A method is proposed to treat with myelin protective agents Alzheimer's disease and other conditions satisfying the retrogenic neuropathologic vulnerability model. These conditions include normal brain aging, mild cognitive impairment and specific non-AD dementing disorders. Such agents are vitamin B–12 (cobalamin), homocysteine modulators (containing vitamin B–12, folate [folic acid], vitamin B–6 [pyridoxine] and/or betaine [trimethylglycine]), a calpain–inhibitor, or interferon–beta. Another treatment is to maintain lipid reparative mechanisms to lessen the progressive destruction of myelin pathways in the patient's brain. Such reparative mechanisms are cholesterol levels or cholesterol transport.
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TREATMENT OF BRAIN CHANGES WITH MYELIN PROTECTIVE AGENTS

Field of the Invention

This invention relates to agents and methods of treatment of normal aging changes in the brain, mild cognitive impairment, progressive Alzheimer's disease, and other retrogenic dementing disorders. It relates to a new use of myelin protective and myelin regenerative agents such as vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12 [cobalamin], folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), calpain-inhibitors, and interferon-beta, as well as the maintenance of optimal lipid reparative mechanisms, such as cholesterol levels and cholesterol transport.

Background of the Invention

Brain aging, mild cognitive impairment, Alzheimer's disease and many other degenerative dementias are largely untreatable at the present time. Nevertheless, substances are currently prescribed in an effort to mitigate some of the symptoms of these conditions or to assist in preventing further deterioration. The only approved compounds for the treatment of Alzheimer's disease in the United States at the present time are cholinesterase inhibitors. There are no approved treatments at the present time for brain aging or mild cognitive impairment. The cholinesterase inhibitors endeavor to treat Alzheimer's disease by replacing a deficient and/or deficiently functioning, brain chemical, known as a neurotransmitter. In the case of the cholinesterase inhibitor treatments, the neurotransmitter affected is acetylcholine.

Perhaps one reason why brain aging, mild cognitive impairment, Alzheimer's disease, and many other degenerative dementias are largely untreatable is that the cause of these conditions is unknown. Alzheimer's disease is known to
be associated with characteristic brain changes, primarily: (1) abnormal accumulation of a substance known as beta amyloid into so-called beta-amyloid plaques or senile plaques, and (2) abnormal accumulation of structures known as neurofibrillary tangles, composed in part of a substance known as tau. Alzheimer’s disease is also known to be accompanied by cellular (neuronal) losses, particularly in certain brain regions. To the extent that non-neuronal changes are seen in the brains of Alzheimer’s disease patients, they have been believed to be largely secondary to neuronal losses. For example brain atrophy has been shown to occur in AD. This is believed to be the result of loss and/or dysfunction in brain neurons and neuronal processes.

The cause of the brain changes seen in normal aging and mild cognitive impairment is also unknown. It does appear that normal aging of the brain and mild cognitive impairment are accompanied by the occurrence of many of the same brain changes as those observed in AD, however the magnitude of these changes in normal aging and mild cognitive impairment is less than in AD.

The cause of non-AD degenerative dementias is also frequently unknown. These other degenerative dementias for which the cause is unknown include Lewy Body dementia, Pick’s dementia, and other so called "frontal lobe dementias" also known as fronto-temporal dementias. There are also degenerative dementias which are believed to be caused by proteinaceous infectious agents known as prions. The major degenerative dementia in humans which is caused by prions is Creutzfeldt Jacob disease (CJD). Degenerative dementias for which the cause is at least partially known include cerebrovascular dementia and spinocerebellar ataxia. Cerebrovascular dementias are believed to relate to strokes and risk factors for stroke. Spinocerebellar ataxias are known to be associated with genetic defects.

We have been studying the symptoms of AD, normal aging and mild cognitive impairment for many years. These studies initially resulted in the description of seven global clinical stages from normal to severe AD in the global
deterioration scale (GDS) (Reisberg, B., Ferris, S.H., de Leon, M.J., et al., 1982). Based on the global deterioration scale, we identified other, optimally concordant progressive changes, including progressive functional changes in AD. We ultimately described 16 successive functional stages and substages in AD with a measure known as the Functional Assessment Staging (FAST) procedure (Reisberg, B., 1986, 1988). We quickly recognized that the FAST stages in AD reversed the pattern of acquisition of the same functions in normal human development. Later we described other changes in AD including loss of capacity in figure drawing (praxis) and feeding abilities, and showed that these progressive AD changes also appeared to reverse the order of acquisition of the same capacities in normal development (Reisberg, B., Patschull-Furalan, A., Franssen, E., et al., 1990).

