3). This may represent intraneural spread of rabiesvirus away from the infected perikaryon in the direction of the flow of axonplasm; axonal spread could explain how virulent street rabiesvirus gains access from ganglion cells to the central nervous system. In this regard, Yamamoto et al. (5) showed by specific immunofluorescence an antigen of virulent street rabiesvirus within axonal processes near involved ganglion cells. However, Johnson (2) found fixed attenuated rabiesvirus restricted to the ganglion cell without involvement of axonal processes. When our results with street virus are compared to Johnson's results with the fixed virus, the absence of axonal spread by the fixed virus might well account for the attenuation of virulent rabiesvirus.

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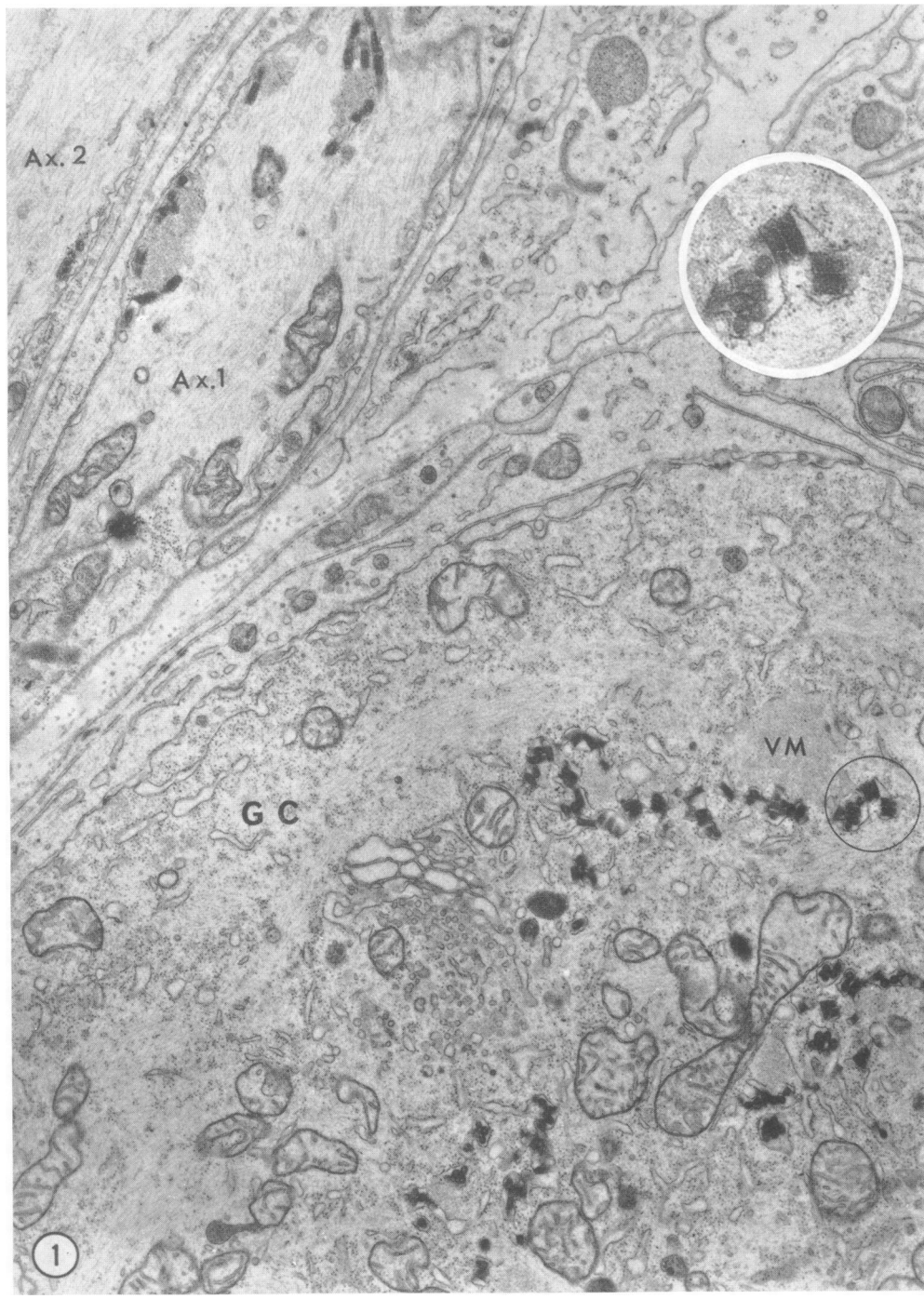


