Comments, Opinions, and Reviews

Dementia Due to Vascular Disease—
A Multifactorial Disorder

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This review was undertaken to evaluate critically the literature pertaining to vascular dementia with the objective of determining a more useful and scientifically supported definition of vascular dementia, its relation to other causes of dementia, and the biologic mechanisms involved in its causation. (Stroke 1988;19:1291-1299)

The term vascular dementia is generally used to describe the dementias that are thought to be caused by thromboembolic cerebral vascular disease. The dementia has been said to be the result of infarction of a significant amount (100 ml) of brain tissue irrespective of the location of the lesion,1,2 a view that seems to conform to the hypothesis of Lashley,3 who correlated severity of memory loss to the volume of brain tissue damaged or destroyed. Smaller and more localized cerebral infarcts strategically located in anatomic structures (such as the hippocampus, mamillary bodies, thalamus, or basal forebrain4-9), the functional integrity of which are essential for normal memory function, are also known to cause severe amnestic syndromes if not all the other characteristics of dementia. These lesions are almost invariably in the vascular distribution of the posterior circulation, particularly in the penetrating branches of the posterior communicating arteries or the posterior cerebral arteries. Ischemic lesions in the vascular distribution of the anterior cerebral arteries produce alterations in awareness, memory deficits, and abulia, which, if not classical dementia, are certainly evidence of altered mental status. Similarly, focal lesions in the frontal, temporal, or parietal lobes may produce disturbances in neuropsychological testing that are characteristic for lesions of those anatomic structures and that may conform to broader definitions of dementia even though verbal memory may not be involved.

Usually, however, the term vascular dementia and, particularly, multi-infarct dementia (MID) applies to a progressive loss of cognitive functions and the accompanying impairment of social skills (orientation, memory dysfunction, language impairment, disturbed arithmetic functions, and judgment defects) that are qualitatively indistinguishable from those seen in Alzheimer's disease (AD) or senile dementia of the Alzheimer's type (SDAT) or from the dementia seen in other neurodegenerative disorders (such as parkinsonism or progressive supranuclear palsy) or from the dementia that may occur in certain brain tumors, in metabolic disorders affecting the brain, or in cerebral infections or intoxications.10-13 The term vascular dementia or MID is applied if investigation fails to reveal evidence of other structural, metabolic, infectious, or toxic brain disorders and if there is evidence of vascular disease, hypertension, and an abrupt onset of the dementia suggestive of cerebral infarction.14-18 In short, the characteristics of the dementia itself are not unique; the diagnosis is based on the presence or absence of other considerations.

This lack of specificity of the clinical syndrome and, particularly, the similarity of the neuropsychological defects in patients with vascular dementia and those with SDAT17 have made it difficult to distinguish these disorders and, therefore, to conduct long-term studies on the natural histories of or management strategies for each. Although the ischemic scale of Hachinsky et al14 is widely used to differentiate clinically between vascular dementia and AD or SDAT, the original study did not include pathologic verification of the clinical diagnosis, nor was there evidence that the authors believed their ischemic scale to be more than a general guide to diagnosis. One subsequent retrospective clinical-pathologic correlation in 14 patients found eight features to be primarily characteristic of vascular dementia.18 These features included abrupt onset, stepwise deterioration, history of stroke, focal neurologic signs, and focal neurologic symptoms; the history or presence of hypertension was of secondary importance. Of the 14 patients examined, five

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were found to have pathologic features (plaques and tangles) of SDAT, four had multiple infarcts without great numbers of plaques or tangles, and five (mixed cases) had both types of pathologic changes. A reasonable conclusion from that study would be that a patient has had a cerebral infarct, but it cannot prove that the patient’s dementia was caused by the vascular lesions. Similarly, although demented patients with motor signs, gait disorders, visual field defects, and urinary incontinence are more likely to have vascular dementia than SDAT, such signs may also occur in patients with SDAT.