Accordingly, we set out to study other symptoms in AD. We found that so called "developmental" neurologic reflexes, which are also known as "primitive" neurologic reflexes, which are present in the infant, reappear in the AD patient in the late stages of the disease (Franssen, E.H., Reisberg, B., Kluger, A., et al., 1991; Franssen, E.H., Kluger, A., Torossian, C.G., et al., 1993). Recently we found that these developmental reflexes can serve as sensitive, specific and accurate markers of the emergence of incontinence in AD patients (Franssen, E.H., Souren, L.E.M., Torossian, C.L., et al., 1997). In other work, we found that the pattern of change in the brain's electrical activity, measured with the computer analyzed electroencephalogram (EEG), occurred in progressive AD in a pattern which also seemed to reverse the pattern of EEG changes in normal human development (Prichep, L.S., John, E.R., Ferris, S.H., et al., 1994; Reisberg, B., Franssen, E.H., Souren, L.E.M., et al., 1998). The progression of these functional, praxis, feeding, neurologic and other changes in AD occurred in a stage specific pattern (Reisberg, B., Franssen, E.H., Bobinski, M., et al., 1996; Reisberg, B. in Sadovoy, J., Lazarus, L., Jarvik, L.F., et al., 1996; Reisberg, B., Patschull-Furalan, A., Franssen, E., et al., 1990). Recently, we recognized that based on the FAST functional level of
deterioration of the AD patient, each stage of AD could be heuristically translated into a developmental age (DA) (Reisberg, B., Franssen, E.H., Souren, L.E.M., et al., 1998). For example, FAST stage 6d corresponds to the development of urinary incontinence in the AD patient, which corresponds to a DA of approximately 3 to 4 years, the age when a normal child achieves urinary continence. Feeding changes, praxis changes, neurologic "developmental" reflex changes, and EEG changes all appear to occur in the AD patient at any particular stage, at a magnitude which might be anticipated from a knowledge of the corresponding developmental age of the AD patient (Reisberg, B., Franssen, E.H., Souren, L.E.M., et al., 1998).

Furthermore, many of the emotional changes which occur in the AD patient can be explained from a knowledge of the corresponding DA (Reisberg, B., Auer, S.R., Monteiro, I., et al., 1998). Additionally, the progressive (consistent) nature of symptoms in AD can be predicted from the DA model, as can the variability of a symptom in AD (Reisberg, B., Franssen, E.H., Souren, L.E.M., et al., 1998). For example, language capacity is acquired continuously in normal development and lost continuously in the degenerative dementia of AD. Similarly, emotional changes are variable in occurrence and course in both normal human development and AD.

**Brief Description of the Invention**

The present invention provides a treatment of Alzheimer's disease, normal brain aging changes, and other retrogenic dementias with myelin protective agents. We have found that these conditions can be treated, or their course slowed, with myelin protective and regenerative agents including vitamin B12 (cobalamin), homocysteine modulators (containing Vitamin B-12 [cobalamin]), folate [folic acid] and vitamin B-6 [pyridoxine] and/or betain [trimethylglycine], calpain-inhibitors, and interferon-beta, as well as maintenance of optimal lipid reparative mechanisms such as cholesterol levels and cholesterol transport. In general, preservation of the myelinogenic pathways provides a treatment for AD and the other mentioned conditions.

Myelin degeneration and/or destruction is not currently believed to be a
cause of AD, normal brain aging, mild cognitive impairment, or other degenerative
dementias. Unexpectedly, and astoundingly, we have discovered that this myelin
degeneration is, in fact, a cause of Alzheimer’s disease, the major form of dementing
disorders. We have also found that myelin degeneration is a cause of the brain
changes seen in normal aging, mild cognitive impairment, and in certain other
dementing disorders. We have made these discoveries by initially discovering a new
general phenomenon which we have termed "retrogenesis", which explains the
pathologic symptoms of AD and certain other dementias. An important specific
mechanism of this general retrogenesis process is another previously undescribed
phenomenon which we have discovered, which we term "arboreal entropy".

**Detailed Description of Preferred Embodiments**

We now believe we have discovered a new general phenomenon, which we
call retrogenesis, which describes the process by which progressive pathologic
changes occur in a sequence which reverses the order of acquisition of the same
changes in the course of normal human development. Satisfactory proof of this
retrogenesis phenomenon required the accumulation of extensive data which we
have now, as a result of more than a dozen years of effort, collected and studied.

