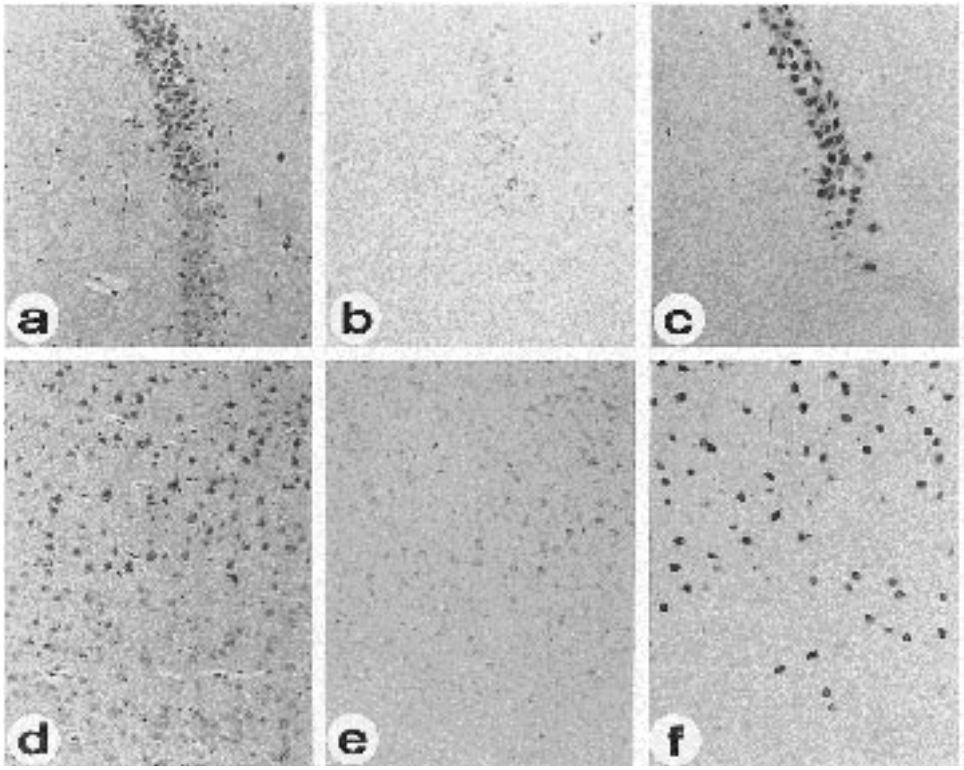
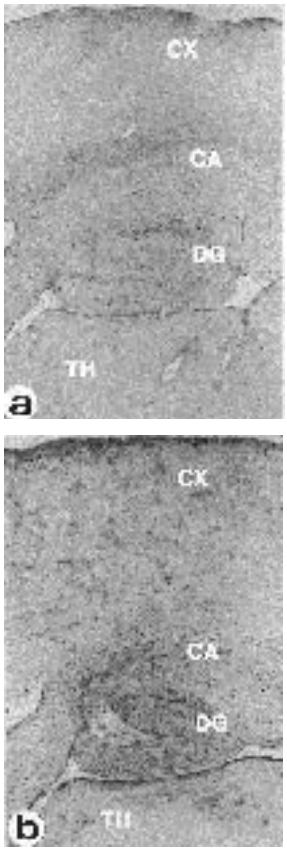
Carol A. Tamminga, M.D., Editor

Clinical Genetics, IV



↑ Evidence of neurodegeneration in brain tissue from transgenic mice who overproduce β-amyloid.



Histologic preparation from normal (a) and transgenic (b) mouse brain, which shows prominent gliosis and β-amyloid overexpression. →

Alzheimer's Disease: From Gene to Pathology

A defining histopathological feature in the brain of subjects with Alzheimer's disease is the presence of diffuse and neuritic plaques; their principal component is the β-amyloid peptide. Humans who genetically "overproduce" β-amyloid protein are prone to develop Alzheimer's disease. Yet, a firm demonstration that β-amyloid overproduction can produce the brain pathology of Alzheimer's disease has only recently appeared.

A transgenic mouse has been developed by using a neuron-specific transcriptional promoter to direct expression of the murine β-amyloid coding sequence such that the β-amyloid peptide accumulates intraneuronally in the transgenic animal. Despite transgene expression in neurons throughout the brain, intracellular accumulation of β-amyloid was detected selectively in regions of the hippocampus (left figure, part b) and cerebral cortex (left figure, part e) of the animals, areas that are known to be particularly involved in the pathology of Alzheimer's disease. Hematoxylin and eosin staining revealed that neurons with intracellular accumulation of β-amyloid have an altered morphology (left figure, parts a and d) and appeared highly degenerative. The eventual death of these cells was by apoptosis (left figure, parts c and f), as revealed by DNA fragmentation determined by TUNEL staining. Moreover, gliosis in the same areas was prominent (right figure, part b) when compared to control litter mates (right figure, part a). Premature death in these animals increased linearly over the first months of life to a mortality of about 50% at 12 months (normal 12-month mortality is about 5%).

This study shows that increased expression of β-amyloid intracellularly in transgenic mice is sufficient to serially induce neurodegeneration, apoptosis, astrogliosis, and, ultimately, spongiosis and is accompanied by seizures and premature death in the mice. Subsequent studies done in human postmortem Alzheimer dementia brain tissue confirm an association between overproduction of β-amyloid, apoptosis, and cell death. This observation that β-amyloid induces neuronal cell death through the apoptotic pathway in vivo suggests therapeutic approaches for the amelioration of Alzheimer's disease. This transgenic mouse model offers several experimental approaches to research in pathophysiology and therapeutics relevant to Alzheimer's disease.

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