New Insights Into Genetics and Pathophysiology of Alzheimer's Disease: What Are the Clinical and Therapeutic Implications?

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *summarizes the highlights of a meeting held December 5–7, 1999, at The Breakers, Palm Beach, Fla. Participants were Michael Mullan, M.D., Roskamp Professor of Biological Psychiatry, Director of Memory Disorder Clinic, Director of Roskamp Institute, University of South Florida, Tampa; George Grossberg, M.D., founder and Medical Director of the St. Louis University Alzheimer's Association Brain Bank, St. Louis University, St. Louis, Mo.; Ravi Anand, M.D., Executive Director and Global Head of CNS Medical Affairs at Novartis Pharmaceuticals Corporation, East Hanover, N.J.; and Albert Enz, M.D., Senior Scientist at Novartis Pharmaceuticals AG, Basel, Switzerland. The symposium and this ACADEMIC HIGHLIGHTS were sponsored by an unrestricted grant from Novartis Pharmaceuticals.*

Genetic Contributions to Causes of Alzheimer's Disease: Current Perspectives and Future Directions

Genetic findings have made an important contribution to the understanding of Alzheimer's disease. The mutations in β-amyloid precursor protein (βAPP) and presenilin 1 (PS1) transmitted in a simple Mendelian manner have provided the basis for our understanding of the central role of β-amyloid in all cases of Alzheimer's. Dr. Mullan suggested that whereas variability at the apolipoprotein E (APOE) locus is clearly associated with the occurrence of disease, for many other genes such clarity is less established. In many cases, Alzheimer's disease occurs in the absence of a prior history of the disease in other family members and is designated as sporadic, and the identified dominantly transmitted mutations occur in less than 1% of all cases. In other cases (perhaps up to 50% of the total), a family history of the disease is noted without clear Mendelian transmission. Such effects are likely the result of several commonly occurring genetic variants that influence the disease process.

One major pathologic characteristic of Alzheimer's disease is the abnormal deposition of β-amyloid peptide in the brain. β-amyloid is derived from βAPP, and mutations in this gene on chromosome 21 have been linked to some early-onset familial cases.[1] βAPP-related Alzheimer's mutations always occur in the region of the β-amyloid portion of the βAPP gene, at sites where α-, β-, and γ-secretase–breakdown pathways operate on the expressed protein. These mutations alter βAPP metabolism, leading to increased total β-amyloid production, or increase the ratio of the 42 amino acid form to the 40 amino acid form. Cleavage of amyloid precursor protein by β- and γ-secretase results in the generation of the β-amyloid peptide, whereas α-secretase cleaves within the β-amyloid sequence and prevents its formation from βAPP. Recent findings suggest that the presenilins might be the sought-after γ-secretase—a finding that would have implications for the design of therapeutics aimed at inhibiting this cleavage.

βAPP mutations account for only 1% to 3% of familial Alzheimer's cases. Most early-onset familial cases of Alzheimer's (40%–50%) are caused by mutations in the PS1 gene on chromosome 14.[1] PS1 is an integral membrane protein whose exact function is unknown. Unlike βAPP mutations, over 70 mutations in PS1 have been identified, which are dispersed throughout the protein. Most of these mutations occur within the transmembrane domain, suggesting that they alter the intramembranous function of PS1. This is particularly significant since the enzyme (γ-secretase) responsible for the intramembranous cleavage of βAPP must have active intramembranous sites. Indeed, in the

absence of PS1, α- and β-cleavage products and C-terminal fragments of βAPP accumulate, establishing the relationship between γ-secretase function and PS1. However, Dr. Mullan noted that "there is some dispute as to whether PS1 is the γ-secretase or activates something else that is the γ-secretase and makes this intramembranous cleavage."[2] This distinction is important because PS1 is clearly a potential target for therapeutic intervention. Preventing the γ-secretase cleavage should prevent β-amyloid formation and, in theory, should prevent the development of Alzheimer's disease.

The presenilin 2 (PS2) gene on chromosome 1 has also been linked to familial cases of early-onset Alzheimer's disease. As with PS1, mutations in PS2 result in elevated levels of β-amyloid 1–42. PS2 is highly homologous with PS1. Of the clear autosomal dominant forms of the disease, PS2-associated Alzheimer's is reminiscent of the common late-onset form in terms of an older age at onset and longer disease duration. Since PS2 mutations are incompletely penetrant and age at onset in carriers is highly variable (40–88 years), elucidation of PS2 mechanisms may reveal factors that modify Alzheimer's and are therapeutically relevant to sporadic Alzheimer's disease.

