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Clinical and Biological Interactions in Affective and Cognitive Geriatric Syndromes

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Clinical and biological complexity is the rule rather than the exception in geriatric psychiatric syndromes. Typically, geriatric psychopathology develops in the context of medical and neurological disorders. Under these circumstances, ascertainment of symptoms and signs is difficult. Moreover, behavioral abnormalities, cognitive deficits, and physical symptoms and signs are often contributed by more than one psychiatric, neurological, or medical condition. Finally, symptoms change over time as various coexisting disease processes progress or subside, further complicating clinical assessment and diagnosis.

Complexity has been viewed as an obstacle to medical research, which by necessity depends on reduction. Biological and psychosocial hypotheses are nothing but logical reductions, designed to permit understanding of a small part of a larger problem. Experimental design is an operational reduction intended at giving the best chance for hypothesis testing. Such reduction processes become complicated by the clinical intricacies of geriatric psychiatry syndromes. Despite the logical and experimental challenges posed by geriatric syndromes, their complexity has begun to provide meaningful clinical and biological information.

Studying depression in Alzheimer's disease patients exemplifies how comorbid geriatric syndromes can help address clinical and biological questions. In the study by Zubenko et al. in this issue [May 2003], the high prevalence of depression in patients with probable Alzheimer's disease was confirmed. The study also observed that the depressive syndrome of Alzheimer's patients is of mild severity and characterized by indecisiveness and diminished ability to concentrate but with limited depressive ideation and sleep disturbances. This symptom profile is difficult to distinguish from an uncomplicated dementia syndrome, thereby contributing to the underrecognition of depression. The increased frequency of psychotic symptoms in depressed Alzheimer's disease patients further complicates ascertainment of depression. The difficulty in diagnosing depression is evidenced by the wide differences in depression prevalence estimates among patients with Alzheimer's disease. Improving the methods of ascertainment (1) and treatment of depression in Alzheimer's patients is critical, since depression contributes to excess disability, personal suffering, family disruption, and premature institutionalization.

In addition to highlighting an important clinical problem, the comorbidity of depression and dementia has served as the stimulus for answering both clinical and biological questions. The early concept of "pseudodementia" was based on the assumption that the biological abnormalities of depression were the unitary cause of reversible

dementia occurring in the context of depression. Follow-up evaluations of patients with pseudodementia have demonstrated that many of these patients progress into irreversible dementia (2). While this observation reduced optimism about the prognosis of patients with depressive pseudodementia, it drew attention to the heterogeneity of this syndrome. Some of the patients with depressive pseudodementia may have a preclinical or an early-stage dementing disorder. In these patients, cognitive dysfunction during depression is an expression of decreased "cognitive reserve capacity" unmasked by the disturbances of the depression. This assertion is supported by longitudinal studies of community-residing elders, which have documented that depressive symptoms often precede development of dementia (3). Another possibility may be that depressive disorders are risk factors or even predispose patients to Alzheimer's disease and other dementing disorders, since depressive symptoms occurring long before the onset of dementia have been shown to increase the risk for Alzheimer's disease (3). A careful review study further supports this view; it concluded that the longer one experiences depression, the higher the risk of cognitive decline or Alzheimer's disease (4).