FIG. 1. *Numerous viral matrices (VM) are present within the perikaryon of a trigeminal ganglion cell (GC). Two adjacent nonmyelinated axons contain rabies virions. In one axon (Ax_1), characteristic "viral factories" (matrix with surrounding virions are noted. In the other axon (Ax_2), varions appear detached and distant from recognizable viral matrix material. ×15,400. Insert: Virus particles (65 nm in diameter) with bullet-shaped configuration appear to "bud" into dilated cisternae. ×33,880.*

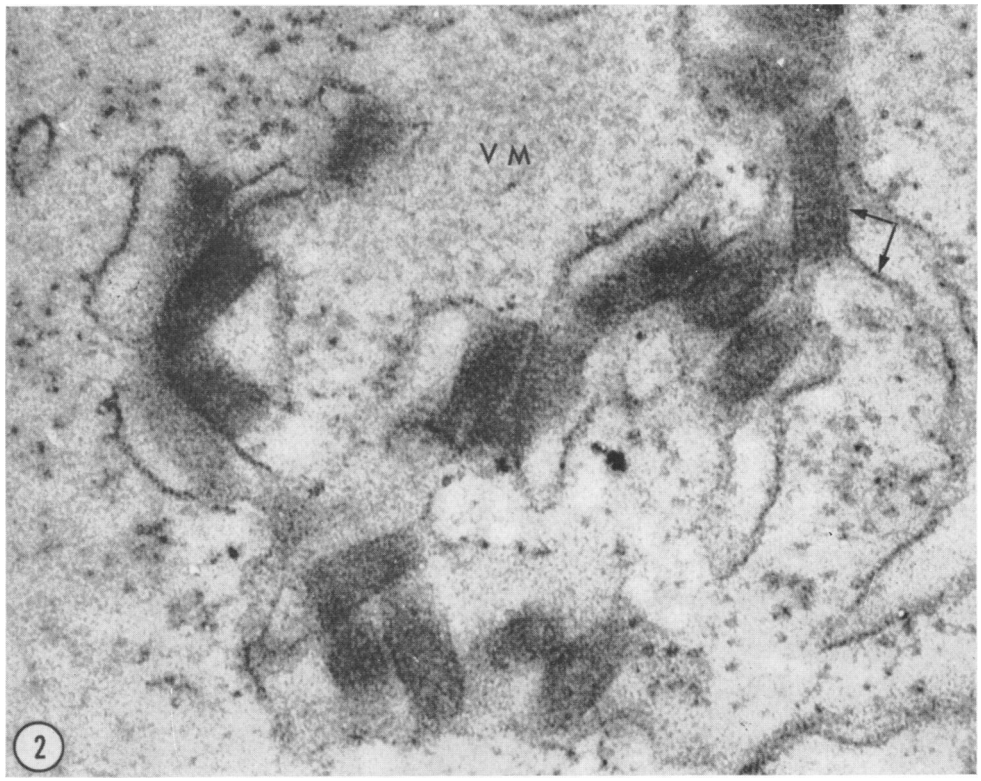
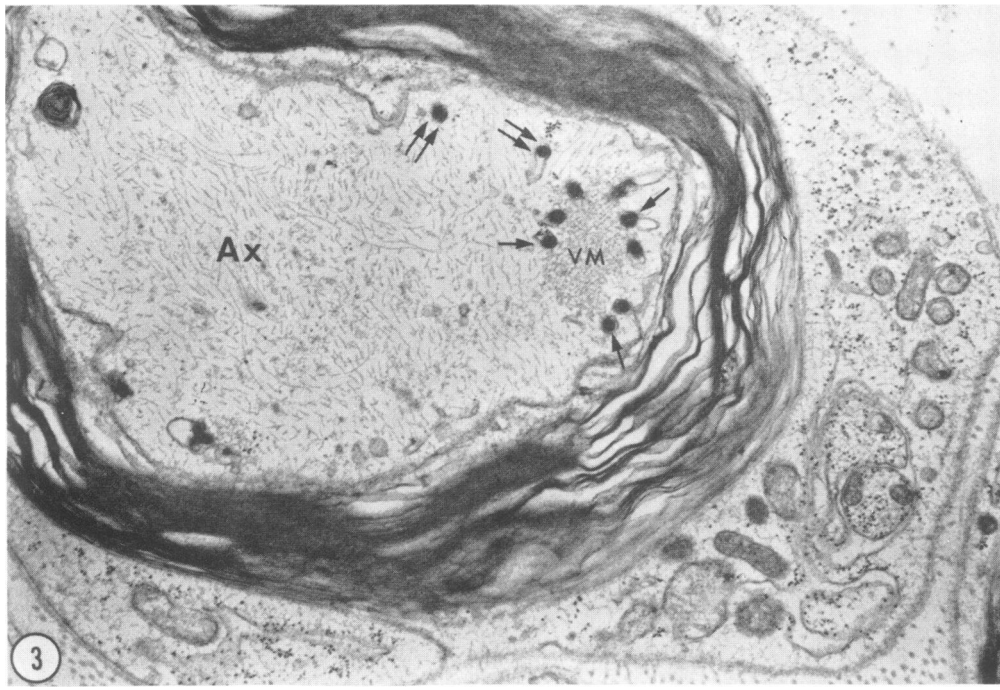