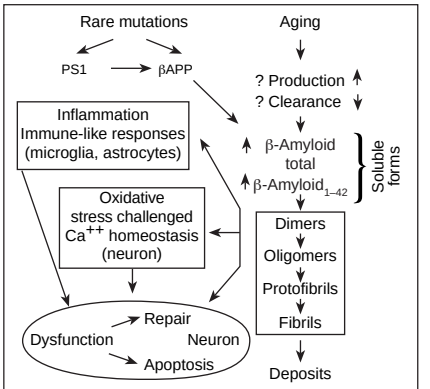
Vassar et al.[3] recently reported the cloning of a transmembrane aspartic protease with all the known characteristics of β-secretase. Overexpression of this protease, termed BACE (for β-site βAPP-cleaving enzyme), increased the amount of β-secretase cleavage products, and these were cleaved exactly and only at known β-secretase positions. Antisense inhibition of endogenous BACE messenger RNA decreased the amount of β-secretase cleavage products, and purified BACE protein cleaved βAPP-derived substrates with the same sequence specificity as β-secretase. Finally, the expression pattern and subcellular localization of BACE were consistent with that expected for β-secretase. These findings suggest that future development of BACE inhibitors may prove beneficial for the treatment of Alzheimer's disease.

Although a link has been established between excess β-amyloid 1–42 and Alzheimer's disease, it is unclear how this protein is able to trigger the pathogenic cascade that results in the disease. Furthermore, why does Alzheimer's disease develop only in mid-to-late age even in people born with one of these mutations? Dr. Mullan indicated that there are many possible approaches to these questions and said that "we still need to be very open minded about how β-amyloid can contribute to the disease process." It is clear that β-amyloid leads to the formation of amyloid fibrils that are somehow able to kill neurons. However, Dr. Mullan suggested that "we need to be much more wide thinking than that."

Dr. Mullan noted some interesting observations made with β-amyloid in the vasculature. He described preclinical experiments in which the presence of β-amyloid enhanced constriction of rat aorta by norepinephrine,[4] increased blood pressure in rats that were already hypertensive,[5] and reduced cerebral blood flow.[6] Evidence has shown that this vasoconstriction results from activation of the arachidonic acid cascade. Thus, very low doses of β-amyloid can trigger a pro-inflammatory response in vascular tissues. This biological activity occurs with freshly solubilized forms of β-amyloid that have low propensity to form aggregates and that are not in a highly aggregated form during these experiments. This suggests that increased soluble levels of β-amyloid could have pathologic effects before classic amyloid deposition occurs.

Dr. Mullan continued by suggesting that vascular disease might have an important relationship with Alzheimer's disease. Patients with previous vascular disease or risk factors for vascular disease, e.g., high cholesterol, appear to have a higher probability of developing Alzheimer's. Dr. Mullan stated, "One of the things we have been pursuing genetically is looking at risk factors for Alzheimer's disease that have been traditionally associated with vascular effects."[7–11]

Figure 1. Working Hypothesis for the Etiology of Alzheimer's Disease[a]



[a]Abbreviations: βAPP = β-amyloid precursor protein, PS1 = presenilin 1.

APOE4, a specific allele of the APOE gene, is frequently associated with sporadic Alzheimer's disease and late-onset familial Alzheimer's. However, Dr. Mullan stressed that APOE4 is not an absolute risk factor for Alzheimer's, but rather it confers a time-dependent increase in risk.[12] This means that the E4 allele increases the risk for Alzheimer's disease by modifying the age at onset. Each copy of the E4 allele may lower age at onset by as much as 7 to 9 years.

It is not clear whether the presence of APOE4 predisposes to cognitive impairment in normal elderly subjects. If it does, that would suggest that APOE4 is a prelude to Alzheimer's disease. However, several studies show that this is not the case, arguing that the APOE4 effect is revealed as the consequence of the disease. For example, it has been shown that recovery from head injury is predicted by APOE

phenotype.[13] Patients with APOE4 do less well after head injury than do patients with APOE3. Clearly, in that setting, APOE is acting in a repair role and is not in any way causative. Dr. Mullan stated that he favors a similar model in Alzheimer's disease. Thus, it is probable that one of the major functions of apolipoprotein E in the central nervous system (CNS) is to mediate neuronal repair, remodelling, and protection, with apolipoprotein E4 being less effective than the E3 isoform.

