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Review and Hypothesis: Alzheimer Disease and Down Syndrome—Chromosome 21 Nondisjunction May Underlie Both Disorders

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Introduction

It has been appreciated for some time that Alzheimer disease has a complex etiology. At least 15% of the cases appear to be due to the inheritance of an autosomal dominant mutation, but the majority are "sporadic," showing no clear association with any identifiable genetic or environmental factor (Feldman et al. 1963; Terry 1978; Heston et al. 1981; Jarvik and Matsuyama 1986). Even identical twins can show a large discordance in the age at onset of the disease (Nee et al. 1987). Yet, despite this variation, Alzheimer disease shows a uniform set of clinical and pathological features—progressive loss of memory and other intellectual functions beginning in middle to late life, coupled with neuronal cell loss in the higher centers of the brain (for review, see Price 1986).

When examined by histochemical stains, Alzheimer disease brains, particularly the hippocampus, neocortex, and amygdala, exhibit certain neuropathological protein deposits that serve as the defining characteristic of the disease. One such deposit, termed the "neurofibrillary tangle," occurs inside neurons and is composed of "paired helical" protein filaments (PHF). Because they can be found in other neurodegenerative diseases, paired helical filaments are likely to be a common feature of dying neurons. The more definitive lesion of Alzheimer disease is the "neuritic or senile plaque," which consists of a spherical, extracellular core of filamentous protein material surrounded by a halo of degenerating nerve-cell processes. Extracellular protein filaments similar to those seen in the cores of neuritic plaques also accumulate in the walls of meningeal and intracortical blood vessels. The deposits of protein filaments in the cores of neuritic plaques and in blood vessels are referred to by the generic term "amyloid."

The first identified constituent of Alzheimer amyloid deposits was purified from meningeal blood vessels and its sequence was determined by Glenner and Wong (1984*a*). This protein, termed "β" or "A4," is an ~42-amino-acid-long fragment of a larger protein that is a normal constituent of the brain and other tissues. A second protein component of Alzheimer amyloid deposits was identified as the serine protease inhibitor α_1-antichymotrypsin (ACT) (Abraham et al. 1988). In the past few years, much has been learned about the biochemistry and expression of the aberrant protein deposits that characterize Alzheimer disease (for reviews, see Abraham and Potter 1989; Müller-Hill and Beyreuther 1989; Selkoe 1989*a;* Neve and Potter, in press). However, no hypothesis has easily explained how both genetic and sporadic forms of Alzheimer disease can be related by a common underlying mechanism.

Perhaps the most interesting clue to the cause of Alzheimer disease is the fact that Down syndrome patients who live beyond the age of 30 or 40 years develop dementia and neuropathology essentially indistinguishable from classic Alzheimer disease (Olson and Shaw 1969; Glenner and Wong 1984*b;* Wisniewski et al. 1988). The implication of this finding is that trisomy for chromosome 21—the pathogenetic cause of Down syndrome—is also capable of causing Alzheimer disease, possibly through the overexpression of a gene residing on chromosome 21 (for discussion, see Schweber 1985). On the other hand, almost all aged humans (and monkeys) develop some amyloid deposits which, by several criteria, appear to be identical to those that accumulate in much larger numbers and at an earlier time in both Alzheimer disease and Down syndrome (Wisniewski and Terry 1973; Selkoe et al.