FIG. 2. *Photographic enlargement of area in Fig. 1 which shows reticulo-granular viral matrix (VM). The membranes of adjacent "budding" rabiesvirus particles are continuous with the membranes of cytoplasmic cisternae (arrows).* ×*107,800.*



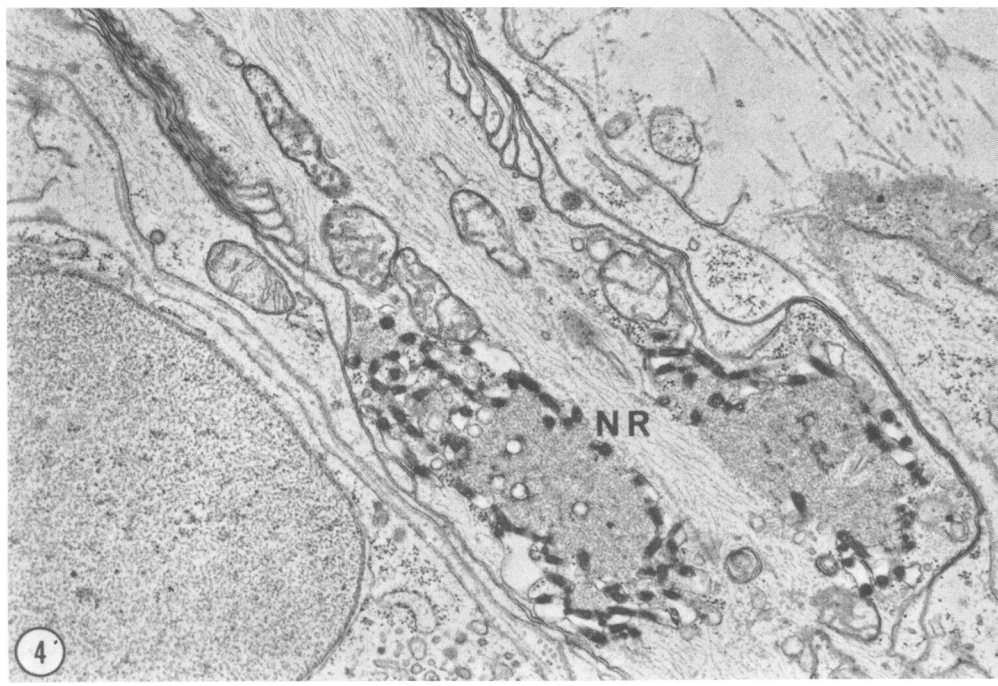


FIG. 3. *A viral factory is noted within a myelinated axon (Ax). Several rabies virions (double arrows), discrete from a viral matrix (VM) and adjacent virions (single arrows), are contained within the endoplasmic reticulum.* ×*30,750.*

FIG. 4. *Developing virus particles associated with large reticulo-granular viral matrices are confined within the peripheral axoplasm at a node of Ranvier (NR).* ×*15,400.*

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