

ating cells in patients with AML, since the disease probably has considerable clonal diversity and susceptibility to mutations. Resistant clones arise rapidly in patients with AML despite effective initial success with induction and consolidation chemotherapy. The results from this study suggest that such cells may differ genetically from the dominant cells in the original leukemic population.

In 1960, Nowell and Hungerford<sup>8</sup> made the sentinel observation that one mutation, the Philadelphia chromosome, was associated with one disease, chronic myeloid leukemia. The 1:1 association between genetic alteration and disease phenotype was a major impetus to a recognition of the importance of somatic genetic changes in the pathogenesis of cancers. Nowell later proposed a more complex model in which multiple tumor phenotypes could develop from a single initiating lesion and in which such tumors would thus consist of a diverse array of clones. Such diversity could account for resistance to chemotherapy and phenotypic evolution.<sup>9</sup> The work by Delhommeau et al. not only improves our understanding of malignant myeloid diseases but supports the vision of Nowell and Hungerford regarding the development of these disorders.

Dr. Carroll reports receiving grant support from Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

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## Cool with Plaques and Tangles

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Survivors to the age of 95 years are a select and hardy few. At current mortality rates, only about 8% of persons will live to the age of 95, and only about half of those will escape dementia. To some extent, they may just be the lucky few. However, there are certainly behavioral, environmental, and hereditary differences that distinguish these older old persons from the rest of us. Many of these differences make these older old persons less vulnerable than younger old persons to a variety of adverse conditions. The biology and experiences of older old persons help us focus on the causes of and ways to survive system failure. However, older old persons have generally accumulated a number of coexisting conditions that complicate the study of single disease processes.

In this issue of the *Journal*, Savva and colleagues<sup>1</sup> provide a clinicopathological update on the Medical Research Council Cognitive Function

and Ageing Study (MRC-CFAS). This prospective epidemiologic study has followed a representative sample of more than 18,000 people since the 1980s. Savva et al. used an algorithmic diagnosis of clinical dementia that is compatible with that in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, and a standardized approach to neuropathological diagnosis and quantification of the plaque and tangle pathological lesions of Alzheimer's disease in 456 people. They observed that although the relationship between cerebral atrophy and dementia persisted into the oldest ages, the strength of the association between the pathological features of Alzheimer's disease and clinical dementia diminished.

It is a rare and outstanding approach to have a population-based study of cognition that extends into very late life and shows neuropathological features at the time of death. Together with

the few other prominent prospective clinicopathological studies such as the Nun Study,<sup>2</sup> the Religious Orders Study,<sup>3</sup> the Memory and Aging Project,<sup>4</sup> and the 90+ Study,<sup>5</sup> this study by Savva et al. highlights the complex relationships between the hallmark pathological lesions and mentation.

Although it is almost indisputable that the pathological features of Alzheimer's disease have a marked effect on brain function, one of the most interesting and underappreciated findings emerging from these studies is that some elderly persons whose brains have high densities of lesions indicative of neurodegenerative disease do not have dementia.<sup>6-9</sup> Such cases are not common, but it is of the utmost importance to understand them. What neurobiologic factors provide the resilience of these people to the effects of neuropathological lesions in the brain?

The question that arises is, Are plaques and tangles themselves toxic or are they epiphenomena of any number of molecular pathways that result in protein misfolding and aggregation, not all of which result in neural dysfunction? Indeed, it has been proposed that at least  $\beta$ -amyloid plaques in the brain may serve a healthy function as "sinks" to absorb and immobilize soluble or oligomeric  $\beta$ -amyloid.<sup>10,11</sup>

Savva and colleagues also show that dementia is closely associated with brain atrophy and that this relationship persists in older old persons. The neurobiologic mechanisms by which neuron death, synapse and dendrite loss, or white-matter loss occur in Alzheimer's disease have not been fully explained. We need a more complete understanding of the complex processes that lead to neurodegeneration.