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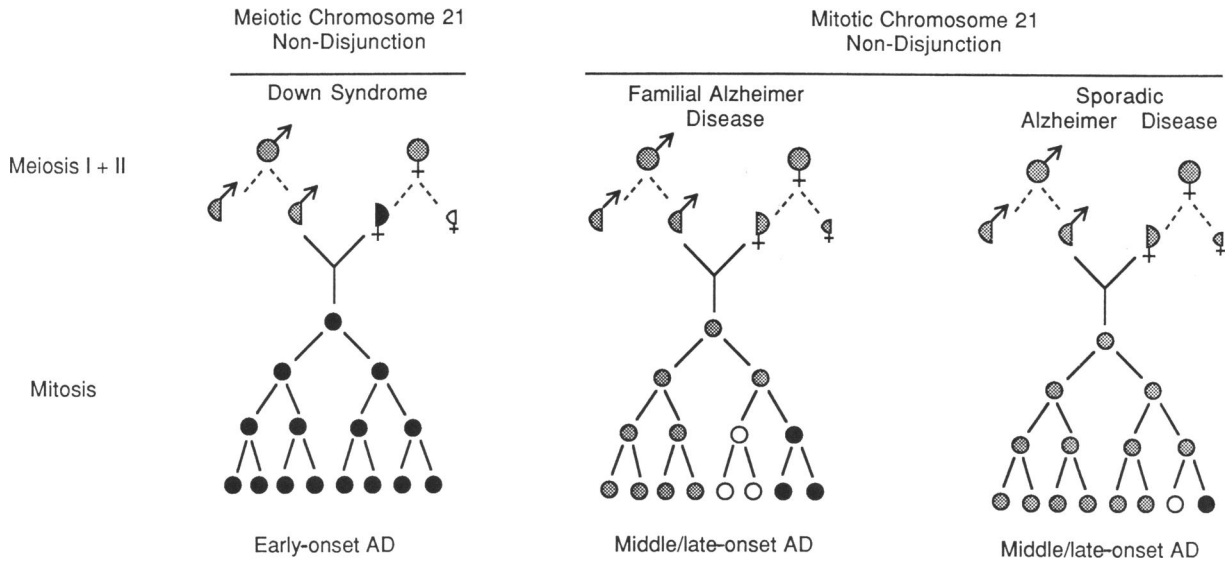

Figure 1 Alzheimer disease model based on mitotic nondisjunction of chromosome 21. Down syndrome patients develop Alzheimer disease by age 40 years and have a trisomy 21 karyotype due to meiotic nondisjunction (*left*). A small proportion of "Down" syndrome is mosaic, probably arising from nondisjunction of chromosome 21 early in development. These patients may not exhibit the classic Down phenotype but can still develop early-onset Alzheimer disease. As discussed in the text, both familial (*middle*) and sporadic (*right*) forms of Alzheimer disease may be similarly explainable as arising from either genetic mutation or environmental agents that increase the frequency of mitotic nondisjunction and thus lead to varying degrees of trisomy 21 mosaicism. The trisomy 21 cells would lead to Alzheimer disease through the same (as yet unknown and possibly multistep) process by which Down syndrome patients develop the disease—but at later ages, because of the modulating effect of the mosaicism. ⊛ = 46 (normal) karyotype cell; ○ = 45 (−21) karyotype cell, ● = 47 (+21) karyotype cell.

1987; Abraham et al. 1989). Thus, any hypothesis for the pathogenesis of Alzheimer disease should be able to explain not only the relation between the familial and sporadic forms of the disease but also how these are related to Down syndrome and to the "normal" process of aging.

Hypothesis

The association between Alzheimer disease and chromosome 21 has been reinforced by a number of recent clinical and experimental findings. This review will consider these and earlier results on the genetics, epidemiology, and cell biology of Alzheimer disease—and, in particular, its association with Down syndrome—and will suggest that both the genetic and sporadic forms of Alzheimer disease can be explained as arising from the accumulation of chromosome 21 trisomy cells during the life of the individual. That is, trisomy 21 cells, developing over time by unequal chromosome segregation during *mitosis,* may ultimately lead to Alzheimer disease through the same (as yet unknown and perhaps multistep) mechanism by which Down syndrome patients acquire the disease—but at a later age, because of the modulating effect of the mosaicism (see fig. 1).

Alzheimer Disease and Chromosome 21

The first specific model linking Alzheimer disease to Down syndrome arose when the gene for the amyloid β-protein was cloned and found to be located on chromosome 21 (Goldgaber et al. 1987; Kang et al. 1987; Robakis et al. 1987; Tanzi et al. 1987*a*). The implication of these results seemed clear—perhaps the accumulation of amyloid in Alzheimer disease is caused by the overexpression of a mutant β-protein gene or by a duplication of the β-protein gene that resides on chromosome 21 and that mimics the gene-dosage effect of Down syndrome. The fact that some Alzheimer disease families could be shown to harbor their autosomal dominantly inherited mutation on chromosome 21 (St. George-Hyslop et al. 1987) and that the β-protein precursor gene was apparently overexpressed in Down syndrome (Tanzi et al. 1987*a;* Neve et al. 1988) further implicated the β-protein gene as a

