Cerebral Amyloid Angiopathy
A Critical Review

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Historical Perspective

The clinicopathologic entity of cerebral congophilic or amyloid angiopathy (CAA) has been recognized since the early part of this century, though it has attained the 'limelight' over the past decade primarily for two reasons: 1) the observation that CAA is the probable cause of nontraumatic primary cerebral hemorrhage producing stroke in a significant proportion of patients, in particular those who are normotensive and elderly; and 2) its close association with the other microscopic hallmarks of Alzheimer's disease (AD), or senile dementia of the Alzheimer type (SDAT). Nevertheless, as with many other conditions that have been recently 'rediscovered,' elegant accounts and illustrations of the pathology of CAA appeared between 1900 and 1970 1-11 though interpretations of its significance and etiology were largely speculative in the absence of the modern molecular tools that have provided insights into its pathogenesis and reasonable hypotheses about its relation to brain aging. Unfortunately, it remains a puzzling entity, and CAA-related cerebral bleeding is likely to continue as a major clinical problem because of one simple fact: the single identifiable risk factor for the development of CAA—aging—is not as amenable to direct therapeutic intervention as other risk factors (e.g., hypertension) for various forms of stroke. 12

The earlier terms used to describe CAA, "drüsige Entartung der Arterien und Kapillären," "angiopathie dyshorique," and congophilic angiopathy, nomenclature implying a specific etiology for the observed microangiopathy, now seem archaic 13 though they retain descriptive value. Dyshoric angiopathy refers to amyloid in capillary walls often adjacent to senile plaques, whereas congophilic angiopathy describes amyloid in arterioles and small arteries. CAA or cerebrovascular amyloidosis (CVA) are synonyms currently used to describe all aspects of the microvascular change. The former will be used throughout this article, the purpose of which is to review the clinicopathologic features of CAA, emphasizing theories of pathogenesis and its importance as a cause of brain hemorrhage.

Pathology of CAA and Nervous System Amyloid

CAA is recognized within the brain tissue by the presence of a characteristic acellular thickening of the walls of small and medium-sized arteries (including arterioles), and less often veins, by an amorphous, intensely eosinophilic material that gives a somewhat 'smudged' appearance by light microscopy. 14 Though vessels involved by CAA have a highly characteristic appearance even in routine hematoxylin and eosin stained sections, several stains can be used to highlight the presence of amyloid in the microvascular walls. These include periodic acid-Schiff, toluidine blue, crystal violet (which produces metachromasia), and thioflavin S or T (fluorescent under ultraviolet light). Amyloid is still most easily and consistently demonstrated by application of the Congo red stain to histologic sections and viewing of stained sections under polarized light, 14-16 which causes amyloid-laden vessels (or any other form of amyloid present in the tissue) to show characteristic yellow-green ("apple green") birefringence (Figure 1). This staining property simply indicates the presence of twisted β-pleated sheet fibrils (a structural configuration common to all forms of amyloid deposited in many organs in the course of numerous diverse diseases) in the vessel wall. 13 Discussion of the immunology, biochemistry, and histochermistry of amyloid is beyond the scope of this review and has been presented in a number of seminal papers and reviews, especially by Glenner.17-25 The presence of CAA may be related to other types of brain amyloid, but is not seen (except in rare instances 26,27) in combination with systemic and visceral amyloidosis.

In CAA, amyloid infiltrates the media and adventitia of the microvasculature—effacement of the affected vessel wall may be so severe that its identification as arterial or venous becomes impossible. Vessels affected by CAA often pass from the leptomeninges into the superficial cortex. Affected vascular channels (particularly those in the leptomeninges) frequently (Figure 1) show a distinctive "double barrel" lumen 28-29 similar in appearance to that seen in small pial arteries overlying borderzone infarcts. 30 Either the outer or inner media of the "double barrel" may show amyloid deposition. Segments of amyloid-laden vessels may also undergo fibrinoid degeneration or necrosis, 28,31 though segments showing fibrinoid change are rendered devoid of visible amyloid. Segmental dilation of vascular segments with microaneurysm formation may also occur.28,32 This observation has important implications for understanding the pathogenesis of CAA-relat-
ed brain hemorrhage (see below). In the past, fibrinoid degeneration of vessels and microaneurysm formation have been associated with hypertension as well as with each other, but this strict interpretation is questionable. Recent studies have described several microscopic vascular changes in cases of CAA, under the rubric CAA-associated vasculopathies (CAA-AV). These include "glomerular" formations of microvessels and obliterator fibrous intimal changes in CAA vessels, but the role of CAA in the genesis of such vasculopathies remains to be proven. The picture is further complicated by the fact that CAA and hypertension may coexist in a given patient.