Recent studies have suggested that depression may both contribute to the cause and also be the effect of brain abnormalities in patients with Alzheimer's disease. Lifetime duration of depression was found to correlate with hippocampal volume reduction, although some disagreement exists (5). Gray matter atrophy has been documented in the subgenual prefrontal cortex of some depressed patients, and glial cell loss has been found in several prefrontal regions, the amygdala, and the hippocampus of depressed patients (5). Excessive secretion of glucocorticoids and other stress-related hormones reduce neurotrophic factors, inhibit neurogenesis, and may promote amyloid neurotoxicity, thus accelerating the pathological cascade of Alzheimer's disease. Conversely, degenerative changes in brainstem aminergic nuclei occurring during Alzheimer's disease have been thought to contribute to depression (6). Therefore, once depression develops as part of the brain changes of Alzheimer's disease, it may further accelerate the progression of Alzheimer's neuropathological changes. These observations suggest that antidepressants may confer benefits beyond decreasing depressive symptoms. Several antidepressants elevate brain-derived neurotrophic factor in the rat hippocampus, an action perhaps mediated by the 5-HT_{2A} and the β-adrenoreceptor subtypes. Through this action, antidepressants may prevent stress-induced inhibition of neurogenesis and increase dendritic branching (7). It remains to be seen whether antidepressants delay the onset and slow down the progress of Alzheimer's disease in patients with depressive symptoms.

While some cases of geriatric depression with cognitive impairment develop amid the background of subclinical dementing disorders, other cases do not progress into irreversible dementia (2). Various factors may contribute to the transient cognitive dysfunction during depression. Severely depressed elderly patients may be unable to participate fully in tests of cognitive function and thus appear demented when they are not. Another possibility may be that cognitive dysfunction is an integral part of geriatric depression. Identification of cognitive and affective processing difficulties in depressed patients has led to studies that have begun to clarify the role of the prefrontal cortex, anterior cingulate, hippocampus, and amygdala (5, 8).

Emerging literature suggests that cognitive dysfunction and its underlying abnormalities are associated with poor outcomes of depression. Overall cognitive dysfunction has been associated with a longer duration of depressive symptoms and a chronic course of depression in community samples (9). Impairment in some executive functions may predict poor response to acute treatment as well as early relapse and recurrence in clinical studies (10, 11). Executive dysfunction is associated with white matter abnormalities (12), which themselves are predictors of poor outcomes of geriatric depression (10, 13–15). The relationship of cognitive impairment to the course of depression suggests that syndromes characterized by both depression and cognitive abnormalities may be targets for therapies focusing on the underlying biological and behavioral abnormalities. As cerebrovascular disease is a common cause of white matter abnormalities, therapies aimed at prevention of cerebrovascular disease may reduce white matter impairment and avert late-onset depression or improve its outcomes. Drugs enhancing the function of frontostriatal circuitry neurotransmitters may improve both depression and cognitive impairment. Dopamine D_3 agonists are such an example. Agents enhancing alertness (e.g., modafinil) may be effective as a single treatment or as an antidepressant augmentation, since reduced alertness and psychomotor retardation often accompany syndromes characterized by depression and executive dysfunction. If such therapies prove effective, they may initiate studies on the role of hypocretins and histamine in depression with cognitive impairment, since these newly discovered neurotransmitters are part of the alertness systems. Finally, preliminary studies suggest that therapies

targeting behavioral deficits resulting from depression and cognitive impairment can be effective in reducing depressive symptoms and improving function (16).

The study by Religa et al. in this issue underscores how the biological heterogeneity of cognitive impairment of psychiatric disorders can guide the development of prophylactic treatments. Demonstrating that the cognitive impairment of older schizophrenic patients is not caused by amyloid deposits suggests that therapies targeting amyloid production may be ineffective in schizophrenic patients who do not have Alzheimer's disease. However, schizophrenic patients are not immune to Alzheimer's disease. The Religa et al. study shows that the levels of amyloid Aβx-42 in schizophrenic patients with Alzheimer's neuropathology was lower than the amyloid levels of patients with Alzheimer's disease alone. This observation suggests that schizophrenia may increase vulnerability to amyloid Aβx-42 so that limited amyloid deposits may be sufficient to cause a dementia syndrome. On the other hand, some neuroleptic agents inhibit amyloid production (17), and nicotine may reduce amyloid toxicity (18). While neuroleptics and smoking themselves are hardly appropriate prophylactic treatments for Alzheimer's disease, they exemplify how comorbidity can initiate a process of new treatment discovery.

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