potential site for the disease locus. Very recently, a β-protein precursor gene variant encoding a mutant β-protein *has* been found in families with hereditary cerebral hemorrhage with amyloidosis of Dutch origin, suggesting that this mutation may be the inherited defect in this disease (Levy et al. 1990; Van Broeckhoven et al. 1990). However, an early study suggesting that the β-protein gene existed in three copies in Alzheimer disease patients was not confirmed. Also, the pattern of expression of the β-protein gene was seen to be subtly altered in Alzheimer brain but not simply overexpressed (for data and discussion of Alzheimer- and Down syndrome–specific changes in the expression of the several β-protein precursor mRNAs, see Tanzi et al. 1987*a;* Higgins et al. 1988; Neve et al. 1988; Palmert et al. 1988; Golde et al. 1990). Finally, the actual location of a potential Alzheimer disease mutation on chromosome 21 in some families was soon shown to be far from the β-protein gene itself and closer to the centromere (Tanzi et al. 1987*b;* Van Broeckhoven et al. 1987; Goate et al. 1989). The finding of some families showing no linkage to any marker on chromosome 21 suggests that the inherited form of Alzheimer disease is genetically heterogeneous (Schellenberg et al. 1988; St. George-Hyslop et al. 1990). Chromosome 19 (Roses et al. 1990) and possibly the region of chromosome 14 now known to be close to the ACT gene (Weitkamp et al. 1983; Rabin et al. 1986) have been proposed as candidate locations for the disease locus. These results indicate that an aberrant biochemical pathway leading to the Alzheimer neuropathology can be initiated by mutation in a number of genes—including one on chromosome 21—but not generally in the β-protein precursor gene itself.

Chromosome 21 was further implicated in the etiology of Alzheimer disease by the discovery that some families in which Alzheimer disease is inherited as an autosomal dominant mutation produce a significantly higher-than-normal number of Down syndrome children (Heston and Mastri 1977; Heston et al. 1981; Heyman et al. 1983). In the first study, the total number of Down cases was 11 of 3,044 Alzheimer disease relatives. The mothers' ages at the birth of their children were given as 21, 26, 30, 35, 39, 40, 41, and 46, and two ages were unknown. The average maternal age (34 years) is higher than the average maternal age for all births, which is approximately 29 years. However, the results would still be significant if, for instance, the children of the two or three oldest mothers were not considered (the frequency of Down syndrome is 1.3/1,000 live births to mothers of all ages). The number of relatives analyzed in the second study was 1,278, including four Down syndrome individuals conceived to mothers of ages 26, 31, 33, and 38 years. These numbers are small, and the average maternal age is a little high, but even if the one case of age 38 years were to be artificially removed, the results would still be statistically significant. In contrast, other researchers have failed to confirm the increased incidence of Down syndrome in families with inherited Alzheimer disease, but they report that the number of relatives they analyzed was too few for the lack of Down syndrome to be statistically significant (Whalley et al. 1982; Amaducci et al. 1986; Chandra et al. 1987). Although more work should probably be carried out to confirm the association between a high frequency of Down syndrome and Alzheimer disease in the same family, the data in the largest studies are statistically significant.

Recently, mouse chromosome 16, which is partially homologous to human chromosome 21, including the β-protein gene, has been shown to result, when trisomic, in neurodegeneration somewhat like that seen in Alzheimer disease (Richards et al. 1991). Because mouse chromosome 16 is much larger and contains many more genes than does human chromosome 21, trisomy 16 mice suffer many developmental abnormalities and do not survive to term. However, the specific effect that this trisomy has on the nervous system can be tested by transplanting embryonic brain tissue from a trisomy 16 embryo into the brain of a normal adult. When the brains of such host mice with their trisomy 16 grafts were examined, it was found that some of the neurons in the graft had accumulated aberrant immunoreactivity similar to that found in and around degenerating neurons in Alzheimer disease. Specifically, thioflavin S, a histological marker for amyloid, showed positive staining within a few cells and around some blood vessels. In addition, antisera to the β-protein precursor, to β-protein itself, to ACT, to PHF, and to phosphorylated epitopes of tau labeled a few percent of cells in the trisomy 16 grafts. There was also some extracellular staining for ACT and β-protein precursor. When dissociated cells from trisomy 16 embryos were transplanted, the effects were not observed (Ault et al. 1990, and personal communication), suggesting that cell-cell interaction or cell degeneration in the bulk trisomy 16 tissue grafts used by Richards and her colleagues may be necessary for the neuropathology to develop. It is interesting that, although β-protein precursor RNA was overexpressed approximately twofold in trisomy 16 fetal

mouse brains, it was overexpressed fivefold in the brains of chimeric (mosaic) mice having 40%–50% trisomy 16 cells, again suggesting that a complex cell-cell interaction affects the expression of this gene (Holtzman et al. 1990).