Ultrastructure of CAA vessels show the expected random arrangement of nonbranching nonparallel fibrils with a mean diameter of approximately 9 nm, common to all forms of amyloid. The fibrils replace smooth muscle cells in the media and produce variable separation of the internal elastic membrane and the external basement membrane, sometimes extending into brain parenchyma. Though the studies have provided valuable information, many reports based on electron microscopy have used suboptimally preserved postmortem material, and the resultant static morphologic findings have sometimes been overinterpreted to suggest dynamic mechanisms of amyloid formation. It is difficult to accept the conclusion, for instance, that in CAA "the initiating degenerative change is thickening of [vascular] basement membrane with accumulation of debris," or that the proximity of amyloid to plasma cells or macrophages indicates that the latter cells accelerate amyloid deposition—they may simply represent a reaction to injury of the vessel wall or amyloid itself. No consistent observations of the endothelium in amyloid-laden vessels have been made. This is unfortunate since one longstanding the-
ory of the origin of CAA hypothesizes that the amyloid precursor originates in blood and would thus have to pass through the endothelium to be deposited in the media (see below). A more salient issue in understanding the pathogenesis of CAA is the origin of amyloid in the vessel walls. Hypotheses have been constructed on the basis of clinicopathologic information and inference. Attempts to discover a mechanism have used two main experimental approaches: 1) immunohistochemical assessment of CAA-laden vessel walls (and frequently other related forms of brain amyloid), and 2) biochemical analysis of isolated vessels severely involved by CAA.

The former approach has yielded intriguing though often divergent results that are difficult to interpret. In view of the importance of immune phenomena, and specifically immunoglobulins, in the etiology of systemic amyloid deposition, it seemed logical to seek similar molecules in CAA and senile plaque amyloid in the brain. Several groups looking primarily at senile plaque and pericapillary amyloid found immunoglobulin components by both light microscopy and ultrastructural immunocytochemical localization. Senile plaque and pericapillary amyloid were found to show histochemical similarity to amyloid found in cells of the amine precursor uptake and decarboxylation (APUD) series, implying that local brain factors were more important than circulating factors in its genesis, but the opposite findings and conclusion were reached by others. Prealbumin was localized to CAA in one study but could not be found by others who proposed that complement factors were prevalent in amyloid-laden senile plaques. Neurofilament proteins have been found in the adventitia of CAA vessels, and amyloid P component has been detected in vessel walls but not senile plaques. Despite the conflicting data, most investigators agree that the frequent finding of many serum proteins in vessel walls involved by CAA implies a relatively nonspecific leakiness of the microvasculature to some macromolecules.

A more direct approach to identifying the amyloid material in CAA has been that of isolating affected microvessels and subjecting them to direct biochemical study. This has been achieved by removing leptomeningeal vessels involved by CAA from autopsy specimens of both AD and Down’s syndrome brains; and more recently by isolating intraparenchymal arterioles from brain tissue with severe AD changes (Figure 2) including parenchymal CAA (WM Partridge, HV Vinters, J Yang, J Eisenberg, TB Choi, WW Tourtellotte, V Huebner, JE Shively; unpublished data). All studies show a remarkably uniform result: the cerebrovascular amyloid has a molecular weight of 4,200 daltons and a unique amino acid composition and sequence. Furthermore, the vascular amyloid material from Down’s syndrome and AD brains differs by only 1 amino acid of the 28 known residues in the sequence. The implications of this fact for understanding the biologic basis of AD and SDAT are discussed below. Antibodies to a synthetic peptide composed of the first 10 amino acids in the sequence have been shown to label parenchymal CAA vessels and the amyloid cores of senile plaques.