Dr. Mullan concluded with a working hypothesis for the etiology of Alzheimer's disease (Figure 1). He stated that although rare mutations (resulting in an increase in total β-amyloid or a relative increase in β-amyloid 1–42) are one way to bring about Alzheimer's disease, in the majority of cases, aging is the trigger. In the case of aging, it is most likely a decrease in clearance of β-amyloid that produces the same result. Dr. Mullan stated that "from a genetic perspective, it would be nice to know what triggers this in aging." He suggested that the specific triggers for the development of Alzheimer's disease during the aging process are likely to be hormonal. The eventual consequences of increased β-amyloid are inflammation and immune-like responses in microglia and astrocytes resulting in neuron dysfunction. ❑

Behavior—The Forgotten Domain in Alzheimer's Disease: Issues in Clinical Management

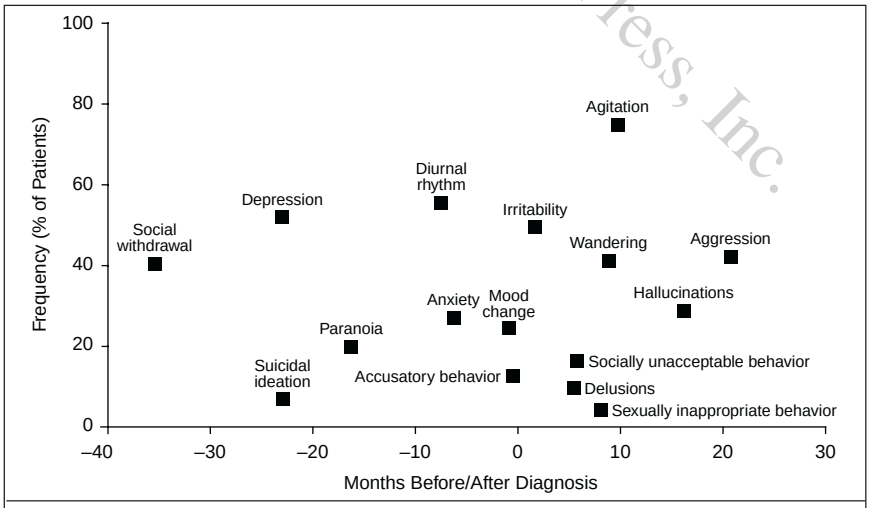
Alzheimer's disease is a disease of the elderly, which means that in an increasingly aging population, the number of patients with the disease continues to increase. Behavioral disturbances are a common feature of the disease. "The disease is progressive so that the evolution of psychiatric or behavioral symptoms depends on which stage of the disease the patient has reached," explained Dr. Grossberg. In the early stages of Alzheimer's disease, depression, anxiety, and some deterioration in social behavior are common, and such symptoms may predate diagnosis by between 3 and 4 years (Figure 2).[14] As the disease progresses, social skills start to decline more significantly, and more difficult-to-manage behavioral problems such as agitation, verbal aggression, and accusatory behaviors begin to manifest. As the disease moves into advanced stages, more psychotic symptomatology develops as well as more overt behavioral disturbances, such as agitation and physical aggression. Even before this stage is reached, many families will already have thought about placing the patient in institutionalized care.

"Behavioral disturbances increase morbidity and mortality, particularly when they are not recognized and promptly treated," stated Dr. Grossberg. "They lead to excessive cost because of the requirement for very intensive care, which impacts not only professional caregivers but also family members struggling to deal with the consequences of these disturbances," he continued.

A focus on behavior has not typically been used as one of the primary outcome measures in clinical trials of Alzheimer's disease therapy. Dr. Grossberg explained that one reason for this has been the lack of suitable instruments for measuring changes in behavior. However, instruments that are now leading the way in clinical trials include the Neuropsychiatric Inventory,[15] which is completed by caregivers and specifically assesses behavior in outpatients as well as nursing home patients with dementia. Other scales include the Cohen-Mansfield Agitation Inventory and a number of observation-based aggression scales,[16–18] which look at both the frequency and other aspects of agitation and aggression.

Dr. Grossberg explained that, although consensus statements for be-

Figure 2. Frequency of Behavioral Disturbances Before and After the Diagnosis of Alzheimer's Disease[a]



[a]From Jost and Grossberg,[14] with permission.

Table 1. Pharmacologic Treatment Options for Neuropsychiatric and Behavioral Disturbances in Alzheimer's Disease

Category	Target Symptoms
Antipsychotics	Psychosis (delusions/hallucinations), hostility, aggression, agitation, violent behavior
Antidepressants	Depressive symptoms
β-Blockers	Agitation
Benzodiazepines	Anxiety, agitation
Estrogen	Agitation
Anticonvulsants	Agitation, aggression
Serotonergic agents	Psychosis?, agitation
Cholinesterase inhibitors	Apathy, psychosis (delusions/hallucinations)?, agitation, anxiety, nighttime behavior?

havioral disturbances in Alzheimer's disease are available, "we need to be more specific and focus on the ones that are the most disabling and the most common." This lack of focus may be another factor that has contributed to behavior as the forgotten domain.