Alzheimer Disease in Trisomy 21 Mosaics

The most recent link between Alzheimer disease and chromosome 21 is evidenced by reports of two women whose lymphocytes were found to be mosaic for trisomy 21 and who, though not mentally retarded, had developed Alzheimer-like dementia by age 40 years (Rowe et al. 1989; Schapiro et al. 1989; for discussion, see Hardy et al. 1989). In one case the woman also had a Down syndrome child. An unusual family with an inherited aberrant chromosome 22–derived marker chromosome was found by Percy et al. (in press) to also have a high frequency of Alzheimer disease. The two living affected members of the family carried the marker chromosome, and one was also found to be mosaic for trisomy 21; only lymphocytes were analyzed from the other patient (see relevant discussion below). The two patients reported by Schapiro and Rowe and their colleagues and possibly the mosaic individual reported by Percy and her colleagues demonstrate that it is not necessary for every cell of an individual to be trisomy 21 for the aberrant effects of this chromosome imbalance to result in early Alzheimer dementia. The later-onset dementia of classic Alzheimer disease could thus result from an even smaller percentage of trisomy 21 cells that may go undetected.

Implications of Model

If it is true that Alzheimer disease and most Down syndrome cases result from unequal chromosome 21 segregation in somatic and germ cells, respectively, then much seemingly diverse data can be more easily understood. For instance, one immediate implication is that any genetic or environmental factor that increases the chances of forming chromosome 21 trisomic cells should increase the likelihood of developing Alzheimer disease. Thus, in the families in which the disease is apparently inherited as an autosomal dominant mutation near the centromere of chromosome 21, perhaps the mutation resides in the centromere itself, so as to cause an increased frequency of nondisjunction of chromosome 21. During mitosis such nondisjunction would build up trisomy 21 somatic cells, eventually leading to Alzheimer disease pathology, while during meiosis it would generate trisomy 21 germ cells and Down syndrome offspring, as the epidemiological evidence suggests. Indeed, there are centromere mutations known in yeast that result in a 100-fold increase in chromosome nondisjunction (Gaude and Fitzgerald-Hayes 1987).

Of course chromosome segregation is a complex process under the control of many gene products (for review, see Murray and Szostak 1985), and an inherited disorder of chromosome segregation could be caused by mutations at a number of loci. In this light, the fact that familial Alzheimer disease appears to be genetically heterogeneous is not surprising, since any one of several mutations could lead to the development of trisomy 21 cells, both somatic and germ line, with the consequent development of Alzheimer disease in the individual and with an increased frequency of Down syndrome offspring. Several researchers have suggested that a specific microtubule defect could lead directly to the neuronal pathology and indirectly to the increase in Down offspring in Alzheimer disease through chromosome nondisjunction (Heston and Mastri 1977; Nordenson et al. 1980; Matsuyama and Jarvik 1989).

Although improper chromosome segregation can result from a genetic mutation, it can also be caused by environmental agents. Of the many exogenous factors that influence chromosome segregation, microtubule-disrupting agents such as colchicine and low doses of radiation are perhaps the best studied (e.g., see Uchida et al. 1975). Aluminum, the consumption of which shows a weak but significant association with the development of Alzheimer disease (e.g., see Martyn et al. 1989), also binds to microtubules and, in the form of aluminum silicate, causes chromosome nondisjunction in cultured cells (Paleker et al. 1987; for discussion, see Ganrot 1986). Thus, the large proportion of Alzheimer disease cases that arise in a sporadic manner not directly attributable to the inheritance of a genetic mutation can also be understood in the light of the chromosome 21 trisomy model.

An important prediction of this model is that it is the dividing cells in an individual that are most likely to develop chromosome 21 trisomy and to lead to Alzheimer disease. Extensive analysis by Rakic (1985) has shown that the only dividing cells in the brains of adult monkeys exposed to ^{3}H-thymidine are glial cells and the endothelial cells lining blood vessels, while neurons, the cells most apparently affected by Alzheimer disease, do not divide. The labeled glia were seen primarily in the hippocampus and the cerebral cortex.