Pathology of Dementia

Attempts to establish reliable pathologic correlates for dementia are not new, but the definitive, sophisticated, prospective, longitudinal clinical studies of patients with dementia followed by detailed, modern, pathologic evaluation of their brains so that the clinical picture is matched with the pathology in a given patient still remains to be done. The history of this effort is interesting and central to an understanding of our present state of knowledge. In 1927, Grunthal performed a careful, comparative, clinical-pathologic study of senile dementia and concluded that, although there was a reasonable correlation between the degree of dementia and the numbers of senile plaques, neurofibrillary tangles (NFTs), and cerebral atrophy, there were also notable exceptions to this correlation, suggesting that a separate, as yet unidentified, morphological factor, possibly inborn, must be added to a particular aged shrunken brain in order to produce dementia. Also, from the clinico-pathologic standpoint, it is probable that between the truly normal old person and the demented, there is not only a quantitative but also a qualitative difference.

Wertham and Wertham reviewed work on this subject and concluded that the field of cerebral arteriosclerosis was confusing, that there was a lack of correlation between mental disturbances and cerebral lesions, and that the investigation required a more biologic approach.

Rothschild published a series of clinical-pathologic studies in 1937–1956. The first of these publications described the pathologic changes in senile psychoses, and Rothschild subsequently addressed the still-unresolved issue of the clinical differentiation of senile and arteriosclerotic psychosis. His clinical criteria were remarkably similar to those used today, and Rothschild clearly recognized and emphasized the presence of hypertension, cardiac or renal disease, the abrupt onset of dementia, hemiplegia, pseudobulbar speech, and dizziness, syncope, or seizures in the syndrome of vascular dementia, and although his neuropsychological testing was not sophisticated by today’s standards it is clear that Rothschild identified the essential features of the dementias in both groups. He concluded that he had failed to identify anything other than the crudest of correlations between the degree of intellectual impairment and histologic change and that pure forms of senile and arteriosclerotic changes occurred less frequently than mixtures of these processes. My discussion will return later to another of Rothschild’s pathologic observations, namely, that diffuse areas of patchy demyelination are observed in the hemispheric white matter of most patients with arteriosclerotic dementia. Such changes had been observed by Binswanger, and interest in the changes and their relation to dementia has recently been revived because of white matter lesions observed in the brains of middle-aged and elderly individuals by magnetic resonance imaging (MRI).

In 1962, Corsellis published a monumental study of 300 patients divided clinically into organic and functional groups, the former subdivided further into psychoses associated with cerebral vascular changes, cerebral senile changes, and others. In general, the clinical criteria for these divisions would apply today, but there was no attempt at careful neuropsychological testing. Corsellis’s conclusions were

The results indicate that the ways in which “organic” deterioration manifests itself during life are more often than not reflected in the ultimate appearance of the brain, even though this reflection may be crude and superficial. Human behavior, however, is fortunately a great deal more subtle than the science of neuropathology.

There followed a series of carefully documented clinical-pathologic correlations on the brains of normal and demented old people by Tomlinson et al. and Blessed et al. in 1968 and 1970, with a summation of these findings by Tomlinson and Henderson in 1976. These studies were done in an attempt to determine if there are specific pathologic markers of dementia, degenerative or vascular. They are remarkable studies, not likely to be repeated soon. Unfortunately, there appears to have been no effort made to distinguish clinically between vascular dementia and SDAT, and there are no recorded observations on the presence or absence of hypertension, clinical evidence of vascular disease, heart disease, or other risk factors for vascular dementia. Detailed neuropsychological findings are not given; testing simply established the presence or absence of dementia. The dementia was neither characterized nor graded in severity. Finally, the 28 nondemented control subjects came from the geriatric unit of a general hospital or from the wards of a mental hospital; eight subjects had purely