Antipsychotic drugs have been the front-line pharmacologic approach to the treatment of agitation and aggression in Alzheimer's disease. However, these drugs have limited indications. In some cases, they did lead to reduction in nonpsychotic symptoms, but occasionally the behavior actually worsened.[19] No therapeutic effect was noted on behaviors such as apathy, withdrawal, and wandering. The older drugs, in particular, were associated with a wide variety of quite disabling side effects, sometimes more disabling than the symptoms being treated.[19] Dr. Grossberg commented, "These drugs have a lot of limitations, and they are not really ideal in this patient population." Consequently, a variety of different approaches have been investigated (Table 1).

Dr. Grossberg indicated that the current focus for therapy is cholinergic therapies, particularly cholinesterase (ChE) inhibitors. Behavior is now being considered as a primary outcome measure and is being incorporated into the clinical development of agents such as rivastigmine. Indeed, in one large open-label study (data presented by Anand et al.[20]) in nursing home patients with moderate-to-severe Alzheimer's disease, rivastigmine improved most behavioral symptoms, including aberrant motor behavior, agitation, anxiety, delusions, irritability, and nighttime behavior. Dr. Grossberg explained that ChE inhibitors were initially believed to be treating only the cognitive symptoms of Alzheimer's. However, he emphasized that it is now clear that their benefits are actually much broader, having significant impact on activities of daily living and behavior. When ChE inhibitors are considered in this expanded role, many former treatment modalities that have been recommended may be usurped.

Nonpharmacologic approaches such as behavioral coping techniques, group programs, environmental modification, and bright light therapy can also play an important role in reducing behavioral disturbances.[19] Combining an effective pharmacologic intervention that decreases the severity of behavioral symptoms with psychosocial or other nonpharmacologic approaches may augment improvement.

Dr. Grossberg concluded by presenting the results of a recent study of autopsy-confirmed Alzheimer's patients (G.G., unpublished data). Behavioral symptoms of Alzheimer's disease, particularly psychotic symptoms, agitation, aggression, and wandering, were a considerable source of caregiver distress and the major reason for institutionalization of patients. He suggested that "appropriate intervention with ChE inhibitors might buy the patient more time at home and perhaps prevent institutionalization." This would consequently have a significant impact on the cost of treating these patients. ❑

Maximizing Cholinergic Function With Rivastigmine: Significant Clinical Benefits Along the Continuum of Alzheimer's Disease

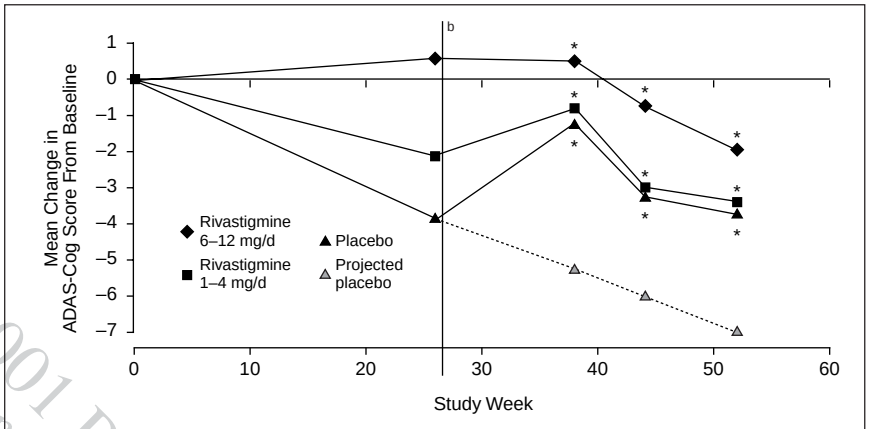
Rivastigmine, a dual-acting acetylcholinesterase/butyrylcholinesterase inhibitor with CNS selectivity, has been indicated for the treatment of mild to moderately severe Alzheimer's disease. The effect of rivastigmine in Alzheimer's has been studied in an extensive phase III program involving 4 placebo-controlled studies. Overall results showed positive benefits on cognition, activities of daily living (ADL), and global functioning.[21–23] Dr. Anand illustrated these findings with results from study B352.[21] In that study, patients receiving rivastigmine, 6 to 12 mg/day, for 26 weeks showed a difference of 4.9 on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) from patients receiving placebo, which is the largest difference reported in any placebo-controlled study to date. After 6 months, global functioning of patients treated with rivastigmine, 6 to 12 mg/day, as measured on the Clinician Interview-Based Impression of Change With Caregiver Input Scale (CIBIC-Plus) was significantly better than at baseline. Dr. Anand stated that some of the more important results are on

ADL. Patients treated with rivastigmine, 6–12 mg/day, showed significantly less deterioration in ADL than untreated patients after 26 weeks as assessed by the Progressive Deterioration Scale.