Many years ago we described the successive functional stages and substages
of aging and AD in the Functional Assessment Staging (FAST) procedure and noted
their apparent occurrence in the reverse order to that of normal development
(Reisberg, B., 1986, 1988; Reisberg, B., Pattschull-Furlan, A., Franssen, E., et al.,
1990). General correlational relationships between the FAST progression and
standard dementia assessments such as the MMSE were also described ( reviewed
in Reisberg, B., Franssen, E., Bobinski, M., et al., 1996). However, the
demonstration that each stage and substage of the FAST in AD is accompanied by
lower values on an independent standard assessment of the magnitude of cognition
in AD, such as the Mini Mental Stage Examination (MMSE) (Folstein, M.E.,
Folstein, S.E., and McHugh, P.R., 1975), required the accumulation of sufficient
data. This research has recently been completed.
We studied 850 consecutive subjects with normal aging, mild memory impairment and Alzheimer’s disease. The mean age of the subjects was $74.0 \pm 9.5$ years and there were 537 women and 313 men. The diagnostic distribution was as follows: 158 normal aged subjects (global deterioration scale (GDS; Reisberg, B., Ferris, S.H., de Leon,M.J., et al., 1982) stages 1 and 2; 103 subjects with mild cognitive impairment (GDS stage 3), and 589 subjects with mild (GDS stage 4, $n = 154$), moderate (GDS stage 5, $n = 171$), moderately severe (GDS stage 6, $n = 146$), and severe AD (GDS stage 7, $n = 118$). Analyzable data was obtained on 847 of the 850 subjects. Within the assessment range of the MMSE, a strictly cognitive measure, with no functional component, each stage and substage of the FAST from FAST stage 2 (subjective impairment only), where the MMSE shows ceiling effects, to FAST stage 7 (doubly incontinent and predominantly averbal), where the MMSE shows floor effects, shows lower mean scores on the MMSE. Specifically, mean MMSE scores on the FAST and the corresponding developmental ages (DAs), in adolescents, children, and infants (see Reisberg, B., Franssen, E.H., Souren, L.E.M., et al., 1998; Reisberg 1986) were as follows: FAST stage 2, DA = normal aged adult, mean MMSE = 28.80 ($n = 186$); FAST stage 3, DA = 12 years through adolescence, mean MMSE = 26.85($n = 75$); FAST stage 4, DA = 8 to 12 years, mean MMSE = 21.27 ($n = 166$); FAST stage 5, DA = 5 to 7 years, mean MMSE = 17.43($n = 109$); FAST stage 6a, DA = 5 years, mean MMSE = 13.43($n = 37$); FAST stage 6b, DA = 4 years, mean MMSE = 11.44 ($n = 34$); FAST stage 6c, DA = 4 years, mean MMSE = 9.7 ($n = 59$); FAST stage 6d, DA = 3 to 4 ½ years, mean MMSE = 8.22($n = 23$); FAST stage 6e, DA = 2 to 3 years, mean MMSE = 4.85($n = 46$); FAST stage 7, DA = 15 months or less, mean MMSE = 0.13($n = 112$). Hence, each stage and substage of the FAST, a measure which mirrors the sequence of functional acquisition, can be shown to be accompanied by a lower cognitive state in the dementia of AD, proving the validity of the retrogenesis clinical model.

We now find that this retrogenesis model can also describe the overall management needs of the AD patient, as well as the AD patient’s emotional disturbances and needs, activity requirements, and overall care needs.
Why does the process of retrogenesis occur in AD? We believe we have now discovered the reason. Furthermore, the mechanism of retrogenesis has resulted in our unanticipated discovery of a previously unsuspected pathologic basis for AD marked by a previously undescribed pathological process for which we suggest the novel terminology, "arboreal entropy", and of a previously unsuspected treatment for AD.

Why does the process of retrogenesis occur in AD? In 1976, Swedish scientists first casually observed that the general pattern of neuropathologic changes in the AD brain resembles, among other things, the ontogenic (i.e., normal human developmental) pattern (Brun, A., Gustafson, L., 1976). Subsequently, based upon observations of brain cell loss in AD and changes in brain metabolism in AD, McGeer and colleagues observed that the general pattern of brain change in AD appears to reverse the pattern of myelination of the developing brain as originally described by Flechsig in 1920 (McGeer, P.L., McGeer, E.G., Akiyama, H., et al., 1990). These general observations were not repeated or further speculated upon in the scientific literature until 1996. In that year, Braak and Braak, noted that the pattern of development of Alzheimer-related neurofibrillary changes in the brain inversely recapitulates cortical myelogenesis (Braak, H and Braak E., 1996). The reason for this phenomenon was unknown. However, these authors have noted that the most recently myelinated brain regions are the most thinly myelinated and therefore, apparently, the most vulnerable.

We now propose that the term retrogenesis also be applied to this process of the most recently myelinated brain regions being afflicted first in AD. This pathologic retrogenesis is based upon another previously undescribed pathophysiologic mechanism for which we suggest the novel terminology, arboreal entropy. Why do these clinical, neurologic, physiologic and pathologic retrogenic processes occur?

We have now discovered the reason for the relationship between clinical, especially functional retrogenesis, and neuropathological (brain change) retrogenesis. The reason requires first a proper understanding of an old theory of
brain development.

Yakovlev and Yakovlev and Lecours hypothesized that the capacity to acquire certain functions in normal human development is dependent upon the myelination of the proper axonal pathways (Yakovlev, 1962; Yakovlev and Lecours, 1967). We conclude on the basis of our observations that the converse is also true. Specifically, we conclude that the loss of capacities in AD is dependent upon the destruction of the proper myelinogenic pathways. Hence, preservation of the myelinogenic pathways should be a treatment for AD. However this conclusion required the solution of two important problems. The first problem, which has not been addressed at all in the scientific literature is: if the degenerative dementia process is attacking the most thinly myelinated brain regions first, and these regions are vulnerable because of "their thin coating', then the most vulnerable brain regions should be those which are unmyelinated, not just thinly myelinated. Why are these unmyelinated regions not vulnerable?

In answering this important question we begin with the important observations of Yakovlev (Yakovlev, 1962) and Yakovlev and Lecours (Yakovlev and Lecours, 1967). They hypothesized that the capacity to acquire certain abilities in normal human development is dependent upon the development of the proper myelogenic pathways. We conclude that in dementia, the destruction of nonmyelinated brain regions does not have functional consequences because these regions have not yet specialized for functional tasks.

The second problem is the relationship between a thinly myelinated brain region and vulnerability. This relationship has apparently not previously been investigated or described.

