ANIMAL MODEL OF HUMAN DISEASE

Primary Amebic Meningoencephalitis, *Naegleria* Meningoencephalitis, CNS Protozoal Infection

Animal Model: Primary Amebic *(Naegleria)* Meningoencephalitis in Mice

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Biologic Features

The use of the mouse as an experimental animal model for studying primary amebic meningoencephalitis (PAM) is uniquely appropriate, since the existence of this disease in man was first suggested following the discovery of fatal meningoencephalitis in mice after intranasal inoculation of a species of *Acanthamoeba*.[1] When PAM was subsequently reported in humans,[2] the remarkable similarity of the disease occurring in man to that produced experimentally was promptly recognized.

In man, PAM is essentially confined to the central nervous system and is almost invariably fatal.[3,4] The disease is world wide. So far, all amebas isolated from fatal cases have been found to be free-living ameboflagellates of the genus *Naegleria*.[3-6]

The infection apparently is contracted by the intranasal instillation of fresh water which contains amebas, most likely occurring during swimming or other water-related sports. In general, victims have been healthy children or young adults, free of predisposing conditions.

Comparison with Human Disease

The basic features of the disease in man[4-6] have all been noted in experimental infections in the mouse:[3-5,7] namely, the same incubation period and portal of entry, residence of amebas in the olfactory mucosa with invasion and migration through submucosal structures and into nerve plexuses, passage of amebas through pores of the cribriform plate into the subarachnoid space, subsequent invasion of olfactory bulbs and lobes with spread to more distant areas of the brain, frequent aggregation of amebas in perivascular spaces and, finally, a predominantly neutrophilic cellular response associated with and superimposed upon wide-

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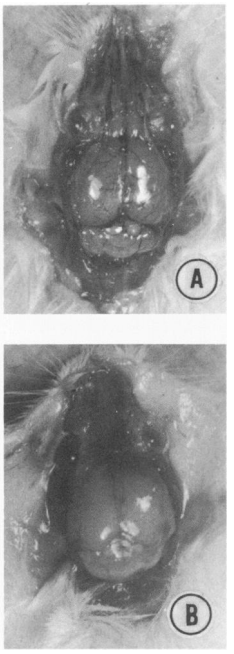

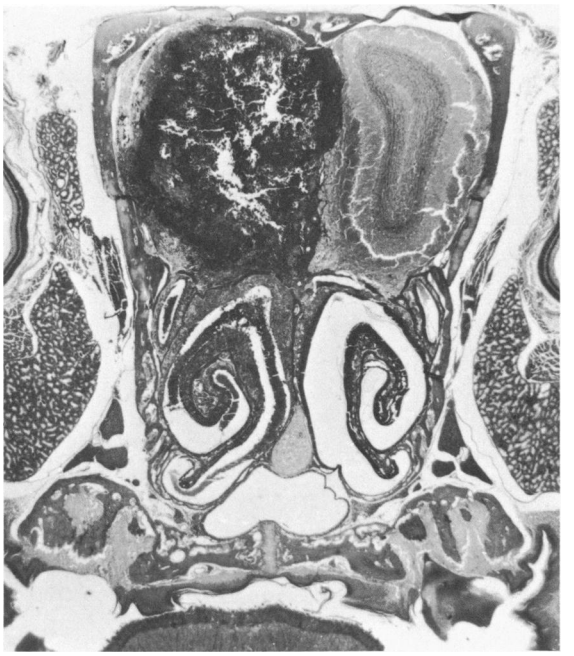

Fig 1A—(left) Normal mouse brain. The calvarium has been removed. Olfactory bulbs, lobes and convexities of cerebral hemispheres are visible. **B**—Five days after intranasal inoculation with *Naegleria.* Note hemorrhagic appearance of olfactory bulb, lobes, and cerebral hemisphere. Note the loss of definition of sulci and dull appearance of cortex due to edema and swelling. **Fig 2—(right)** Five days after intranasal inoculation with *Neagleria.* Coronal section at the level of the eyes showing hemorrhagic necrosis of the right olfactory lobe. Note inflammation and edema of nasal structures on ipsilateral side (H&E × 10).

spread areas of hemorrhagic necrosis (Figure 1–3).

In man the natural disease is characterized by a brief incubation period (5 to 6 days), followed by a short (usually less than 72 hours) hospital course consisting of rapid central nervous system deterioration, coma and death. Using the same pathogenic amebas isolated from fatal human cases, a similar if not identical infection can be regularly induced in white Swiss (SW) mice by intranasal instillation of approximately 10^3 to 10^4 viable trophozoites. With this inocula, about 45% of mice develop the disease and die 5 to 7 days afterwards. Gray and white matter are both affected, and the pathologic changes are characterized by an acute inflammatory reaction associated with hemorrhage, edema, disintegration of neural structures and widespread invasion by amebas. (Figures 2 and 3). Trophozoites may be seen in the perivascular spaces adjacent to the adventitia of arterioles and capillaries. The nasal and olfactory mucosal epithelium are extensively in-