Most reports of the efficacy of ChE inhibitors in Alzheimer's disease are in patients with mild-to-moderate disease, and there are few data on patients with moderately severe or severe Alzheimer's. The rivastigmine phase III program included a large number of patients with moderately severe to severe Alzheimer's disease. Dr. Anand described an analysis of study B352 (data presented by Ferris[24]) in which patients were divided in terms of their Global Deterioration Scale (GDS) score at baseline. Patients with mild-to-moderate Alzheimer's were represented by a GDS score < 5 and moderately severe to severe patients were represented by a GDS score ≥ 5. At week 26, almost 70% of moderately severe to severe patients receiving rivastigmine, 6 to 12 mg/day, showed improvement in cognition, with 33% showing significant clinical improvement (≥ 4 points) and 20% showing highly significant clinical improvement of a ≥ 7-point increase in ADAS-Cog score. In these patients, the drug-placebo difference was about 8 points, which was greater than that seen in patients overall. Dr. Anand stressed that this contradicts the notion that ChE inhibitors should be restricted to patients with mild-to-moderate Alzheimer's disease because of the belief that patients with more severe Alzheimer's will not be able to respond.

Dr. Anand went on to explain that great overlap exists between patients with Alzheimer's disease and patients with vascular disease. Therefore, the efficacy of rivastigmine in Alzheimer's patients with vascular risk factors, including hypertension, was evaluated in a subgroup of patients included in the U.S. clinical studies. Results showed that rivastigmine, 6 to 12 mg/day, significantly improved cognition in patients with vascular risk factors (Modified Hachinski Ischemia Score [MHIS] > 0) compared with the placebo group.[25] Furthermore, rivastigmine, 6 to 12 mg/day, produced a significantly larger effect in patients with vascular risk factors compared with nonvascular patients (MHIS = 0) receiving the same dose of rivastigmine. Similar results were seen on ADL and on the Mini-Mental State Examination (MMSE).

Figure 3. Long-Term Effects of Rivastigmine on Cognition: Mean Change in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) From Baseline at Week 52[a]



[a]Data presented by Anand et al.[20]
[b]All patients were taking rivastigmine after week 26. *p < .05 vs projected placebo.

The long-term benefits of rivastigmine have been studied in an open-label extension of study B352 (data presented by Anand et al.[20]). All patients were offered treatment with rivastigmine after the initial 26 weeks of blinded treatment. All patients were readjusted to their maximum tolerated dose, and dosing remained flexible throughout. At 52 weeks, patients who received continuous treatment with rivastigmine, 6 to 12 mg/day, from the first day attained superior clinical benefit than patients who had a 6-month delay before starting treatment with rivastigmine (Figure 3). Dr. Anand explained, "This means that patients originally treated with placebo benefit, but their level of benefit never reaches the level of benefit of patients who received rivastigmine, 6 to 12 mg/day, right from the start." Furthermore, cognition declined less in patients treated continuously with rivastigmine, 6 to 12 mg/day, at the end of 1 year than in untreated patients after only 6 months. Therefore, in patients treated with rivastigmine, 6 to 12 mg/day, throughout, there is a delay in the progression of cognitive symptoms. Dr. Anand argued that this result suggests that rivastigmine may delay the progression of Alzheimer's disease. In addition, these results indicate the importance of starting treatment early in the course of the disease.

Patients in the open-label extension study have now been followed for 2 years. After 2 years, patients with moderately severe to severe Alzheimer's disease who were treated with rivastigmine, 6 to 12 mg/day, from the start showed a 5- to 6-point decline in ADAS-Cog score. In contrast, patients originally treated with placebo for the first 6 months declined by about 16 points (data presented by Anand et al.[20]). Dr. Anand stated that "this argues clearly for a stabilization or a

reduced rate of deterioration." The disease-stabilizing effects of rivastigmine are currently being evaluated in an international placebo-controlled study in 900 patients with mild cognitive impairment.

Behavioral symptoms are present in all stages of Alzheimer's disease, but manifest differentially by stage of disease. The etiology of behavior may be related to cholinergic deficits, suggesting that ChE inhibitors may improve these symptoms. Initial evidence of significant behavioral benefits of rivastigmine in Alzheimer's disease patients has been demonstrated in an open-label study of nursing home patients (data presented by Anand et al.[20]). These patients had moderate-to-severe Alzheimer's disease and prominent behavioral symptoms. Behavioral symptoms were assessed using the nursing home version of the Neuropsychiatric Inventory (NPI).