Pathogenetic considerations aside, CAA is associated with several entities (Table 1), though often it remains unclear which is cause and which effect or even if a cause–effect relation exists. The one exception to this caveat seems to be CAA-related brain hemorrhage, to be discussed below. AD, SDAT, and Down’s syndrome brains commonly show CAA. Microvascular and parenchymal amyloid can be seen in late postirradiation necrosis of brain, and in a demyelinating disorder that resembles multiple sclerosis. Leukoencephalopathy like that seen in Binswanger’s subcortical encephalopathy has been described. Many brains with severe CAA demonstrate cortical microinfarcts attributed to the angiopathy, and this may have a clinical counterpart in the occurrence of transient ischmic attacks (TIAs). CAA has been identified in cases of spongiform encephalopathy, in particular the slowly progressive Gerstmann–Sträussler–Scheinker variant, though in the latter disease the severity of CAA (when present) is usually much less than that of disseminated parenchymal amyloid plaque deposition. Lepomeningeal microvascular amyloid is noted as part of a rare hereditary degenerative condition with extensive meningeal, brain, and vitreous amyloid deposits. The latter disorder is of particular interest because it represents a situation in which there is widespread vascular amyloid in the viscera and pronounced involvement of meningeal microvessels with relatively minor brain parenchymal CAA. Severe and widespread CAA has been described in a 14-year-old boy who died after a long illness characterized by intellectual deterioration and incoordination, and patchy CAA is seen in other degenerative conditions, e.g., with cerebellar ataxia.

One intriguing, though rare, association is between CAA and isolated cerebral vasculitides. The vasculitis has been either similar to that seen with rheumatoid disorder (characterized by segmental fibrinoid necrosis, adventitial inflammation, and obliterator arteritis) or like granulomatous angiitis, with prominent giant cells. Despite their rarity, these examples are of interest because they suggest a pathogenetic mechanism of CAA in some cases, i.e., chronic inflammation. An important consideration, however, is that the inflammation (especially the giant cell response) may be in reaction to amyloid, which behaves as a foreign material in the perivascular region of brain. (The author has encountered instances of very severe CAA in which an occasional perivascular multinucleate giant cell was seen, apparently as part of a reaction to the amyloid, supporting the latter mechanism.) Of related interest was a patient with heavily amyloid-laden vessels in the depths of a cerebral plasmacytoma. Amyloid has been detected in the vessel walls of a small proportion of cerebral and even visceral vascular malformations.
Tumor-like amyloid formation (amyloidoma) in the brain and adjacent structures is seen. Detailed examination of these cases again suggests origin of the amyloid from the vasculature. The peripheral nervous system is often directly involved by amyloid, in either hereditary disorders or plasma cell dyscrasia, and may be secondarily involved by amyloid infiltration of the carpal tunnel. A myopathic syndrome with amyloid involvement of the muscle microvasculature, microscopically quite similar to CAA in individual vessels, has been described. Visceral ischemia has been shown to result in very rare instances from a similar sort of systemic microvascular amyloid deposition. Systemic amyloid may produce other types of "remote" effects on the central nervous system (CNS).

CAA occurs in aged individuals of several species of animals, but at present a practical animal model to allow careful study of its pathogenesis does not exist.

**CAA-Related Intracranial Hemorrhage**

Despite the recognition of CAA as a nosologic entity for most of this century, the fact that it can cause devastating brain hemorrhage has been appreciated for
Table 1. Clinicopathologic Entities Associated With Cerebral Amyloid Angiopathy