In general, the role of myelin has been viewed as providing an aide in impulse conduction in the axon (nerve fiber) which it surrounds, not as a role in providing protection. There is no evidence for direct injury to myelin or to axons in dementia, such as the kind of injury which is produced by a cut or a tear. Known mechanisms of neuronal and axonal death include Wallerian degeneration, necrosis and apoptosis. However, none of these mechanisms could explain the vulnerability
of the most thinly myelinated regions. In other organs, thicker linings, for example ectodermal tissue such as skin, protect primarily by sloughing off of cells. However, this cannot occur in the myelin, which does not consist of cells.

A well known mechanism of myelin damage is that which occurs in multiple sclerosis. In this condition, a so called patchy degeneration occurs. However, this patchy degeneration process does not affect the most recently or the most thinly myelinated regions preferentially. The result is a generally reversible clinical process in multiple sclerosis which is very different from the clinical process of retrogenesis in AD.

What is the mechanism for the destruction of myelin in AD? We have discovered that there is a new and previously undescribed pathologic process for which we propose the novel term "arboreal entropy". This process involves a general dissolution of the myelin. In this general dissolution, the thinner the myelin, the more vulnerable it is to arboreal entropy. In a certain sense the myelin protects the axon in a similar manner to the way bark protects a tree. The thinner the bark on a tree, the more vulnerable the underlying twigs, branches and trunk are to external insults such as weather conditions, etc. Similarly, when a tree rots from within, the regions with the thinnest bark are first to rot and die.

The discovery of this arboreal entropy is based upon a series of basic findings which we have uncovered based upon previously described risk factors for AD. We have discovered that many risk factors for dementia in general and AD in particular, are agents of myelin destruction and degeneration.

For example, low serum levels of vitamin B-12 have been associated with increased risk of AD (Clark, R., Smith, D., Jobst, K.A., et al., 1998). Other conditions, sometimes biochemically related to Vitamin B-12 deficiency, have also been associated with increased risk for AD. These other conditions include folate deficiency and the biochemical markers of chemical B-12 deficiency, i.e., serum homocysteine and methylmalonic acid (Clark, R., Smith, D., Jobst, K.A., et al.; Stabler, S.P., Lindenbaum, J., and Allen, R.H; Kristensen, M.O., Gulmann, N.C., Christensen, J.E.J., et al., 1993; Diaz- Arrastia, R., 1998).
Vitamin B-12 deficiency is known to be associated with demyelination, especially in the spinal cord, but also in the brain (Lovblad, Ramelli, Reonda, et al., 1997). Vitamin B-12 is necessary for the biochemical reaction in which cells convert L-methylmalonyl-CoA into succinyl-CoA, a reaction which is catalyzed by the enzyme adenosylcobalamin (Allen, in Cecil Text book of Medicine, 21st Edition, 2000, p.861). A deficiency of vitamin B-12 (cobalamin), results in decreased succinyl-CoA production and an increase in methylmalonic acid and in propionyl-CoA. The increase in propionyl-CoA results in an increase in odd chain numbered fatty acids (Ramsey, Scott, and Banik, N.L., 1977). This increase in odd chain fatty acids changes the fatty acid composition of myelin. Consequently, myelin becomes more vulnerable to destruction in the case of B-12 deficiency, a risk factor for AD. The myelin vulnerability in the case of vitamin B-12 deficiency has previously been related to the demyelination which occurs primarily outside of the brain in association with vitamin B-12 deficiency. Some authors have also related this myelin vulnerability to demyelination and white matter changes which can occur inside the brain in the case of vitamin B-12 deficiency (Lovblad, K., Ramelli, G., Remomda, L., et al., 1997; Chatterjee, A., Yapundich, R., Palmer, C.A., Marson, B.C., and Mitchell, G.W., 1996; Stojsavljevic, N., Lević, Z., Drulovic, J., and Draguninovic, G., 1997). However, these effects of vitamin B-12 on myelin have not been previously related to the role of vitamin B-12 in increasing the risk of AD in accordance with the retrogenesis and arboreal entropy models described in the application. Demyelination is different from arboreal entropy in that demyelination does not selectively affect the most recently or the most thinly myelinated axons, as is the case in the arboreal entropy which occurs in AD. Consequently, demyelination which occurs in vitamin B-12 deficiency or, most classically, in multiple sclerosis, would not explain the nature of the clinical or the retrogenic type brain changes seen in AD. We suggest that vitamin B-12 deficiency does indeed produce a form of myelin destruction in which the most recently and thinly myelinated brain regions are relatively affected and that this explains the role of vitamin B-12 as a risk factor for AD.
The same mechanism would explain why increased serum methyl-malonic acid is a risk factor for AD. Specifically, a biochemically relevant decrease in vitamin B-12 activity (with or without, an actual decrease in serum B-12), results in decreased succinyl-CoA production and an increase in methylmalonic acid levels. These increases in methylmalonic acid levels are accompanied by increments in propionyl-Co-A resulting in increased odd chain fatty acids and increased myelin vulnerability.