Rivastigmine treatment resulted in a broad range of behavioral benefits, with baseline scores improving by about 15% to 18% after 26 weeks. Individually, most behavioral symptoms improved as a result of treatment, including aberrant motor behavior, nighttime behavior, apathy, and hallucinations. Dr. Anand noted that "all of the symptoms that add to nursing/caregiver burden seem to have some degree of benefit. For each behavioral symptom, at least 50% of patients improved by at least 1 point over baseline. Furthermore, over 30% of patients showed a 30% improvement in total score [see Anand et al.[20]], which is the magnitude of benefit you might expect to see with an antipsychotic drug."

Behavioral benefits achieved with rivastigmine resulted in a significant reduction in the use of antipsychotic drugs such as risperidone and haloperidol. The number of patients receiving antipsychotics fell from 58% at week 8 to 11% at week 52 (data presented by Anand et al.[20]). After 1 year of treatment with rivastigmine, no single patient was receiving both antipsychotics and minor tranquillizers. Dr. Anand argued that "these data give us a sense about the robust, meaningful effects of rivastigmine."

The significant behavioral benefits of rivastigmine have been confirmed in an international placebo-controlled study[26] in patients with dementia with Lewy bodies. As with Alzheimer's disease, dementia with Lewy bodies is associated with a substantial underlying cholinergic deficit. These patients do not respond well to antipsychotic drugs. The mean baseline score on the 10-item NPI was 24, indicating that these patients had considerable behavioral problems similar to those seen in more advanced stages of Alzheimer's disease. In this study, the primary efficacy measure was a modified 4-item NPI. Delusions, hallucinations, apathy, and depression were identified as the key symptoms. After 20 weeks, rivastigmine-treated patients showed improvement in both 4-item and 10-item NPI score, and the difference between drug and placebo was statistically significant. Furthermore, about 50% of patients treated with rivastigmine showed clinically significant improvement. Dr. Anand stated, "The basic symptoms of psychosis in these patients are improved. In addition, all of the other symptoms—aggression, irritability—are benefited, and this benefit is derived purely from a cholinergic treatment." Patients treated with rivastigmine also showed improvement in cognition assessed using the sum of speed/attention scores from the computerized battery (Cognitive Drug Research).

Dr. Anand ended his presentation by emphasizing that the benefits of rivastigmine in patients with Alzheimer's disease are seen along a continuum of severity from mild to severe disease. With cognition, in mild patients there is stabilization, in moderate patients there is improvement, and in more severe patients an 8-point drug-placebo difference has been shown on the ADAS-Cog. Dr. Anand suggested, "The magnitude of beneficial change is a function of severity and perhaps directly related to the underlying cholinergic dysfunction in these patients."

Benefits of rivastigmine on ADL are also seen along the continuum of disease severity. Depending on the stage of illness, rivastigmine improves functioning in those areas where greatest impairment is seen (Table 2). In patients with mild disease (GDS score ≤ 3), clinical benefits with rivastigmine are observed for high-level ADL such as ability to handle money and tell time, i.e., ADL typically impaired at this stage. In patients

Table 2. Activities of Daily Living That Improved Significantly With Rivastigmine Compared With Placebo[a]

Item	Mild Alzheimer's Disease[b]	Moderate Alzheimer's Disease[c]	More Severe Alzheimer's Disease[d]
Ability to handle money	✓		
Ability to tell time	✓		
Time spent on hobbies	✓		
Participation in family finances		✓	
Ability to dress properly		✓	✓
Reduced forgetfulness		✓	✓
Time rearranging objects		✓	✓
Ability to use phone			✓
Confusion in different settings			✓
Proper eating manners			✓

[a]Data from Ferris.[24]
[b]Global Deterioration Scale (GDS) score ≤ 3.
[c]GDS score = 4.
[d]GDS score ≥ 5.

with moderate Alzheimer's (GDS score = 4), rivastigmine again improves activities most impaired at this stage, such as dressing properly. In more severe Alzheimer's disease (GDS score ≥ 5), rivastigmine also benefits basic ADL such as eating and using the phone.

