Alzheimer's "Other Dementia"

David J. Libon, PhD, Catherine C. Price, PhD,† Kenneth M. Heilman, MD,‡ and Murray Grossman, MD§*

Abstract: A short history of Alzheimer disease and vascular dementia is presented. The socio-medical events that led to the dominance of Alzheimer disease are discussed. Alzheimer's contributions to our current understanding of vascular dementia are reviewed.

Key Words: Alzheimer disease, vascular dementia, subcortical dementia, leukoaraiosis, Binswanger disease, history of dementia

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HISTORICAL PERSPECTIVE

Dementia is a common problem seen in clinical practice. Patients who suffer from vascular disease also represent a common problem. When considered as separate entities, neurologic disease associated with either dementia or vascular disease engender little controversy. But when the terms "dementia" and "vascular" are cojoined to form the term "vascular dementia" controversy ensues.[1] The reasons for this controversy are unclear. One explanation for this situation might be termed the "Alzheimerization" of dementia.[1] This refers to the tendency to view most cases of insidious, progressive, idiopathic dementia within the spectrum of Alzheimer disease (AD), even if rigorous diagnostic criteria for the diagnosis of AD are not necessarily met.[2] The purpose of this paper is to understand the historical roots of this controversy. Some of the historical events that led to the dominance of AD within the family of the dementias are discussed. We also review an aspect of Alzheimer's work that has received little attention, that is, his many and important contributions to our current understanding of vascular dementia.

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From the *New Jersey Institute for Successful Aging, University of Medicine and Dentistry of New Jersey, School of Osteopathic Medicine, Stratford NJ; Departments of †Clinical and Health Psychology and Anesthesiology; ‡Department of Neurology, University of Florida, FL; and §Department of Neurology, University of Pennsylvania, Philadelphia, PA.

Reprints: David J. Libon, PhD, New Jersey Institute for Successful Aging, University of Medicine and Dentistry of New Jersey, School of Osteopathic Medicine, Suite 1800, 42 East Laurel Road, Stratford, NJ 08084 (e-mail: libondj@umdnj.edu).

ALZHEIMER, KRAEPELIN, AND BIOLOGIC PSYCHIATRY

What we now understand as AD stems from the observations of Alzheimer's seminal cases, of Auguste[3] and Johann[4]. To place Alzheimer's scientific thinking into its proper perspective, however, we must consider Emil Kraepelin's influence, not only on Alzheimer himself, but also within the medical and psychiatric community of their day.

During the early 20th century little was understood about the biologic mechanisms that might be associated with neuropsychiatric illnesses. There was, however, considerable emphasis on the classification of neuropsychiatric illnesses on the basis of clinical symptoms.[5] In this regard, Kraepelin's classification of *Dementia Praecox* and *Manic-Depressive* disorders earned him considerable fame.[6] Moreover, the discovery that syphilis was associated with general paresis of the brain and was caused by the infection of the spirochete *treponema pallidum* was a seminal event in that a specific biologic substrate could now be associated with a specific neuropsychiatric illness. This event contributed to the beginning of what has come to be understood as biologic psychiatry. Thus, for Kraepelin and his associates, the degree that specific pathologic alterations could be associated with a specific set of clinical characteristics or symptoms became *the* methodology for the classification of disease states. It was this clinical-pathologic methodology that guided much of Alzheimer's work.

Concomitant with the development of this clinical-pathologic methodology, Alzheimer and Nissl contributed to the development of new histologic staining methods. Alzheimer and Nissl were friends, colleagues, and eventually worked with Kraepelin.[6,7] Alzheimer was highly respected as a neuropathologist. Interestingly, he believed his most important work was not the 2 case studies that ultimately led to the designation of the disease that currently bears his name, but his 1904 thesis *Histological Studies of the Differential Diagnosis of Progressive Paralysis*. In this work he provided an integration of clinical and pathologic data as related to what was then considered a major neuropsychiatric illness (see Ref. 6, p. 2).

It has been suggested that Alzheimer's over arching hypothesis was to show how certain catabolic products might provide evidence of biologic markers for neuropsychiatric conditions.[8] For Alzheimer these biologic markers in combination with clinical symptoms would ultimately lead to a diagnosis. Thus, the *zeitgeist* of the

era suggested that medical scientists would ultimately be able to associate specific alterations in tissue with specific clinical symptoms and/or disease states.[5] It is within the context of what must have been such an incredibly stimulating and rich intellectual environment that Alzheimer concluded his 1907 description of Auguste: "We must reach a stage in which the vast well-known disease groups must be subdivided into many smaller groups, each with its own clinical and anatomical characteristics." These ideas are prescient considering our current interest in possible physiologic overlap between AD and vascular dementia.[9]

Much has been written regarding why or how it was that Kraepelin created the eponym *Alzheimer's disease* which first appears in the 1910 edition of his textbook.[6,8,10] By the year 1910, only 5 cases had been described in the literature, 2 of which were Alzheimer's patients. Nonetheless the combination of clinical characteristics, including the comparatively early (ie, presenile) onset and rapid course of dementia, the prominence of focal behavioral symptoms such as aphasia, agnosia, and apraxia, and neurofibrillary tangles, a comparatively new histologic alteration, seemed to be sufficient justification for Kraepelin to christen a new disease entity. Amaducci et al[10] stress the political nature of Kraepelin's actions (ie, his competition with Pick's neuropathologic laboratory in Prague). As has been pointed out by other researchers,[5] Kraepelin's scientific methods coupled with Alzheimer's interest in integrating histologic findings with a set of relatively unique clinical and pathologic characteristics seemed to justify the designation of a new disease state and confirm the merits of Kraepelin's clinical-pathologic methodology.