Elevated levels of serum homocysteine have also been identified as a risk factor for AD (Clark, N., Smith, D., Jobst, K.A., et al.). Because vitamin B-12 is necessary for the biochemical reaction in which homocysteine is converted into the amino acid methionine, there is known to be a relationship between vitamin B-12 deficiency and elevated serum homocysteine levels. However, elevated homocysteine appears to be a risk factor for AD in the apparent absence of elevated serum B-12 levels. The mechanism for the relationship between elevated serum homocysteine and increased risk of AD is believed to be related to the increased risk of vascular disease which is associated with high serum homocysteine (Clark, R., Smith, D., Jobst, K.A., et al.). However, we conclude that this increased risk is due to myelin destruction. We have reached this conclusion because vascular disease is seen in the brain as white matter pathology. White matter pathology in contrast to primary neuronal pathology, has also been implicated in the etiopathogenesis of other potentially dementing conditions. For example, anoxia. Basic studies in rats have shown that occlusion of the common carotid artery combined with hypoxemia "causes white matter necrosis in the ipsilateral cerebral hemisphere originating and spreading from myelinogenic foci" (Rice, J.E., Vannucci, R.C., Brierley, J.B., 1981; Azzarelli, B., Caldemeyer, K.S., Phillips, J.P., De Meyer, W.E., 1996). Subsequent studies have supported these observations (Tomimoto, H., Akiuchi, I., Wakita, H., Kimura, J., 1997). Azzarelli, et al. have studied this phenomenon in detail in neonates (Azzarelli, B., Caldemeyer, K.S., Phillips, J.P., De Meyer, W.E., 1996). They concluded that at the moment of insult, damaged brain areas are ones which have greatest susceptibility to oxygen deprivation. Consequently, we infer that at
any given developmental age, tissues having higher metabolic rates for glucose should be particularly sensitive to oxygen deprivation. Furthermore, they note that myelination is related to increased neuronal oxidative activity in oligodendroglia. Hence, brain areas most involved in myelination, are the most sensitive to hypoxic damage. Others have noted that the highly specialized architecture of myelinated axons renders them vulnerable to injury (Stys, P.K., 1998). During anoxia, myelin, in contrast to glial cell bodies and proximal processes, accumulates ionic calcium (LoPachin, R.M., Stys, P.K., 1995). The result may be relative vulnerability of oligodendroglia and related myelin to free radical damage, glutamate toxicity and anoxia per se (Wender, M., Szezech, J., Godlewski, A., Grochowalska, A., 1998; Oka, A., Belliveau, M.J., Rosenberg, P.A., Volpe, J.J., 1993; Husain, J., Juurlink, B.H., 1995; Juurlink, B.H.,1997; Mc Donald, J.W., Althomsons, S.P., Hyra, K.L., Choi, D.W., Goldberg, M.P., 1998). This vulnerability would actually include the anoxia resulting from vascular, and, more specifically, cerebrovascular damage. Consequently, we conclude that the deleterious effects of homocysteine, and the reason elevated homocysteine levels are a risk factor for AD, is due to the myelin damage.

Low serum folate levels have also been associated with increased risk of AD (Clark, R., Smith, D.A., Jobst, K.A., Refsum, H., Sutton, J., Ueland, P.M., 1998). Although others have not directly related this risk factor to myelin damage, we conclude that myelin damage is indeed the cause of increased AD risk from folate deficiency. This is because in folate deficiency there is a lack of 5-methyltetrahydrofolate. As a result of this deficiency, there is decreased methylation of homocysteine to methionine, a reaction which requires the transfer of the methyl group of 5- methyltetrahydrofolate to homocysteine, to form methionine. The resultant build up of homocysteine in cases of folate deficiency, causes myelin destruction for the reason which we have outlined above.

Depression is a condition which has long been known to be associated with a potentially or frequently reversible dementia. Depression also appears to be an independent risk factor for AD (Agbayewa, D., 1986; Baker, F.M., Kokmen, E.,
Chandra, V., Schoenberg, B.S., 1991). A series of recent studies have related late life depression to increased white matter hyperintensities in neuroimaging brain studies (Coffey, C.E., Figiel, G.S., Djang, W.T., Weiner, R.D., 1990; Zubenko, G.S., Sullivan, P., Nelson, J.P., Belle, S.H., Wolf, G., 1990; Rabins, P.V., Pearlson, G.D., Aylward, E., Kumar, A.J., Dowell, K., 1991; Hickie, I., Scott, E., Mitchell, P., Wilhelm, K., Austin, M.B, Bennett, B., 1995). The cognitive impairment sometimes noted in late life depression can be difficult to distinguish from AD (Kiloh, L.G., 1961; Wells, C.E., 1979; Reifler, B.V., Larson, E., Hanley, R., 1982). The reasons for these similarities appear to be explainable on the basis of the retrogenesis model. Specifically, the most vulnerable brain regions to the white matter insults would be the same ones as in AD, and hence the presentations of these conditions in the context of progressive dementia would be similar.