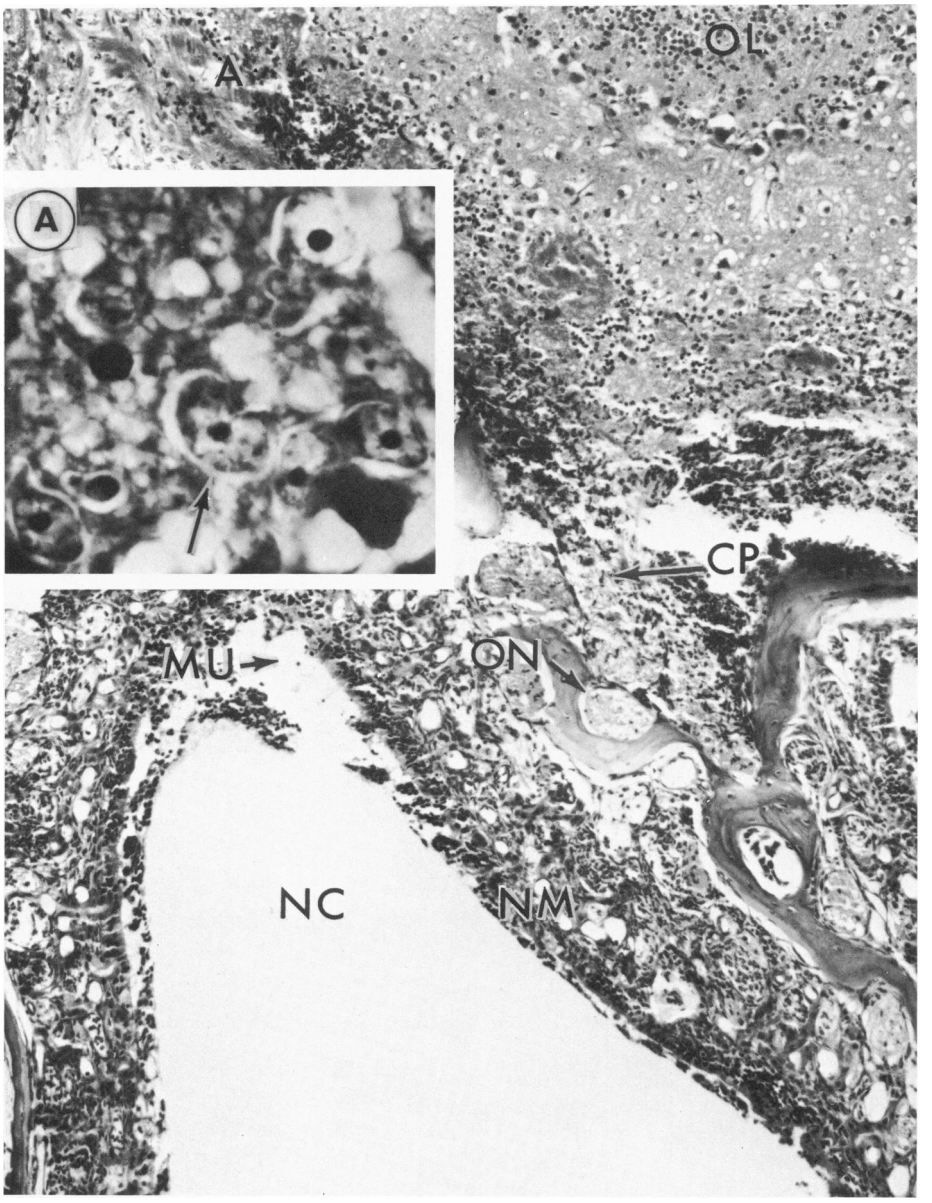

Fig 3—Five days after intranasal inoculation with *Naegleria*. Section at the level of cribriform plate showing acute inflammatory reaction of olfactory and nasal mucosal epithelium, subarachnoid space, and gray matter. Numerous amebas may be seen within the nasal structures, as well as within the subarachnoid space and brain. *NC* = nasal cavity, *NM* = nasal mucosa, *MU* = mucosal ulceration, *ON* = olfactory nerve, *CP* = cribriform plate, *OL* = olfactory lobe, *A* = amebas (H&E × 100). **Inset**—Amebas within neural parenchyma (H&E × 1000).

filtrated by actively multiplying motile amebas. Numerous organisms may be seen invading sustentacular cells, between sustentacular and sensory cells and other intercellular spaces, around small blood vessels and within the submucosal nervous plexuses (unmyelinated axons). At the surface of the nasal olfactory epithelium, swelling and partial disintegration of microvilli, sensory cilia and kinocilia are frequently noted, especially in those cells in direct contact with organisms.

Potential Usefulness of the Model

Important problems to be studied and clarified are the mechanisms of penetration by amebas through the nasal and olfactory epithelium, factors regulating proliferation of amebas within the nasal mucosa, host factors involved in invasion or spread of the organism and effects of chemotherapeutic agents and antibiotics on preventing or controlling infection. The use of this animal model provides an opportunity to examine the pathogenesis of the disease, mode of action of invasive ameboflagellates, epidemiology and control of the disease. Therefore, the model should contribute greatly to the clarification and understanding of its counterpart, human PAM.

Availability

Pathogenic strains of *Naegleria* were isolated in 1967, 1968 and 1969 by Dr. E. Clifford Nelson from 4 patients with terminal primary amebic meningoencephalitis in Virginia. These strains have been maintained in axenic culture in the Parasitology Laboratory, Microbiology Department, and in the Laboratory of Dr. Richard J. Duma, Division of Infectious Diseases at the Medical College of Virginia in Richmond.

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