Thus cell division in the brains of adult primates occurs in those general regions that develop neuropathology in Alzheimer disease, Down syndrome, and normal aging. It is interesting that astroglia in the hippocampus and cortex of Alzheimer disease brain overexpress ACT and that astrocytes can be induced by kainic acid lesions to overexpress the β-protein precursor (Pasternack et al. 1989; Siman et al. 1989; for discussion of how overexpression of ACT or β-protein precursor can lead to amyloid formation, see Abraham and Potter 1989). Recently, two rapidly dividing peripheral tissues—skin and intestinal mucosa—have been reported to contain preamyloid deposits of β-protein in sporadic Alzheimer patients and in some aged, normal subjects (Joachim et al. 1989). Another region of active cell division, which has been shown to exhibit pathological changes in Alzheimer disease, is the olfactory epithelium (Talamo et al. 1989). Thus there seems to be a rough correlation between regions of cell division and areas where Alzheimer pathology can develop. Of course, mitotic nondisjunction could also occur early enough in embryogenesis to generate trisomy 21 in nondividing adult cells such as neurons.

Although it would seem reasonable that amyloid should develop in the regions immediately surrounding aberrant cells (e.g., trisomy 21 cells), the precedent provided by other amyloidoses suggests that this need not be the case. For instance, the autosomal dominantly inherited diseases familial amyloidotic polyneuropathy and hereditary cerebral hemorrhage with amyloidosis of both the Dutch and Icelandic types have very specific regions of amyloid deposition despite the fact that all cells in the body carry the point mutation in the affected amyloid gene (transthyretin, cystatin C, or β-protein precursor, respectively) and that these genes are expressed in many parts of the body where the amyloid does not deposit (for review, see Castaño and Frangione 1988). Thus, by analogy, the trisomy 21 cells that are relevant for the formation of amyloid pathology in Down syndrome (and, according to the hypothesis, in Alzheimer disease) need not reside in the brain at all. Indeed, some researchers believe that the β-protein is transported to the brain by the circulation, having been generated elsewhere (for recent data and discussion, see, e.g., Selkoe 1989*b*).

In sum, both genetic and sporadic forms of Alzheimer disease can be explained as arising from the effects of trisomy 21 cells accumulating during the life of the individual. A propensity to develop such cells could be genetic in origin (either due to an aberrant chromosome 21 centromere or to a mutation occurring elsewhere in the genome and affecting all chromosome segregation), or it could be caused by environmental factors. A combination of genetic and environmental influences on the formation of trisomic 21 cells could yield the observed variation in the age at onset of Alzheimer disease in identical twins and in Alzheimer disease families. In addition, the fact that almost 50% of the population over the age of 85 years show some symptoms of Alzheimer disease dementia (Evans et al. 1989) and that an even larger proportion shows some of the same neuropathological lesions indicates that all individuals may, to some degree, be subject to stochastic events that lead to aberrant chromosome segregation with increasing age. The possibility that further biochemical or genetic events may be required before full Alzheimer neuropathology arises is indicated by the mature age (20s–30s) at which Down syndrome patients begin to accumulate amyloid deposits.

Aneuploidy in Aging and Alzheimer Disease

Cytogenetic analysis of Alzheimer diseases patients has been carried out in a number of laboratories, with mixed reports of increased aneuploidy or other abnormalities as measured directly (Jarvik et al. 1974; Ward et al. 1979; Nordenson et al. 1980; White et al. 1981; Buckton et al. 1983; Moorhead and Heyman 1983). Furthermore, premature centromere division (PCD), a correlate and potential cause of improper chromosome segregation in vitro and in vivo, was found to be positively correlated with age and to be increased in women with familial Alzheimer disease (3.6% vs. 0.6% in age-matched controls), particularly affecting the X chromosome (Fitzgerald et al. 1975; Moorhead and Heyman 1983). Trisomy 21, 18, and X occurred in the lymphocytes and fibroblasts of a woman apparently prone to PCD, who also had three trisomy 21 conceptuses (Fitzgerald et al. 1986). Patients with Roberts syndrome, a rare autosomal recessive disorder characterized by growth and mental retardation and by craniofacial abnormalities, also shows PCD—there can be significant aneuploidy, usually involving chromosome loss rather than gain (except for trisomy 7) (see Römke et al. 1987; Jabs et al. 1989). PCD can also be found that appears limited to the X chromosome and that results, presumably by nondisjunction, in many cells with one or three X chromosomes (Fitzgerald et al. 1975). Since Roberts syndrome families with extensive PCD have also been found that exhibit normal karyotypes and phenotypes (Madan et al.

