al., 1992), subjects who survived the initial three-year trial in one of the two active medication conditions, were randomly assigned to an additional two years of full-dose pharmacotherapy or placebo. Once again, active medication was significantly superior to placebo ($p < 0.006$) in protecting against new episodes, this time in a group of patients who had all previously sustained a remission of almost 3.5 years prior to random to that apparently required in manic-depressive illness. What remains to be elucidated is: (1) whether more frequent maintenance psychotherapy can provide adequate protection against recurrence and (2) whether there are subgroups of recurrent unipolar patients who can ultimately discontinue treatment without adverse consequences.

GENETICS OF ALZHEIMER'S DISEASE: APP, APOE, AND THE CHROMOSOME 14 LOCUS

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At least three genetic loci can predispose towards AD. These are the APP gene, the ApoE gene and a locus on chromosome 14. Besides summarizing the role of APP mutations in disease pathogenesis, I shall present 4 series of analyses.

1) data indicating that ApoE genotype modulates onset age around 55 years in families with APP mutations with ApoE4 causing an earlier, and ApoE2 a later onset age relative to ApoE3.

2) data indicating that ApoE genotype does not modulate onset age in families with chromosome 14 locus encoded AD.

3) data confirming that ApoE4 shows a strong association with late onset AD.

4) genetic information confirming, but not further refining the position of the locus causing very early onset AD located between D14S52 and D14S55.

These data have been generated in collaborations with the Dementia and Prion groups at St. Mary's Hospital, London, the Alzheimer's Group at the Karolinska Institute, Sweden, the Department of Pathology, at the University of Helsinki, Finland and the Alzheimer's Genetic Group at the University of Antwerp, Belgium.

Gene Transfer in Astrogial Cells in a Rat Model of Parkinson's Disease

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Intracerebral transplantation of embryonic dopaminergic cells have shown, in particular, that local striatal restoration of dopaminergic neurotransmission may compensate for sensori-motor impairment associated with the nigro-striatal degeneration in animal models of Parkinson's disease. We are studying gene transfer as a tool to express the neurotransmitter synthesizing enzyme tyrosine hydroxylase (TH) locally in the striatum.

We are exploring both the retroviral system and the adenoviral one, with the aim of comparing their efficiency and safety. Initially, we have constructed two human TH recombinant retroviruses using either the Long Terminal Repeat (LTR) from the Moloney murine leukemia virus or the immediate early promoter from the cytomegalovirus to drive the expression of TH into primary cultures of embryonic striatal cells. Retroviruses only permit the genetic modification through incorporation into chromosomal DNA of dividing cells. We therefore made use of the ability of glial cells to divide in the presence of foetal calf serum or growth factors to allow their infection *in vitro* by the recombinant retroviruses. We could thereby modify up to 100% of glial cells as characterized by their endogenous GFAP, an astroglial marker, as well as the exogenous TH protein expression. The genetically modified astroglial cells were found to release DOPA in a constitutive manner *in vitro*. The functional capacity of the TH-expressing astroglial cells as well as their survival properties were studied after grafting to striatum of rats with 6-hydroxydopamine lesions. Two weeks after transplantation, apomorphine-induced turning was reduced by mean of 60%. TH immunoreactive cells were observed in the denervated striatum three weeks post-grafting. The adenovirus allows the infection of dividing as well as of non-dividing cells such as neurons, resulting in the introduction of recombinant genes in an episomal form. The relative efficiency of this system with that of the retrovirus system will be discussed.