Still, during Alzheimer's lifetime there was no absolute consensus that Alzheimer's description of so-called presenile dementia actually constituted sufficient evidence for the labeling of a new disease state. In 1912, Solomon Carter Fuller,[11] a prominent psychiatrist and neuropathologist from Massachusetts, reviewed the existing literature on AD (15 cases; see Ref. 8 for a review). Not all cases presented with both senile plaques and neurofibrillary tangles; in some cases arteriosclerosis seems to be present, and in other cases other medical conditions were noted. It was also known during Alzheimer's life that neurofibrillary tangles and senile plaques were found not only in the brains of patients suffering from other neuropsychiatric conditions but also in the brains of individuals who, in life, did not seem to be demented. These facts have been recently rediscovered.

Alzheimer himself could be counted among the "doubters" who did not necessarily believe that AD represented anything but a precocious form of senile dementia.[8] It is interesting to note that Alzheimer's macroscopic description of Auguste's brain included evidence of vascular disease, that is, "The larger cerebral vessels show arteriosclerotic changes" (Alzheimer[3] translated by Jarvik and Greenson, 1987, p. 8). The recent discovery of Alzheimer's original case notes on Auguste[12] suggests that she may have also suffered from arteriosclerosis of the small vessels of the brain. Nonetheless, many of Alzheimer's contemporaries, some of whom were his former students, readily embraced the new eponym, *Alzheimer's disease*, to designate the presenile onset of dementia.

ALZHEIMER AND VASCULAR DEMENTIA

So what about vascular dementia? Roman[13,14] has written extensively on the history of vascular dementia. Often the history of vascular dementia begins with Binswanger's description of *Encephalitis Subcorticalis Chronica Progressiva* (1894; Refs. 15,16). In the 1840s, however, Max Durand-Fardel[17,18] described a number of vascular lesions, including lacunar infarcts, etat crible, and interstitial atrophy of the brain. Durand-Fardel's observations are certainly relevant today. For example, his description of *interstitial atrophy of the brain* is similar to the recent description of leukoaraiosis.[19] In Alzheimer's day, dementia caused by syphilis versus vascular disease was a common differential diagnosis. Until the work of Hachinski,[20] *arteriosclerotic dementia* was not only a well-established form of dementia, but various subtypes of cerebrovascular dementia were recognized.

An aspect of Alzheimer's work that has received virtually no attention is his contribution to our current understanding of vascular dementia. Just as Dr Geschwind is best remembered for his research on aphasia and disconnection,[21] rather than his work on neuromuscular disease, Alzheimer wrote many more papers on vascular dementia (1895, 1897, 1898, 1902, and 1913, see Refs. 22–24; Table 1) than on presenile dementia. Hans Forstl and colleagues have translated 3 of Alzheimer's papers on vascular dementia. Alzheimer's goal in his short report published in 1895[22] was to show that "arteriosclerotic degeneration can be distinguished easily from general paresis." Many of the clinical features we now commonly associate with multi-infarct dementia were discussed.

In 1898, Alzheimer reviewed a number of neuropsychiatric conditions of "old age" and offered a nosology of the vascular dementias.[23] Indeed, the recently proposed diagnostic criteria for vascular dementia[25–28] have drawn upon the work of both Kraepelin and Alzheimer. In his 1898 paper, Alzheimer described 4 subtypes of vascular dementia.[23] For Alzheimer, the clinical characteristics of *arteriosclerotic brain atrophy* include "a step-wise deterioration with shorter or longer intervals." Alzheimer also emphasized changes in personality, the emergence of depression, and the value of focal neurologic signs in the differential diagnosis. Alzheimer discusses a second form of vascular dementia, that is, Binswanger's *encephalitis subcorticalis chronica progressiva* and confirmed many of Binswanger's observations.[15–16] Alzheimer goes on to offer a short discussion of 2 other forms of vascular dementia: *perivascular gliosis* or vascular dementia associated with embolic strokes and *dementia apoplectica* or vascular dementia due to hemorrhagic stroke.