Although neither the signs nor the treatment of late life depression have previously been related to myelin vulnerability, we conclude on the on the basis of the anoxic effects of white matter lesions and the association of these anoxic effects with myelin vulnerability and on the basis of the clinical retrogenic process which we have discussed, and the occasionally similar course of late life depression, that this risk factor for AD (late life depression) is secondary to myelin vulnerability and destruction in association with an arboreal entropy process. Another AD risk factor which is well established is the occurrence of the ε4 allelic genotype of the apolipoprotein E (APOE) gene (Strittmatter, M.J., Saunders, A.M., Semaechel, D, et al., 1993). Whereas the ε4 allele is associated with an increased risk of AD, the APOE ε2 allele is associated with decreased risk of AD. APOE has a major role in lipid and lipoprotein metabolism (Amoyel, P., Richard, F., Lambert, J.C., Chartier - Harlin, M.C., and Helbecque, N., 1999). APOE polymorphism is associated with variations in the transport and clearance of lipids as well as other compounds (Amoyel, P., Richard, F., Lambert, J.C., Chartier - Harlin, M.C., and Helbecque, N., 1999; Weisgraber, K.H., and Mahley, R.W.). Furthermore, the APOE genotypes are associated with cerebrovascular and cardiovascular disease risk factors, in a manner consistent with their role in association with increased AD risk. For example,
persons with the APOE ε4 allele have higher low density lipoprotein cholesterol levels and persons with the APOE ε2 allele have lower low density lipoprotein cholesterol levels (Luc, G., Bard, J.M., Arveiler, D., 1994). Consequently, the risk of myocardial infarction is increased in persons with an APOE ε4 allele and decreased in persons with an APOE ε2 allele (Luc, G., Bard, J.M., Arveiler, D., 1994). Therefore, APOE genotype risk for AD is readily related to cardiovascular and cerebrovascular pathology, as well as maintenance of brain lipids. Although not described by others previously, we conclude that the APOE ε4 allele genotype is a risk factor for AD because of its role in myelin destruction in accordance with the process of arboreal entropy resulting in the clinical retrogenesis process. The process is as follows:

The APOE ε4 allele promotes cerebrovascular disease, which increases cerebral anoxia, which renders the brain regions with the highest metabolism most vulnerable, such as the oligodendroglia. The oligodendroglia with the highest metabolic rates, which are most involved in myelin production, are affected to the greatest extent. Consequently, the most recently and thinly affected myelin regions are most vulnerable, resulting in the arboreal entropy and retrogenic clinical process of AD.

Having concluded on the basis of the discoveries described that myelin preservation is a treatment for AD, we also presently conclude that myelin preservation is also a treatment for normal aging brain changes and for mild cognitive impairment. We came to this conclusion regarding normal aging and mild cognitive impairment for the following reasons: (1) myelin changes occur in normal aging and mild cognitive impairment, (2) the pattern of neuropathologic and neuroradiologic changes in the brains of normal aged persons and persons with mild cognitive impairment has been recently found to occur in reverse order to the pattern of myelin acquisition in the course of normal human development as originally described by Flechsig in 1920 (Raz, in press), (3) therefore, we conclude on the basis of our discoveries of Alzheimer's retrogenesis and arboreal entropy, described above, that this process of retrogenesis and progressive myelin
destruction also occurs in normal aging and in person with mild cognitive impairment, and that myelin protective agents will be useful in the treatment of normal aged and mild cognitive impairment related brain changes, both for the treatment of clinical symptoms accompanying normal aged and mild cognitive impairment related brain changes and for the prevention of AD.

Interestingly, non-AD dementias sometimes follow, to a greater or lesser extent, the AD clinical retrogenic pattern. This pattern, as noted previously, is outlined most clearly with the Functional Assessment Staging (FAST) procedure. Some dementing disorders follow the retrogenic sequence expressed by the FAST staging procedure more or less precisely (Reisberg, B. in Wimo, A., Jönsson, B., Karlsson, G., et al., eds., 1998). Other dementias, do not follow this sequence (Reisberg, 1986). We conclude that to the extent that a degenerative dementing disorder follows the clinical retrogenic sequence, neuropathologic retrogenesis is likely to be operative, and myelin protecting agents will be useful in treatment and prevention of the dementing disorder.

We have discovered that myelin protective agents can be useful in the prevention and treatment of: (1) Alzheimer’s disease, (2) normal aging brain change, (3) mild cognitive impairment and (4) retrogenic dementing disorders other than AD. Our discovery is based upon the following method:

(1) the identification of the characteristic functional course of normal aging, mild cognitive impairment and Alzheimer’s disease,

(2) demonstration that cognition is lost progressively with the succession of each functional stage of normal aging, mild cognitive impairment and Alzheimer’s disease,

(3) recognition that this characteristic functional course in AD reverses the normal human developmental pattern,

(4) the identification of optimally concordant (with functioning and with each other), clinical changes accompanying the evolution of AD, including changes in praxis (figure drawing) capacity, feeding abilities, and neurologic reflex changes,

(5) recognition that the concordant clinical changes occur in reverse order to
the sequence of changes in these processes in normal human development,

(6) recognition that each functional stage in AD can be translated into a corresponding developmental age (DA),

(7) demonstration that the functional, praxis, feeding and neurologic reflex changes in AD, at any given stage, occur at the optimal point which might be anticipated from the corresponding DA on the basis of the normal human developmental literature,

(8) recognition that the developmental reversal process uncovered from steps 1 to 7, represents a distinctive physiologic process, previously undescribed, for which the novel terminology, retrogenesis, is proposed,

(9) recognition that neuropathologic changes in AD affect the most ontogenically (developmentally) recently myelinated regions first, followed by successively, myelogenically older and consequently, more thickly myelinated regions,

(10) recognition that this neuropathologic process described in step 8, is a novel process, for which we suggest the terminology arboreal entropy, which is different from known mechanisms of neurons and axonal death and/or degeneration,