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physical illnesses of a serious nature, 13 were admitted in terminal confusional states, and six were suffering from affective disorders. This is admittedly not an ideal control group. It is clear from these studies that there is no invariable pathologic marker of dementia, vascular or degenerative. Patients who had 14 senile plaques per high-power microscopic field were always demented, but those who had fewer plaques may not have been demented; 16 of 50 patients with dementia had no senile plaques. Many patients with dementia had no NFTs, but many NFTs in the cortex were invariably associated with dementia. Nondemented control subjects often had a substantial amount of infarcted brain tissue, but patients who had more than 100 ml of infarcted brain tissue were invariably demented. The majority of cases of arteriosclerotic dementia were associated with one or more large areas of infarction that destroyed much of the cortex and white matter of a hemisphere or with many lesions ranging in diameter from a few millimeters to several centimeters. The authors emphasized the grossness of these areas of brain destruction and implied that arteriosclerotic dementia is not caused by subtle pathologic lesions. Tomlinson and his coauthors did not exclude the possibility that multiple, widely scattered white matter softenings with considerable destruction of the corpus callosum and hippocampus may contribute to dementia in patients in whom the total quantity of destroyed tissue is not gross, but they cautioned that small lesions in these territories are compatible with normal old age and the absence of dementia. These studies clearly demonstrated that the pathologic changes in the brains of demented old persons are of mixed senile and vascular etiology in at least 40%. It is further evident that the presence of a stroke or vascular disease does not establish the etiology of a dementia as vascular. The absence of cerebral vascular disease and cerebral infarcts probably excludes a vascular etiology for dementia, and in such instances, the diagnosis of SDAT depends on the presence of "large numbers" of NFTs in the cortex and of senile plaques in other parts of the brain. Based on the evaluations of Tomlinson and coworkers and these conclusions, the various studies purporting to characterize different neuropsychological deficits in vascular dementia and SDAT are unconvincing.

The studies of Tomlinson and others have rightly been considered the gold standard of clinical-pathologic correlations of dementia and of the differential pathologic diagnosis of degenerative versus vascular dementia. These authors recognized and repeatedly emphasized that the pathologic markers of both degenerative and vascular dementia were quantitative and qualitative, that substantial degenerative or vascular pathologic changes or both existed in normal individuals, and that dementia occurred in patients in whom such changes were insubstantial. "Our experience also shows that one must never assume that because multiple infarcts are present, that this is the sole cause or contributing factor of the dementia..." They further point out that... it would be totally naive to suppose that senile changes of the type described and massive ischemic disease were the only contributing morphological changes present in the brains of these subjects. What these other contributing factors are, however, is not at this moment clear and investigation of other possible factors is needed. . . .

These cautionary remarks do not seem to have received the attention and emphasis they deserve.

Other features of the studies of Tomlinson and his colleagues bear comment. It is interesting that in their "myelin stains there was usually only a moderate diminution in staining intensity, and gliosis of white matter was either minimal or totally absent..." despite their emphasis on areas of shrinkage and great reduction in white matter. They made no comment on the possible role of white matter disease in causation of the dementia, a point that I will discuss later. The original article indicated that they had embarked on an effort to study the cerebrovascular supply of their demented old people by injection techniques, but I was unable to find further reference to this valuable projected study in later literature. As previously mentioned, neither did their publications include historic data that would have allowed the reader to appraise the influence of hypertension, systemic vascular disease, heart disease, or other stroke risk factors on their clinical and pathologic findings in either degenerative or vascular dementia. They made no comments about lacunar infarcts contributing to dementia.

The above references to classical observations are offered in view of the importance of the authors' work and the impact it made on subsequent investigators. Tomlinson and his colleagues were careful to suggest that dementia in the elderly is probably multifactorial, suggested additional studies, and recognized what their studies did not include.

**Dementia Due to Lacunar Infarction**

The role of lacunar infarcts in the causation of dementia remains in dispute. Marie's original article was basically a pathologic study, and the first modern clinical-pathologic correlations were made by Fisher, who considered dementia to be rare even in the presence of multiple (<10) lacunar infarcts, which he defined as small (12-15 mm in diameter) infarcts that result from occlusion of deep penetrating cerebral arterioles. The arterioles usually show lipohyalinosis, and the patients are usually elderly and hypertensive. Many investigators have used the term lacunar infarct to describe any small infarct regardless of vascular pathology or location and, in addition, the term lacunar dementia has been used to characterize the dementia that may occur in individuals who present with a vari-
able neurologic picture that may include focal motor
defects, gait disturbances, pseudobulbar palsy, and
urinary incontinence, with or without hyper-
tension.\textsuperscript{38,39} The literature that purports to prove
the existence of lacunar dementia does not make a
convincing case. The clinical correlations are mostly
retrospective, obtained from records initially gener-
ated by other physicians, and incomplete. The
dementia syndromes described are variable, lacunes
were sometimes identified by computed tomogra-
phy (CT) rather than pathologically, and there was
little or no correlation between the number and
distribution of the lacunes and the severity of the
dementia. As Roman\textsuperscript{38} mentioned, dementia \ldots
does not occur necessarily even in severe cases
with multiple lacunes.\textsuperscript{1} Most importantly, the patho-
logic studies did not exclude other causes of demen-
tia, such as SDAT. The clear lesson from the work
of Tomlinson et al\textsuperscript{2} is that the examiner cannot
assume that the dementia was caused by vascular
disease unless pathologic markers for SDAT are not
present and perhaps not even then. No published
study that describes the entity of lacunar dementia
has observed this caveat.