1987), PCD need not result in nondisjunction, but, when it does, severe developmental abnormalities can result if the autosomes are affected. The report by Fitzgerald et al. (1986) is the only case of PCD in which trisomy of chromosomes other than the X chromosome were prevalent. Why Roberts syndrome generally results in chromosome loss rather than gain is not clear. Perhaps, because of the severe mental retardation exhibited by these patients, neurological and pathological tests for Alzheimer disease have not been reported.

The fact that the chromosomes that exhibit PCD in an individual do not necessarily correspond to those which ultimately are lost or gained to give an aberrant karyotype (there is a prevalence of trisomy 21, 18, and X in the general PCD case of Fitzgerald et al. [1986]) probably reflects differential cell viability. For instance, lymphocyte cultures from trisomy 21 mosaic individuals often show a lower proportion of trisomy cells than do, for instance, fibroblast cultures. Indeed, some patients with over 10% trisomy 21 fibroblasts can show a normal karyotype in lymphocytes (out of, e.g., 30 metaphases) (Pagon et al. 1979; Ford 1981). Thus, the fact that cytogenetic studies on Alzheimer patients have almost always relied on peripheral blood lymphocytes (e.g., see Jarvik et al. 1974; Ward et al. 1979; Nordenson et al. 1980; White et al. 1981; Buckton et al. 1983; Moorhead and Heyman 1983) may have prevented trisomy 21 mosaicism from being detected and linked to Alzheimer disease. In these studies, fewer than 100—or even in some cases, fewer than 50—lymphocyte metaphases per sample were examined, and the few percent with increased aneuploidy (generally a loss) for any chromosome in Alzheimer disease was usually not significantly different from that in controls. The specific frequency of trisomy 21 was too low to be useful or was not stated.

Future Directions

Further cytogenetic studies of Alzheimer and normal aged patients are the best way to test the proposed model linking trisomy 21 mosaicism to Alzheimer disease. Both analysis of dividing cells from affected areas of the brain—glia, endothelial cells of the meningeal and cortical vessels, and the olfactory epithelium—and, possibly, analysis of skin fibroblasts may be expected to be most useful. Procedures have recently been developed (Lichter et al. 1988; Fuscoe et al. 1989) that allow the number of chromosomes 21 to be counted in both metaphase and interphase nuclei. The methodology is based on in situ hybridization with, for instance, biotin-labeled chromosome 21–specific probes that are then visualized by fluorescein-labeled streptavidin. The advantage that this approach has over standard cytogenetics is that both dividing and nondividing cells can be studied and, more important, that the number of chromosomes in interphase nuclei in tissue sections can be counted (Lichter et al. 1988). Because the number of cells that might harbor three copies of chromosome 21 in Alzheimer brain or peripheral tissue might be very small, the finding of a small cluster of trisomy cells would be far more significant than finding the same number of cells one at a time among a population of thousands of other cells after they have been disaggregated and induced to divide in culture to yield metaphase chromosome spreads. The large number of "normal" aged individuals who show some symptoms of Alzheimer disease and some Alzheimer pathology (neurofibrillary tangles and amyloid deposits) will make it necessary to carry out careful comparisons between Alzheimer disease patients and age-matched controls. Such an analysis would, of course, be made easier by concentrating on earlier-onset (often familial) Alzheimer cases. Although initial studies would seem to be best directed at searching for trisomy 21 cells in the brain, the possibility (discussed above) that Alzheimer amyloid deposits may arise from aberrant cells in the periphery suggests that a similar in situ hybridization analysis should also be carried out on various other tissues, such as skin and the intestinal mucosa.

If Alzheimer's disease patients are found to be mosaic for trisomy 21, then we might expect them to exhibit some other abnormalities of Down syndrome in addition to dementia—e.g., hypersensitivity to acetylcholine agonists and antagonists (Berg et al. 1959; Harris and Goodman 1968; Sacks and Smith 1989). Such characteristics, together with in situ hybridization for chromosome 21, might form the basis of a diagnostic test for Alzheimer disease.

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