(11) recognition that in normal human development, the acquisition of functional capacity is dependent upon the development and acquisition of necessary myelination pathways,

(12) recognition that in normal human development, the disappearance of so-called "developmental" or "primitive" neurologic reflexes is dependent upon the development and acquisition of necessary myelination pathways,

(13) recognition that the developmental model, described in steps 11 and 12 is applicable to dementia as well as normal development and that therefore, the functional and related losses, and neurologic reflex changes in AD are occurring as a result of the destruction of myelin pathways, retrogenically affecting the most recently myelinated pathways, through the previously undescribed mechanism of arboreal entropy,

(14) recognition that many of the previously identified risk factors for AD
are operable as a result of myelin destruction in accordance with the arboreal entropy/retrogenesis model, including,

(14a) vitamin B-12 (cobalamin) deficiency,
(14b) increased serum methylmalonic acid levels,
(14c) elevated serum levels of homocysteine,
(14d) low serum folate levels,
(14e) presence of the apolipoprotein E, ε4 allele,

(15) recognition that these risk factors are largely the result of anoxic effects on the cerebral vasculature,

(16) recognition that these anoxic effects would be most deleterious to the most metabolically active brain regions,

(17) recognition that the oligodendroglia, the brain cells which are producing new myelin, are among the most metabolically active, and consequently, anoxic sensitive, brain structures,

(18) recognition that this oligodendroglial sensitivity explains both the retrogenesis clinical phenomenon and the arboreal entropy process, as well as the sensitivity of these brain structures to anoxia and, hence, many of the aforementioned AD risk factors,

(19) recognition that unmyelinated, as opposed to thinly myelinated, brain regions, are not selectively vulnerable because they are not as metabolically active nor are these regions as functionally relevant,

(20) recognition that this myelinogenic loss in AD is a fundamental reason for AD pathology and that therefore, treatment with myelin protective and/or myelin regenerative agents will be efficacious in preventing the development of AD, and/or, slowing the course of AD, and/or, treating the symptoms of AD,

(21) recognition that in the course of normal aging of the brain and in the course of mild cognitive impairment, the most ontogenically recently, and therefore, the most thinly myelinated brain regions, are the first to be affected by neuroradiologically observable changes and neuropathologically observable changes,
(22) recognition that in the course of normal aging and in mild cognitive impairment, successively ontogenically less recently myelinated brain regions are successively affected by neuroradiologically observable changes and neuropathologically observable changes,

(23) recognition that myelin pathway loss is therefore also a fundamental mechanism of normal brain aging changes and mild cognitive impairment brain changes,

(24) recognition that because of the processes uncovered in steps 14 to 16, myelin protective, and/or myelin regenerative agents, will be effective treatments for normal brain aging and mild cognitive impairment, including, the slowing of normal brain aging and mild cognitive impairment, and for treating the common clinical symptoms of normal brain aging and mild cognitive impairment, such as subjective complaints of forgetfulness and decreased executive level functioning,

(25) recognition that non-AD dementia disorders may sometimes follow the clinical retrogenic pattern described, for example, with the FAST staging procedure,

(26) recognition that the extent to which non-AD dementia disorders follow the clinical retrogenic pattern is indicative of the extent to which neuropathologic retrogenesis and arboreal entropy are applicable in these disorders,

(27) recognition that non-AD retrogenic dementias are therefore also treatable with myelin protective agents, and that these myelin protective agents will be useful in the prevention of non-AD retrogenic dementias, as well as for slowing the progression and symptomatic treatment of these non-AD retrogenic dementias.

As the result of this methodology we have made the following discoveries:

1. The discovery of a new fundamental physiologic process, for which we propose the term retrogenesis, whereby clinical and pathophysiologic processes and mechanisms reverse the order of occurrence in the course of normal human development.

2. The discovery that functional losses in AD are the result of the progressive loss of myelin pathways, just as in normal human development, the acquisition of functional capacities is dependent upon the development of
appropriate myelin pathways,

3. The discovery that neurologic reflex changes in AD, particularly, the appearance of "developmental", also known "primitive reflexes" are the result of progressive loss of myelin pathways, just as in normal human development, the acquisition of functional capacities is dependent upon the development of appropriate myelin pathways,

4. The discovery that the process of retrogenesis in AD, including the progressive retrogenic functional losses, and the progressive, retrogenic neurologic losses, is the result of progressive destruction of myelin pathways.

5. The discovery that this progressive destruction of myelin pathways represents a previously undescibed physiologic process, for which we propose the term arboreal entropy, whereby the most thinly and recently myelinated brain regions, but not unmyelinated brain regions, are selectively affected.

6. The discovery that arboreal entropy is occurring in part because of the metabolic activity and consequently, the metabolic vulnerability, of the successively most recently myelinated brain regions.

7. The discovery that this metabolic vulnerability and, consequently, anoxic vulnerability, explains many of the known risk factors for AD.