Available clinical-pathologic evidence, therefore,
does not support the assertion that dementia can result from cerebral infarcts that destroy a substantial amount of brain tissue regardless of cerebral localization\textsuperscript{1,2} or from small, discrete, localized infarcts that damage or destroy cerebral areas concerned with memory and cognition.\textsuperscript{4,5} Qualitative aspects of the dementia may vary in these different groups of patients. It is also evident that the association of dementia with a history of stroke does not prove that the cause of the demen-
tia is vascular,\textsuperscript{1,2,17} nor can the diagnosis of vascular
dementia be made on the basis of CT or MRI.\textsuperscript{40}

\textbf{Hypertension and Dementia}

Since hypertension is the most important risk
factor for stroke\textsuperscript{41,42} and since some form of stroke
or severely impaired cerebral perfusion is the major
cause of vascular dementia, it follows that hyper-
tension is also the most important risk factor for
vascular dementia. It is generally accepted that
hypertensive vascular disease increases the inci-
dence of occlusive stroke by at least two mecha-
nisms, by accelerating atherosclerosis and arterial
occlusion and by causing subintimal hyperplasia
and lipohyalinosis and occlusion of arterioles. The
infarcts resulting from the latter mechanism are
usually small and may be lacunar.\textsuperscript{35} The role of
hypertension in the etiology of vascular dementia
may be more complex than these mechanisms imply,
however. There has not been a good study that
correlates the prevalence of hypertension and vas-
cular dementia. We have no evidence, for example,
that the prevalence of vascular dementia (or demen-
tia of any etiology) has decreased \textit{part passu} with the
presumed reduction of stroke incidence and
mortality, which is believed to be due primarily to
better control of hypertension.\textsuperscript{47} Such information

is difficult to obtain in view of the problems involved
in distinguishing vascular from degenerative demen-
tia. Nor is there evidence that the prevalence of
vascular dementia is greater in blacks than in Cau-
casians, even though it is generally acknowledged
that the prevalence of hypertension and stroke is
greater in blacks.\textsuperscript{43-45} There is evidence that hyper-
tension per se is related to intellectual changes in
the aged,\textsuperscript{46} and at least one study\textsuperscript{47} purported
to show that control of hypertension improved cogni-
tion in patients with MID. The latter study implies
that at least a portion of dementia is caused by
reversible physiologic changes and not infarction.

Are there, then, mechanisms whereby hyperten-
sive vascular disease induces brain changes that
result in dementia but are not infarcts? Hyperten-
sive vascular disease increases cerebral vascular
resistance (CVR), which can be reduced by reduc-
ing blood pressure. The elevation of CVR is the
result of autoregulation, the physiologic mechanism
responsible for maintaining normal cerebral blood
flow (CBF) during changes in mean arterial blood
pressure (MABP). Because the lower limit of MABP
at which autoregulation is impaired is higher in
hypertensive than in normotensive individuals, mod-
erate hypotension is more likely to impair CBF in
hypertensive individuals. Reduction in cerebral per-
fusion may result in cerebral ischemia, particularly
in vulnerable areas; severe reductions in cerebral
perfusion may result in cerebral infarction. One
longitudinal study\textsuperscript{48} reported lower values for hemi-
spheric CBF in asymptomatic patients with hyper-
tension than in age-matched normotensive controls
and suggested that progressive cerebral ischemia
antedates cerebrovascular symptoms by 2 years.