TABLE 1. Alzheimer's (1898) Classification of the Vascular Dementias

Arteriosclerotic Brain Atrophy	
Clinical characteristics	Pathologic characteristics
Stepwise onset and course	Focal brain lesions
Early onset of depression	Arteriosclerosis kidney disease
Focal neurologic signs	Brain/body vascular atheromatosis
Motor speech dysfunction	Myocardial hypertrophy
Encephalitis subcorticalis chronica progressiva (Binswanger disease)	
Clinical characteristics	Pathologic characteristics
Slow insidious onset and course	Widespread atheromatous vascular disease
Focal neurologic signs may be present	Severe white matter atrophy
Dementia apoplectica	
Clinical characteristics	Pathologic characteristics
Apathy, labile mood	Evidence of hemorrhage
Poor memory, confabulation	
Sluggish, slow speech	
Tremor, exaggerated reflexes	
Perivascular gliosis	
Clinical characteristics	Pathologic characteristics
Focal behavioral alterations depending on site of pathology	Evidence of old, prior infract(s) Focal glial proliferation

Abstracted from Alzheimer A. Recent studies on dementia senilis and brain disorders caused by atheromatous vascular disease (translated by Forstl H, Howard R) Alzheimer's Dis Assoc Dis. 1898;5:257–264. (see Ref. 23).

Alzheimer's 1902 paper entitled "Mental Disturbances of Arteriosclerotic Origin" has not received the attention it deserves.[24] Here, again, Alzheimer generously credits Binswanger's prior work.[15–16] A most interesting aspect of this paper revolved around Alzheimer neuropsychologic description of dementia associated with subcortical white matter disease. Alzheimer's discussion of the neuropsychologic deficits associated with subcortical white matter disease clearly anticipated the now accepted differentiation between cortical and subcortical dementia. For example, Alzheimer described the memory impairment associated with subcortical white matter disease as a retrieval deficit, that is, "difficulty in retrieving certain ideas, and not a true deficit." Alzheimer also associated "prolonged reaction times" (ie, bradyphrenia) with subcortical white matter dementia. It is unfortunate that Alzheimer's cogent clinical observations of vascular disease states coupled with his meticulous histologic examinations have been unappreciated.

RISE AND DOMINANCE OF ALZHEIMER DISEASE

From the time of Alzheimer's death (1915) to the 1970s neither AD, nor dementia in general, occupied the first rank of neuropsychiatric illnesses. This is reflected in the contemporaneous neurology textbooks. For example, in the ninth edition of Wechsler's *Clinical Neurology* (1963; first published in 1927; Ref. 29) both AD and Pick's disease are summarized in short paragraphs. It is interesting to note that both these forms of dementia are appended to a chapter entitled "Circulatory Disturbances of the Brain." In the fifth edition of Meritt's *A Textbook of Neurology* (1975; first published in 1955; Ref. 30) the author writes "Both Alzheimer's disease and Pick's disease are rare" (p. 443).

The dominance of AD within the family of the dementias can be traced to certain demographic and scientific events occurring in the late 1960s and 1970s. During this time, life expectancy was lengthening and there was an expectation that aging should be associated with a higher quality of life. The work of M. Powell Lawton and Elaine Brody,[31,32] Robert Kastenbaum,[33] Robert Katzman,[34] and many other researchers firmly established gerontology and geriatric medicine as important areas for scientific inquiry. Indeed, in 1975, the federal government invested in the developing interest in aging through the establishment of the Geriatric Research and Educational and Clinical Centers.

An important scientific development that led to the dominance of AD revolves around the Newcastle-Upon-Tyne studies of Martin Roth and colleagues. The paper of Blessed et al[35] was seminal. This study combined the meticulous neuropathologic descriptions of the brains of dementia patients with neuropsychologic and behavioral data. The authors studied the brains of 60 patients. They found a strong association between the numbers of senile plaques found throughout the brain and performance on neuropsychologic and functional tests. For the first time a systemic analysis of behavior could be *directly* associated with pathology.

When viewed within a narrow context, the research of Blessed et al[35] tends to validate Kraepelin's clinical-pathologic methodology. The broader context of this study, however, was far-reaching, that is, the apparent linear relationship between pathology and behavior meant that an operational clinical-pathologic definition/diagnosis of AD could now be made. Therefore, the

dominance of AD, which dates from the middle 1970s, is the result of the realization that AD was not only quite prevalent (ie, "a major killer," see Ref. 34, p. 609), but that the illness could be subjected to systematic clinical-pathologic study.

ALZHEIMER'S "OTHER DEMENTIA"

Throughout the 1980s and until the introduction of magnetic resonance imaging technology, vascular dementia was essentially abandoned and assigned inferior status. Within the family of the dementias, vascular dementia was definitely *the problem child* and like the late Rodney Dangerfield simply *got no respect*. The introduction of magnetic resonance imaging technology did much to rehabilitate and reclaim vascular dementia from the orphanage of neglected neurologic illnesses. Today, much of the controversy revolves around many of the same issues that were debated in Alzheimer's day. For example, some studies have shown that the incidence of so-called pure AD might be lower than previously believed.[36–38] Other research has suggested that vascular disease might modify the expression of the neuropathology associated with AD.[39–41] In transgenic animals, ischemic damage has been shown to facilitate the formation of β-amyloid plaques.[39] Finally, a prodromal state syndrome associated with vascular dementia termed "VCI" or vascular cognitive impairment has received much interest.[42–44] When we consider these contemporary data in conjunction with Alzheimer's own observations, perhaps it might be appropriate to view vascular dementia as Alzheimer's "other dementia."

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