Autopsy studies are by nature cross-sectional, and provide little information about the dynamics of neurodegeneration. It is tempting to assume that those who did not have dementia at 95 years of age had very low levels of neuropathological changes when they were 75 years of age — levels similar to those in persons without dementia who died at the age of 75. However, a long, slow accumulation of plaques and tangles could be easier to manage than a rapid profusion. For example, with slow accumulation, cell-repair mechanisms may be able to limit the damage. Also cognitive compensation might have a better chance of minimizing the effects of neuron loss. A more rapid accumulation of pathological features might overwhelm these mechanisms.

Slow accumulation may also imply that these persons have traits that prevent or slow a cascade of events resulting from feedback loops that would accelerate the production of neuropathological changes. For example, the plaque and tangle lesions of Alzheimer's disease are accompanied by an inflammatory reaction in the form of proliferation and activation of astrocytes and microglia. Although the full scope of activated glial functions is not known, these cells do secrete cytokines that promote inflammation. Both  $\beta$ -amyloid and extracellular paired helical filaments of the protein tau appear to act as irritants that activate microglia and cause a cascade involving cytokines, complement factors, acute-phase reactants, oxygen free radicals, and excess glutamate. The role of microglia in the disease process is complicated by the fact that they may also secrete  $\beta$ -amyloid. It is possible that some older old people have traits that protect them from a rapid cascade of inflammation and neurodegeneration. Such traits might allow them to avoid or delay both dementia and early death due to a variety of common causes associated with inflammation, such as coronary heart disease and stroke.

On the one hand, nontoxic lesions, slow adaptation, neuroplastic repair and compensation, or sheer cerebral reserve may allow a person to sustain good cognitive functioning until overwhelmed by pathological changes in the brain. On the other hand, other deleterious factors not accounted for in the neuropathological studies of very old persons may add to, compound, or confound the effects of Alzheimer's disease on cognition in very late life in complex ways, thus weakening the statistical relationship between Alzheimer's disease lesions and dementia. Coexisting medical conditions, such as pulmonary disease, heart failure, renal insufficiency, and the systemic effects of other failing organs can all affect cognition. Allostatic load, "wear and tear" due to a lifetime of physiological or psychological stresses and adaptations, also appears to contribute to cognitive decline in late life, independently of the pathological features of Alzheimer's disease.<sup>12</sup> Even in the absence of accumulating Alzheimer's disease lesions, these factors could drive the relationship between atrophy and dementia that was observed by Savva et al. Conversely, the absence of these other factors might allow a person to remain cognitively intact despite some accumulation of plaques and tangles.

There is more that can be learned from autopsy studies. In particular, studies of neuropathological changes in the very old have been limited in the range, sensitivity, and quantitation of the neurodegenerative-disease markers assessed. Immunohistochemical analysis of current molecular markers such as  $\alpha$ -synuclein for Lewy bodies or TAR DNA binding protein (known as TDP-43) for the inclusions found in frontotemporal lobar degenerations and other neurodegenerative diseases, including Alzheimer's disease, may reveal additional lesions that also contribute to dementia.

There is much we need to learn from our elders. New techniques, such as brain imaging with amyloid ligands and biochemical measurements of  $\beta$ -amyloid and tau in the cerebrospinal fluid, provide opportunities to observe aspects of the trajectories that lead to the pathological features observed at autopsy. In addition, several new therapies to limit the accumulation of amyloid deposits are in late-phase clinical trials. The degree of effectiveness of these therapies will provide information about the extent to which amyloid deposits relate to brain atrophy and the progression of dementia. As we learn more about the common course of Alzheimer's disease, it will become even more important to understand the atypical cases of older old persons who are cognitively intact despite having neurodegenerative-disease lesions.

Dr. Arnold reports being a principal investigator or an investigator in clinical trials sponsored by Eli Lilly, Elan/Wyeth, and Baxter. No other potential conflict of interest relevant to this article was reported.

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