<table>
<thead>
<tr>
<th>Condition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalic hemorrhage</td>
<td>(see Table 2)</td>
</tr>
<tr>
<td>Age-related</td>
<td>97, 147-152</td>
</tr>
<tr>
<td>Familial (e.g., Icelandic, Dutch)</td>
<td>14, 29, 54,</td>
</tr>
<tr>
<td>Alzheimer’s disease and SDAT</td>
<td>144, 160,</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>55, 75</td>
</tr>
<tr>
<td>Dementia pugilistica</td>
<td>66</td>
</tr>
<tr>
<td>Vasculitis*</td>
<td>72-76</td>
</tr>
<tr>
<td>Cerebral microinfarcts</td>
<td>28, 29, 98</td>
</tr>
<tr>
<td>Leukoencephalopathy†</td>
<td>59, 60</td>
</tr>
<tr>
<td>Late postirradiation necrosis</td>
<td>58</td>
</tr>
<tr>
<td>Spongiform encephalopathy†</td>
<td>62, 63</td>
</tr>
<tr>
<td>Miscellaneous (non-Alzheimer) degenerative diseases</td>
<td>70, 71</td>
</tr>
<tr>
<td>Within vascular malformations</td>
<td>78, 79</td>
</tr>
</tbody>
</table>

SDAT, senile dementia of Alzheimer type.
*Includes giant cell arteritis and vasculitis with features similar to rheumatoid vasculitis.
†Includes a disorder resembling multiple sclerosis and a disease similar to Binswanger’s subcortical encephalopathy.
\(^{\text{a}}\) Including familial, Gerstmann-Straussler-Scheinker disease variants.

only a relatively brief time. Though the usual difficulties arise in assigning precedence to the description of this association, significant credit for the discovery must be shared by several authors who drew attention to the phenomenon in the early and mid-1970s. An earlier autopsy report showed CAA and a parenchymal hemorrhage in the same brain but interpretation of the case was complicated by the presence of a vascular malformation adjacent to the hematoma. Previous otherwise comprehensive clinicopathologic accounts of primary brain hemorrhage made no mention of CAA, and it is of interest that even more recent studies often fail to discuss CAA, even when considering lobar cerebral hemorrhages. Despite this, CAA must now be accepted as an important etiologic factor in primary nontraumatic brain hemorrhage, one likely to increase in relative significance as the proportion of elderly individuals in the population rises.

At present, though incidence figures vary and are likely to change, CAA accounts for 5-10% of primary nontraumatic brain hemorrhages, which in turn account for approximately 10% of all strokes.

Table 2 summarizes the salient clinical and pathological details reported in over 100 patients with (nonfamilial) CAA-related intracranial hemorrhage (ICH). Hereditary CAA-related hemorrhage will be considered separately. The listing is not intended to be exhaustive; e.g., studies in which the location of hematomas was not given have been arbitrarily excluded from tabulation. This summary suffers from the shortcomings of any material abstracted from heterogeneous sources, it is not exhaustive, and the author takes full responsibility for any misconceptions that are thus conveyed. However, certain demographic and pathological features of affected patients, which may not be apparent in smaller series, emerge. By definition, all patients recorded in the table had a tissue diagnosis of CAA made either at brain biopsy (for hematoma evacuation) or autopsy.

CAA-related ICH is a disease of the elderly, though surprisingly large numbers of cases are reported in patients in the sixth or seventh decade of life. There is no overall sex preponderance of cases, despite that observed in smaller series. Hemorrhage tends to occur at the same age in men and women. That some patients have a “mixed microangiopathy” (with both hypertensive and CAA microvascular changes) is not surprising when one considers that a significant proportion (over 30%) of individuals with CAA-related ICH have clinically documented hypertension. Indeed, high blood pressure may exacerbate the tendency to CAA-related hemorrhage or vice versa, and the occurrence of some types of microvascular pathology (microaneurysms, fibrinoid necrosis) common to hypertension and CAA has been discussed above. Occasionally morphologic sequelae of hypertension (e.g., left ventricular hypertrophy, cardiomegaly) are found at necropsy (and should be carefully sought) when the condition has not been diagnosed during life.

Over 40% of patients with CAA-related ICH have some degree of dementia during life, and at least a similar proportion show Alzheimer’s disease (AD) changes at autopsy. Table 2 clearly gives an erroneously low estimate of the latter, since AD may be difficult to diagnose on a small cortical biopsy which otherwise shows florid CAA as the cause of an ICH. As well, it is not uncommon to find AD changes in a patient at necropsy when relatively normal or borderline mental function was observed during life, prior to the ictus. The relationship between CAA and AD is further discussed below.