8. The discovery that AD can be prevented, the course of AD can be slowed, and the symptoms of AD can be treated, with, myelin protective and regenerative agents including vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12 , folate [folic acid], vitamin B-6 [pyridoxine], and/or betain [trimethylglycine]) calpain-inhibitors, and interferon-beta, as well as maintenance of optimal lipid reparative mechanisms such as cholesterol levels and cholesterol transport,

9. The discovery that because neuropathologic retrogenesis also applies to normal aging brain changes and the brain changes in mild cognitive impairment, therefore, normal aging and mild cognitive impairment can be treated with myelin protective and regenerative agents including vitamin B-12 (cobalamin),
homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), calpain-inhibitors and interferon-beta, as well as maintenance of optimal lipid reparative mechanisms such as cholesterol levels and cholesterol transport,

10. The discovery that the clinical process of retrogenesis applies to certain non-AD dementias as well as to AD.

11. The discovery that clinical retrogenic procedures can be used to determine the extent to which arboreal entropy, as well as clinical retrogenesis, is applicable for non-AD dementing disorders.

12. The discovery that, to the extent clinical retrogenesis applies, myelin protective and myelin regenerative agents such as vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine], and/or betain [trimethylglycine]), calpain-inhibitors, and interferon-beta, as well as maintenance of optimal lipid reparative mechanisms, such as cholesterol levels and cholesterol transport, can be used to prevent, slow the progression of, and treat, the clinical symptoms of non-AD dementia disorders.

Although our invention has been described in terms of the methodology by which the discovery was made and the specific suggestion for the treatment of previously incurable disorders, this disclosure will suggest to others skilled in this field further treatments and developments. Accordingly, the scope of protection provided by this patent should not be limited to the specific example cited but should be determined by the proper construction of the following claims:
We claim:

1. The method of treating functional losses in an AD patient, a person having normal aging brain changes, a person with mild cognitive impairment, or non-AD dementing disorders with a functional degenerative course similar to AD, comprising administering medications to lessen the progressive loss of brain myelin.

2. The method of treating functional losses of claim 1, wherein said medications comprise myelin protective and regenerative agents.

3. The method of treating functional losses of claim 2, wherein said agent is vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), a calpain-inhibitor, or interferon-beta.

4. The method of claim 1 where such functional losses are manifested by the appearance of developmental or primitive reflexes.

5. The method of treating functional losses of claim 4, wherein said agent is vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), a calpain-inhibitor, or interferon-beta.

6. The method of treating retrogenesis by administering medication to lessen the progressive destruction of myelin pathways in the patient’s brain.

7. The method of treating functional losses of claim 6, wherein said medication is vitamin B12 (cobalamin), homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), a calpain-inhibitor, or interferon-beta.
8. The method of claim 6, wherein said retrogenesis includes progressive retrogenic functional losses, and progressive, retrogenic neurologic losses.

9. The method of treating functional losses of claim 8, wherein said medication is vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), a calpain-inhibitor, or interferon-beta.


11. The method of treating functional losses of claim 10 wherein said lipid reparative mechanisms are cholesterol levels or cholesterol transport to lessen the progressive loss of said myelin pathways.

12. The method of treating functional losses in an AD patient of claim 10, comprising maintenance of optimal lipid reparative mechanisms.

13. The method of treating functional losses of claim 12 wherein said lipid reparative mechanisms are cholesterol levels or cholesterol transport to lessen the progressive loss of said myelin pathways.

14. The method of claim 10 where such functional losses are manifested by the appearance of developmental or primitive reflexes.

15. The method of treating retrogenesis comprising maintenance of optimal lipid reparative mechanisms to lessen the progressive destruction of myelin pathways in the patient’s brain.
16. The method of treating functional losses of claim 15 wherein said lipid reparative mechanisms are cholesterol levels or cholesterol transport to lessen the progressive loss of said myelin pathways.

17. The method of claim 15, wherein said retrogenesis includes progressive retrogenic functional losses, and progressive, retrogenic neurologic losses.

18. The method of treating Alzheimer’s disease and other conditions satisfying the retrogenic neuropathologic vulnerability model by administering myelin protective agents.

19. An dosage of medication chosen to lessen the progressive loss of brain myelin selected from the group consisting of vitamin B-12 (cobalamin), homocysteine modulators (containing vitamin B-12, folate [folic acid], vitamin B-6 [pyridoxine] and/or betain [trimethylglycine]), a calpain-inhibitor, or interferon-beta effective for treating functional losses in an AD patient, a person having normal aging brain changes, a person with mild cognitive impairment, or non-AD dementing disorders with a functional degenerative course similar to AD.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07610

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/44, 31/70, 31/205, 38/00, 38/28
US CL. : 514/12, 52, 345, 556
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/12, 52, 345, 556

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of database and, where practicable, search terms used)
REGISTRY, HCAPPLUS, WPIDS, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>Y</td>
<td>Database HCAPPLUS on STN, (Columbus, OH, USA), No. 130:320696, RAMAKRISHNA, T. et al, 'Betaine reverses toxic effects of aluminum: implications in Alzheimer's disease (AD) and AD-like pathology,' abstract, Curr. Sci., 1998, 78(11), 1153-1156, see entire abstract.</td>
<td>1-19</td>
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<td>A</td>
<td>Database HCAPPLUS on STN, (Columbus, OH, USA), No. 129:259173, WEBER, F. et al, 'Synergistic immunomodulatory effects of interferon-.beta.1b and the phosphodiesterase inhibitor pentoxifylline in patients with relapsing-remitting multiple sclerosis,' abstract, Ann. Neurol., 1998, 44(1), 27-34, see entire abstract.</td>
<td>1-19</td>
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☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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