The issue of whether chronically impaired cerebral
perfusion can cause significant neurologic deficits
and, particularly, dementia is of considerable impor-
tance in understanding the pathogenesis of Binswan-
gers subcortical arteriosclerotic encephalopathy
(BSAE) as well as in explaining the diffuse white
matter lesions that have been described by CT and
MRI in a variety of circumstances\textsuperscript{49-58} and that
have been described pathologically in patients with
AD, SDAT, and MID.\textsuperscript{59}

\textbf{Binswanger's Subcortical Arteriosclerotic
Encephalopathy}

BSAE has received a great deal of attention in the
recent literature, primarily as a result of increased
identification of diffuse and patchy cerebral white
matter lesions by CT and MRI.\textsuperscript{49-58,60-62} Binswan-
gers original article\textsuperscript{25} described eight patients with
dementia who he had studied pathologically, and he
made the point that these patients were to be
distinguished from those with other causes of demen-
tia of the aged. Binswanger described subcortical
white matter lesions, normal cerebral cortex, and
dilated ventricles accompanied by advanced ather-
omatous disease of the cerebral arteries. He con-
cluded that \ldots the subcortical loss of fibers is
caused by the deficiency of the blood supply resulting from arteriosclerosis . . .”, a rather prescient observation in view of subsequent findings. The clinical picture is somewhat variable but usually includes the following key features: history of hypertension, slowly progressive dementia with temporary alterations in severity, evidence of systemic vascular disease, and prominent motor signs. Various pathologic lesions (including lacunar infarcts in the basal ganglia and thalamus, hydrocephalus ex vacuo, and cystic lesions in the periventricular white matter) have been reported in this syndrome, but the pathology that is most consistent and without which the diagnosis cannot be made is periventricular demyelinization (which may involve a large percentage of the white matter of the cerebral hemispheres, including the centrum semiovale, but may spare the subcortical arcuate fibers) and severe sclerosis and fibrohyaline thickening of small arteries and arterioles. The arteriolar lesions resemble those seen in chronic hypertension, although a history of hypertension is not invariably present. The perivascular spaces are usually dilated (état crbilité), and there is per arteriolar demyelinization in the white matter. The dementia is presumed to be caused by the white matter lesions because other parenchymal pathology may be minimal.

The dementia of BSAE has no special characteristics with which to distinguish it from AD, SDAT, or MID. It is thought to be a type of disconnection dementia in that the cortical neuronal centers, which are intact, are dis connected from each other by the white matter lesions. The white matter lesions are not true infarcts and are described by pathologists as incomplete infarctions, changes similar to those observed in the transitional zone surrounding a complete infarction. The biologic mechanism responsible for these lesions is not, in fact, known, but many observers have speculated that the lesions result from marginal perfusion, that blood flow in these areas must be locally reduced (acutely or chronically) to below levels required to maintain normal metabolic function, with resultant death of oligodendroglia and loss of myelin, but not so low as to result in tissue infarction. The theory is not new but it is certainly attractive because the periventricular white matter receives its blood supply from long, penetrating medullary arteries that enter at the pial surface and terminate at or near the wall of the ventricle. For the most part, these are end arterioles with little or no collateralization. One could reason that the perfusion pressure and CBF at the distal end of these arteries must always be substantially lower than at the cortical surface and that this disparity is worsened by the lipohyalinosis that affects the origin of these medullary arteries in patients with hypertension, arteriosclerosis, or old age. Some observers contend that a major contributing cause for the pathology is hemodynamic, related to episodes of hypotension, syncope, or cardiac failure.

The issue of cardiogenic dementia is still controversial, and there has been no convincing proof of the failed perfusion theory of periventricular demyelinization described above. Although many studies have demonstrated decreases in CBF and metabolism with normal aging and in patients with chronic, severe hypertension and brain lesions, the techniques for CBF measurement in humans, mainly using xenon-133 and multiple scintillation detectors, are greatly biased toward cortical or gray matter blood flow. It is difficult to obtain quantitative values for local CBF in the periventricular area with xenon-133 or by positron emission tomography (PET). PET studies that have measured oxygen extraction fraction (OEF) in elderly persons have not shown a significant increase in OEF with advancing age in either gray or white matter. This is puzzling because as CBF decreases due to vascular disease, one would expect OEF to increase to maintain the metabolic rate. If a chronic condition of marginal perfusion obtained in the periventricular region, one would anticipate increased OEF in the same area. Further studies with higher-resolution instruments are needed to elucidate this important point.