Dr. Anand reiterated the results from earlier in his presentation, which showed that the behavioral benefits with rivastigmine have also been demonstrated over the course of the illness. He concluded by stating, "Virtually all patients with Alzheimer's disease can benefit from treatment." ❑

Cholinesterase Inhibition in Alzheimer's Disease: the Pharmacologic Basis of Efficacy

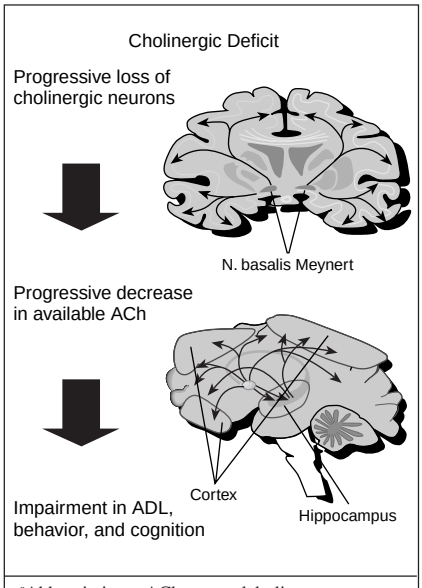
Alzheimer's disease is characterized by disturbances in 3 key domains: ADL, behavior, and cognition. These domains represent the "ABCs" of Alzheimer's patients' ability to function in daily life. The clinical symptomatology is associated with an underlying cholinergic deficit (Figure 4). Progressive loss of cholinergic neurons, particularly in the cortex and hippocampus, results in the gradual decline of the available acetylcholine (ACh) and subsequent impairment of ADL, behavior, and cognition. To date, cholinesterase (ChE) inhibitors are the only proven effective therapies approved worldwide for the treatment of Alzheimer's disease. Results presented by Dr. Enz show that inhibition of butyrylcholinesterase (BuChE), as well as acetylcholinesterase (AChE), is important in order to achieve significant clinical benefit along the continuum of disease severity.

Initially, cholinergic therapy focused on AChE inhibition. Under normal conditions, AChE is the only enzyme involved in the degradation of ACh in the brain. Furthermore, BuChE activity normally accounts for only a small percentage of the total ChE activity in the brain. However, AChE is gradually lost in the Alzheimer's disease brain, and at the same time, there is a parallel increase in BuChE levels in the cortex and hippocampus to 40% and 60% of the total ChE activity, respectively (Figure 5).[27] This rise in activity is due in part to an increased secretion from glial cells, which are the main source of BuChE in the brain.

The increase in BuChE activity occurs in areas of the brain most affected by Alzheimer's disease and correlates with an increase in the markers of disease progression, such as β-amyloid deposition.[28] Dr. Enz explained, "This means that BuChE plays an important role over the course of illness." Dr. Enz also suggested, on the basis of findings from Mesulam and Geula,[29] that BuChE may be implicated in the transformation of benign diffuse β-amyloid into neurotoxic plaques and that inhibition of BuChE might therefore slow disease progression.

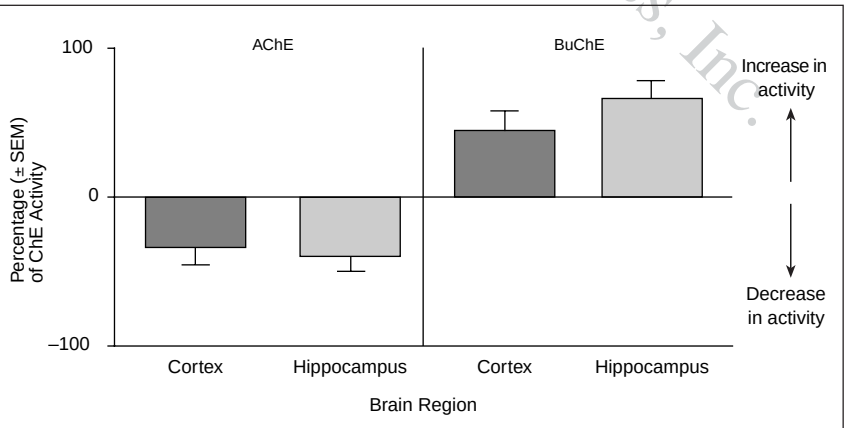
Experiments show that specific BuChE inhibitors can increase extracellular cortical ACh levels in animals.[30] This finding has led to the concept of 2 pools of functional ChE in

Figure 4. The Cholinergic Deficit in Alzheimer's Disease Underlies the Clinical Symptomatology[a]



[a]Abbreviations: ACh = acetylcholine, ADL = activities of daily living.

Figure 5. Activity of Acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE) in the Brain of Alzheimer's Disease Patients as a Percentage of the Activity in Normal Brain[a]



[a]Adapted from Perry et al,[27] with permission. 0% signifies the baseline value in normal brain.

