diagnosis and appropriate therapy can be disastrous, especially in elderly patients in whom the condition is most frequently encountered. If erythromycin is to be advocated for treatment of colonic pseudo-obstruction, it should only be after controlled clinical trials.

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Amyloid precursor protein gene mutation in early-onset Alzheimer's disease

SIR,—A mutation within the amyloid precursor protein (APP) gene has been reported as the possible cause of Alzheimer's disease (AD) in two families in which the disease was apparently inherited as an autosomal dominant disorder.[1] This mutation results in a valine-to-isoleucine substitution at position 717 in the gene product. However, other genes seem to be involved[2,3] and the role of the 717 APP mutation as a cause of early-onset AD in the general population remains to be established.[4] To assess the proportion of early-onset AD that may be explained by the 717 APP mutation, we have screened 100 familial and sporadic cases.

Patients were derived from a population-based epidemiological study[5] aimed at a complete ascertainment of prevalent and incident cases of AD diagnosed before the age of 70 in four northern provinces of the Netherlands and in metropolitan Rotterdam. The clinical diagnosis was independently confirmed by a standardised protocol.[6] The patient response rate was 99%. Blood was collected from a sample of 100 of the 198 participating patients. The mean age of onset of dementia was 57 (SD 5) years. 48 cases were sporadic—ie, there were no first-degree relatives known with AD or dementia—and the other 52 had at least one first-degree relative with dementia. Among the 52 familial cases the pedigree was consistent with autosomal dominant inheritance of AD in 14—ie, there were at least 3 patients with dementia in two generations and at least 2 patients had detailed medical records on the clinical diagnosis of AD. Genealogy studies of second, third, and fourth degree relatives of these 14 patients did not reveal any relation between them.

DNA was extracted by the phenol-chloroform procedure and screened for the 717 APP mutation. The mutation creates a *Bcl*I restriction site that allows detection of the corresponding polymorphism within the polymerase chain reaction (PCR) product. For PCR we used the intron primers GTTGGGCAGA-GAATATACTGA and GCCTAATTCTCTCATAGTCT, generating a DNA fragment of 355 base pairs. PCR conditions were: 50 µl volume containing 0·1–0·2 µg DNA, 1·5 mmol/l $MgCl_2$, 0·05 mmol/l KCl, 10 mmol/l "tris" pH 8·3, 0·001% weight/volume gelatin, 0·2 mmol/l nucleotide triphosphates, 50 pmol of each primer, and 2 units of *Taq* DNA polymerase (BRL), and samples were covered with 50 µl mineral oil, 30 three-step cycles (1·5 min 94°C, 1·5 min 60°C, 2 min 72°C) being done in a Cetus 'Thermocycler' apparatus. PCR products were then digested with *Bcl*I (BRL) for 4 h at 50°C and analysed on 3% agarose (2·5% 'Nusieve' and 0·5% 'Seakem' [FMC]) at 2·5 V/cm for 5 h. A sample of family F23 which showed the 717 APP mutation,[1] was used in each screening as a positive control.

None of the 100 early-onset patients carried the mutation. At a confidence level of 95%, this finding suggests that the APP mutation accounts for less than 3·6% of all cases with early-onset AD. The corresponding upper limit of the 95% confidence interval for the 52 patients with a family history of dementia was 6·8% and for the 14 patients in families in which the disease was apparently inherited as an autosomal dominant disorder it was 23·2%. This study suggests that the 717 APP mutation is not a common cause of early-onset AD in the general population. Screening of patients with late-onset AD has also failed to show the 717 APP mutation.[1] Its presence in late-onset patients is less likely because families with late-onset AD do not show linkage to chromosome 21.[7] Despite the importance that the 717 mutation in the APP gene may have for our understanding of the pathogenesis of AD, for case diagnosis it seems to be of little value.

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Mis-sense mutation Val→Ile in exon 17 of amyloid precursor protein gene in Japanese familial Alzheimer's disease

SIR,—Genetic linkage studies suggest that familial Alzheimer's disease (FAD) is not a single entity but that some form of early-onset FAD is linked to chromosome 21.[1-4] It has also been suggested that some form of late-onset FAD is not linked to chromosome 21.[3,4] Goate et al[5] have identified a mis-sense mutation (Val→Ile) in exon 17 of amyloid precursor protein (APP) gene in 2 out of 16 early-onset FAD families. The mutation creates a new restriction site for *Bcl* I, and can be identifed by a *Bcl* I restriction fragment length polymorphism (RFLP). Goate et al did not find the mutation in 100 unrelated normal controls and 9 families of late-onset FAD. We urgently need to find out whether the mutation is the cause of FAD or merely a rare polymorphism associated with some FAD families. If the mutation were found frequently in FAD patients of different ethnic origin, that would strengthen the hypothesis that this mutation in the APP gene is a cause of FAD.

We have studied 3 Japanese early-onset FAD patients from three unrelated families, 12 sporadic cases of AD, and 30 unrelated normal individuals. Of the 3 FAD patients, case 1 (FAD1, figure) had histologically confirmed AD whereas cases 2 and 3 were diagnosed as FAD on clinical criteria.

1 µg genomic DNA was amplified by the polymerase chain reaction (PCR). The PCR products were digested with *Bcl* I. 2 of 3 FAD patients had the Val→Ile mutation in exon 17 of the APP gene; none of the 12 patients with sporadic AD and none of the 30 unrelated normal controls showed the *Bcl* I RFLP. Direct sequencing analysis of the PCR product revealed a mis-sense mutation identical to that described by Goate et al.[5]

The results strongly indicate that the Val→Ile mutation in exon 17 of the APP gene is associated with some cases of early-onset Japanese FAD. Since the mis-sense mutation has been identified in subjects of different ethnic origins and, furthermore, not identified in 130 unrelated normal individuals in two studies, it is very likely