White Matter Lesions and Dementia

The problem is further complicated by the fact that periventricular and other white matter lesions are commonly seen on MRI and are usually described as areas of increased signal intensity on T2-weighted images. The significance of these lesions seen on MRI is not yet understood because of still-inadequate pathologic correlation and because it is now evident that, although there is a reasonably linear correlation with vascular disease, hypertension, aging, and dementia (including AD and SDAT), such lesions are also observed in clinically normal individuals and can be identified in 22% of persons under the age of 40 years.

These MRI abnormalities are seen consistently in patients with AD and SDAT, which, of course, raises the question of why the lesions should be present in patients whose pathology is not thought to be vascular. The study of Brun and Englund has focused attention on this important question because these authors demonstrated the presence of white matter lesions essentially identical to those found in BSAE in 60% of patients with clinically and pathologically diagnosed AD and SDAT. Brun and Englund called this phenomenon incomplete infarction confined to the white matter. The lesions were associated with hyaline fibrosis and stenosis of arterioles and smaller vessels, but there were no complete or cavitating infarctions and no hypertensive vascular changes. Brun and Englund attributed these white matter changes to "... hypoperfusion of the concerned white matter territories, since, in addition to the white matter hyaline vascular stenosis, these cases show signs of cardiovascular disease, usually with hypotension." Their theory as to the mechanism responsible for these lesions can
certainly be challenged but their observations cannot, and what emerges is the notion that our ideas as to the pathogenetic mechanisms responsible for the dementia of AD and SDAT require additional review. Previous pathologic studies on AD and SDAT have not seriously looked for these white matter changes by appropriate staining. If it follows from the study of Brun and Englund that this characteristic white matter pathology of incomplete infarction is present in 60% of patients with AD and SDAT, one must ask whether the dementia is the result of cholinergic neuronal degeneration, cortical disconnection due to the white matter lesions, or both. The next obvious and almost heretical question is whether we are overlooking or ignoring a vascular component to the dementia of AD and SDAT.

**Cerebral Amyloid Angiopathy**

This question becomes even more pertinent if we consider another vascular abnormality that is usually but not invariably associated with dementia. As a clinical and pathologic entity cerebral amyloid angiopathy (CAA) has been recognized since 1910, but it has only recently been recognized as the cause of primary cerebral hemorrhage (usually lobar, occasionally multiple) in elderly normotensive patients. Many hemorrhages are clinically benign, and the patients make excellent recoveries; multiple episodes of bleeding have been reported in the same patient. The patients are usually elderly and demented (some mildly and others severely); probably more than half the patients who present with intracerebral bleeding due to CAA are demented. CAA increases strikingly with aging. It is most severe in AD and SDAT, occurring in as many as 92% of affected brains, but it is also found in elderly people in the absence of Alzheimer’s changes.

The pathology of CAA is characterized by an acellular thickening of the walls of small and medium-sized arteries (including arterioles) by an amorphous, intensely eosinophilic material that gives a "smudged" appearance on light microscopy. A variety of stains including Congo red can be used to emphasize the amyloid in the vascular walls. Vessels affected by CAA are those that pass from the leptomeninges into the cerebral cortex. Although small infarcts have been observed in the brains of patients with severe CAA, large infarcts should never be attributed to it. CAA is often associated with white matter lesions almost identical to those observed in BSAE (namely, myelin loss, periventricular location, U fiber sparing), and it has been suggested that this represents incomplete infarction secondary to hypoperfusion.

Recent work has focused on the concept that a specific form of amyloid may be a key molecule in the pathogenesis of AD, SDAT, and Down’s (trisomy 21) syndrome. Senile plaques in AD contain an amyloid core, the composition of which appears to be identical to that of the CAA amyloid. Amyloid plaque cores are often found immediately adjacent to amyloid-laden capillaries. Thus, although normal aging and a number of other conditions may be associated with CAA, its close association with AD, SDAT, Down’s syndrome, and dementia pugilistica, the identification of amyloid in senile plaques and CAA, and the proximity of the plaque and vascular amyloid certainly seems to be more than coincidental.