CAA-related ICH tends to present in a clinically consistent fashion. It occurs in elderly, frequently demented individuals as a cerebral lobar hemorrhage, and over time several lobes on both sides of the brain may be involved. In Table 2, a total of 171 hemorrhages were identified in 107 patients, though in some cases this simply indicates that the hemorrhage involved more than one arbitrarily defined brain region from the outset. With rare exceptions, hemorrhages involve the cortex and subcortical white matter. A single series has found that CAA-related ICH is predominantly ganglionic, as are hypertensive bleeds, but this is not the common experience. Deep central gray nuclei, corpus callosum, and cerebellum are primarily involved on rare occasions, and CAA is almost never seen as a cause of primary brainstem hematomas. Because of the location of CAA-related hemorrhage, blood may pass directly into the subarachnoid space (a very rare occurrence with hypertensive, intraparenchymal bleeding) as well as into the ventricles. Rare instances of purely subarachnoid and subdural hemorrhage in the
Table 2. Summary of Clinicopathologic Series Describing Nonfamilial CAA-Related Brain Hemorrhage

<table>
<thead>
<tr>
<th>Series (reference)</th>
<th>Sex</th>
<th>Mean age (range)</th>
<th>HBP</th>
<th>Locations of hemorrhages‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Jellinger, 1977 (98)</td>
<td>8</td>
<td>7</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>n = 15</td>
<td></td>
<td></td>
<td>(64-86)</td>
<td>(65-79)</td>
</tr>
<tr>
<td>Toracl, 1975 (99)</td>
<td>0</td>
<td>3</td>
<td>—</td>
<td>70</td>
</tr>
<tr>
<td>n = 3</td>
<td></td>
<td></td>
<td>(62-76)</td>
<td></td>
</tr>
<tr>
<td>Gilbert, 1983 (29)</td>
<td>8</td>
<td>3</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>n = 11</td>
<td></td>
<td></td>
<td>(61-79)</td>
<td>(67-79)</td>
</tr>
<tr>
<td>Okazaki, 1979 (28)</td>
<td>8</td>
<td>1</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td>n = 9</td>
<td></td>
<td></td>
<td>(60-84)</td>
<td></td>
</tr>
<tr>
<td>Cosgrove, 1985 (110)</td>
<td>7</td>
<td>10</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>n = 17</td>
<td></td>
<td></td>
<td>(62-87)</td>
<td>(62-88)</td>
</tr>
<tr>
<td>Kalyan-Raman, 1985 (111)</td>
<td>5</td>
<td>5</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>n = 10</td>
<td></td>
<td></td>
<td>(54-88)</td>
<td>(61-83)</td>
</tr>
<tr>
<td>Gilles, 1984 (112)</td>
<td>5</td>
<td>6</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>n = 11</td>
<td></td>
<td></td>
<td>(60-81)</td>
<td>(64-75)</td>
</tr>
<tr>
<td>Ishii, 1984 (113)</td>
<td>3</td>
<td>4</td>
<td>81</td>
<td>75</td>
</tr>
<tr>
<td>n = 7</td>
<td></td>
<td></td>
<td>(66-94)</td>
<td>(67-85)</td>
</tr>
<tr>
<td>Wagle, 1984 (114)</td>
<td>5</td>
<td>2</td>
<td>71</td>
<td>73.5</td>
</tr>
<tr>
<td>n = 7</td>
<td></td>
<td></td>
<td>(62-84)</td>
<td>(73-74)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
<td>11</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>(115-125) n = 17</td>
<td></td>
<td></td>
<td>(58-76)</td>
<td>(59-78)</td>
</tr>
<tr>
<td>TOTALS n = 107</td>
<td>55</td>
<td>52</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>% of total</td>
<td>51.4</td>
<td>48.6</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

All series are designated by first author, year, and bibliographic reference. CAA, cerebral amyloid angiopathy; M, male; F, female; L, left; R, right; F, frontal; T, temporal; P, parietal; O, occipital; DCGM, deep central gray matter; Cer, cerebellum; AD, Alzheimer’s disease; Dem, dementia; HBP, hypertension; Clin, clinical; PM, autopsy evidence; NA, information not available; pt., patient; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage. Mean age in years.