Table 3. Cholinesterase (ChE) Inhibitors: 2 Classes for the Treatment of Alzheimer's Disease[a]

Class	Inhibit
Dual ChE inhibitors	Both AChE and BuChE
Rivastigmine	
Physostigmine	
Tacrine	
Metrifonate	
Single ChE inhibitors	AChE
Donepezil	
Galantamine	

[a]Adapted from Weinstock.[33]
Abbreviations: AChE = acetylcholinesterase, BuChE = butyrylcholinesterase.

the brain. Under normal conditions, ACh is metabolized by AChE. However, as Alzheimer's disease progresses, AChE is gradually lost, and BuChE secreted from glial cells progressively becomes the more important enzyme responsible for the inactivation of ACh.[31] Consequently, BuChE inhibition plays a significant role over the course of illness. Furthermore, animal studies at the National Institutes of Health have shown that specific BuChE inhibitors improve cognition without causing cholinergic side effects.[32]

Dr. Enz described how the different ChE inhibitors that are used in Alzheimer's therapy can be divided into 2 classes according to which ChE enzyme they inhibit (Table 3).[33] Single ChE inhibitors such as donepezil and galantamine are specific inhibitors of AChE, while rivastigmine, a dual ChE inhibitor, inhibits both AChE and BuChE. "The dual inhibitory action of agents such as rivastigmine translates into improved clinical benefit," claimed Dr. Enz.

The magnitude and duration of central AChE and BuChE inhibition by rivastigmine have been determined in a study of Alzheimer's patients.[34] As expected, rivastigmine significantly inhibited AChE in the cerebrospinal fluid of these patients. In addition, rivastigmine inhibited BuChE with equal potency, but over a much longer period of time. Dr. Enz explained that, in healthy volunteers, "the same dose of rivastigmine inhibits AChE to a similar extent, but has no effect on BuChE. This suggests that a novel or altered form of BuChE is present in Alzheimer's patients, and rivastigmine inhibits this form."

Further results from that study showed that the cognitive benefits associated with rivastigmine treatment correlated with both AChE and BuChE inhibition. In fact, BuChE inhibition actually showed more significant correlation with cognitive benefit than AChE inhibition (Table 4).[35] "It is clear that BuChE certainly plays a role in Alzheimer's disease," emphasized Dr. Enz.

Concluding his presentation, Dr. Enz claimed that the ability of rivastigmine to inhibit both AChE and BuChE could explain the significant clinical results reported in patients with mild, moderate, and more severe Alzheimer's disease. Rivastigmine improves daily functioning along the continuum of the disease. He concluded that "both AChE and BuChE contribute to the cholinergic deficit and the underlying symptoms. The greater the deficit, the greater the magnitude of beneficial change expected with dual ChE inhibition. Inhibition of both enzymes maximizes the ABCs of daily functioning." ❑

Table 4. Inhibition of Butyrylcholinesterase (BuChE) Is Better Correlated With Cognitive Benefits in Alzheimer's Disease[a]

Cognitive Performance	AChE	BuChE
CNTB summary score	*	**
CNTB subtest		
Finger tapping right		*
Paired associated learning		*
Paired associated learning/ delayed recall		**
Visual memory		*

[a]From Cutler et al,[35] with permission.
Abbreviations: AChE = acetylcholinesterase, CNTB = Computerized Neuropsychological Test Battery. *p < .05. **p < .01.

Conclusion

Genetic findings have aided our understanding of the underlying pathology of Alzheimer's disease and have identified a number of risk factors for the disease. Furthermore, a number of potential therapeutic targets have been identified by these studies, such as BACE inhibitors and presenilin inhibitors. The ultimate aim of such agents is a reduction in the production of β-amyloid. However, such agents have yet to reach the clinic. At present ChE inhibitors remain the only agents approved for the treatment of Alzheimer's. Certain ChE inhibitors have demonstrated considerable efficacy against the key symptoms of Alzheimer's disease: cognition and ADL. Furthermore, new data with rivastigmine suggest that these agents can also improve behavioral disturbances, the forgotten domain of the disease. Behavioral problems are now recognized as a significant cause of premature institutionalization of the Alzheimer's patients, which leads to the enormous cost of care.

The symptoms of Alzheimer's disease are associated with an underlying cholinergic deficit. Both AChE and BuChE contribute to this deficit. As the disease progresses, AChE decreases and BuChE increases in the areas of the brain associated with amyloid deposition. Thus, the role of BuChE becomes gradually more important during the later stages of Alzheimer's disease. Therefore, an agent such as rivastigmine, which is able to inhibit both AChE and BuChE, can maintain cholinergic function across the continuum of Alzheimer's disease and maximize the ABCs of dementia. Clinical results with rivastigmine support this hypothesis. ❑

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