Therefore, we have two well-known syndromes, both characterized by dementia, by extensive and characteristic white matter demyelination, and by specific but differing types of vascular disease. In addition, we observe that CAA has a high degree of association pathologically with AD and SDAT and that recent pathologic studies have indicated that incomplete infarctions are noted in 60% of patients with clinically and pathologically diagnosed AD and SDAT. A final link is that MRI reveals white matter lesions of an identical image type in patients with vascular disease, in patients with AD or SDAT or other types of dementia, and to a variable degree in patients over 60 years of age. Are the white matter lesions the result of hypoperfusion as has been suggested by some but not proven? Do the white matter lesions per se cause dementia? Does the high degree of correlation between these white matter lesions and AD and SDAT indicate that vascular disease and hypoperfusion may contribute to these forms of dementia? Finally, does the progressive increase in the incidence of these white matter lesions with advancing age suggest that cerebral hypoperfusion is a common denominator of aging and may, in fact, be the common denominator of all dementias of the elderly? These questions merit consideration.

Earlier, I raised the question of how hypertension causes brain damage. If hypertension is, indeed, an important risk factor for vascular dementia (although, as has been seen, it is not the only risk factor), further knowledge about the natural history of the effects of hypertension on cerebral arteries and arterioles, on the blood–brain barrier (BBB), on regional CBF and metabolism, and on the reaction of arterial endothelium to injury and further information about the effects of specific drugs on all of these would be of enormous value. It is unlikely that such studies will ever be done systematically in humans. In 1963 Okamoto and Aoki developed a strain of spontaneously hypertensive rats, and in 1974 Okamoto et al developed a substrain of these rats that is stroke-prone (SHRSP). SHRSP have been used extensively to study the mechanism of hypertensive damage in the brain. It has been demonstrated, for example, that one of the earliest changes leading to stroke is breach of the BBB and that the arterioles of SHRSP show hyalinosis, fibrinoid necrosis, small aneurysms adjacent to small infarcts, white matter rarefaction, and loss of myelin. Several studies have demonstrated the importance of diet in the etiology of stroke in...
SHRSP; they developed strokes only if fed a specific low-protein fish meal diet. Tobian et al observed that increased dietary K⁺ greatly reduced strokes in SHRSP even though there was little or no effect on blood pressure, the implication being that K⁺ has an effect on blood vessels independent of its effect on blood pressure. Tobian et al pointed out that the dietary intake of K⁺ is lowest among blacks in the southeastern US and in certain parts of Japan; areas of Japan where apples (high in K⁺) comprise an important dietary staple have a much lower incidence of stroke. The mechanisms by which dietary K⁺ or any dietary ingredient may influence the effect of hypertension on cerebral vessels and the cerebrum itself are not well understood. Some effects of specific diets were difficult to anticipate. For example, an epidemiologic study of coronary heart disease and stroke in Japanese men living in Japan and Hawaii showed that the incidence of thromboembolic stroke in Japan was three times higher than that in Hawaii, but there were no differences in blood pressure. An index of animal protein intake was inversely related to total stroke incidence, and Takeya et al concluded that the large difference in stroke incidence between the two cohorts may be due to the fact that the intake of animal protein and saturated fat, which is inversely associated with stroke incidence, is much greater in Hawaii than in Japan. It would not have been predicted that dietary animal protein and saturated fat exert an inhibitory effect on the incidence of stroke.

These examples illustrate the extraordinary number of variables that may influence the development of cerebral vascular lesions in hypertension and, by projection, in vascular dementia. Studies on SHRSP may provide vital information applicable to the generic problem of vascular dementia. It is not unreasonable to conclude from the various studies presented that, despite enormous progress in neuropathology, neuropsychology, neuropharmacology, and cerebral imaging, we are still a long way from understanding the dementias of the elderly, that the biologic differentiation among these dementias is far from clear, and that while terms like MID or lacunar dementia or even AD or SDAT may provide a sense of diagnostic comfort to the clinician, there is considerable evidence that the precise pathology in any given instance may not be predicted clinically and that the etiology may be multifactorial. Finally, the literature makes it very evident that vascular dementia may be a complex process and raises anew the question of the role of cerebral perfusion in AD and SDAT.

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