*Autopsy evidence of hypertension includes cardiomegaly, left ventricular hypertrophy, nephrosclerosis.

†The diagnosis of Alzheimer’s disease is either designated by the author(s) of the report, or assigned by reference to necropsy information provided — e.g., presence of senile plaques, neurofibrillary tangles, granulovacuolar degeneration.

‡Hemorrhages tabulated are all those documented in time and space in all individuals — e.g., right parieto-occipital would be included under right parietal (PR) and right occipital (OR) columns.

§Percent in this and 5 following columns are for % of total hemorrhages (n = 171), rather than patients.

context of CAA are seen, which is not surprising when one considers that meningeal vessels may be heavily involved by CAA and that subarachnoid blood (from any cause) may dissect into the subdural space. Meningeal and subpial hemosiderosis from repeated episodes of bleeding has been described with CAA. Commonly, miliary and petechial hemorrhages and "spindle" or "slit"-shaped hemorrhages are noted within the affected brain, as are scattered microinfarcts. Despite the well-established association between CAA and brain hemorrhage, the actual site of bleeding from an amyloid-infiltrated microvessel is rarely identified, though this is not surprising in view of the tissue destruction that occurs with any brain hemorrhage. Observation of heavily amyloid-laden microvessels suggests that they may be structurally brittle, unable to withstand trauma or blood pressure changes, and anecdotal support for this conclusion is found in reports of CAA-related hemorrhage that occurs after minor head injury and especially after relatively uncomplicated neurosurgical procedures (e.g., shunt placement) likely to be performed in members of such a patient population. This suggests that when CAA-related hemorrhage is strongly suspected on clinical and radiologic grounds, conservative (nonsurgical) management of the patient may be prudent since local rebleeding may become problematic. Many patients seem to make a surprisingly excellent recovery from numerous successive episodes of intracranial bleeding.
Though the clinical presentation and neuroradiology of CAA-related ICH is rather stereotyped, other causes of multiple hematomas or bleeds in unusual locations must be considered in the differential diagnosis. If surgical evacuation of the clot is undertaken, a portion must be submitted for pathological assessment. It is then incumbent on the pathologist to consider CAA as a possible diagnosis and to look for the appropriate microvascular alterations in the clot and surrounding brain material. When patients with brain hemorrhage of obscure etiology come to necropsy, a similar careful search for the cause must be undertaken. Only in this way will our understanding of pathogenetic mechanisms important in primary non-traumatic ICH increase.

A final comment is in order on the distribution of CAA-related hematomas and its relationship to the topography and incidence of CAA in general, i.e., in the absence of hemorrhage, as a function of aging. Lobar hematomas that result from CAA are most common in the frontal and parietal regions, less common in the temporal and occipital lobes (Table 2). Severity of CAA is age-related and is noted to some degree in over 50% of patients by the tenth decade of life. Detailed assessment of CAA distribution shows the microangiopathy, when severe, to be most commonly observed in the parieto-occipital regions, though studies based on much smaller numbers suggest that the frontal lobes are most affected. Age-related CAA is rare within white matter, deep central gray nuclei, or posterior fossa structures, and when seen in the latter location is likely to be most prominent in the leptomeninges. The high incidence of frontal hematomas with CAA is thus probably a function of factors (presently unknown) other than the simple presence of CAA.

Familial CAA and Related Syndromes

Hereditary syndromes of CAA, though rare, are of particular interest for the following reasons: 1) they show remarkable similarities to, and differences from, age-related CAA in terms of neuropathology and associated clinical features, e.g., dementia, ICH, and other forms of stroke; and 2) their relatively clear-cut patterns of inheritance in almost every kindred studied suggest that molecular techniques used to unravel other hereditary disorders may soon be applied to allow an understanding of some forms of CAA at the level of the genome.

Most varieties of hereditary generalized or systemic amyloidosis, as described above, characteristically spare the CNS but may affect the peripheral nervous system (PNS). The converse is also true—severe CAA is usually seen in the absence of systemic amyloid deposition. The one syndrome of amyloidosis in which the viscera and the CNS are linked has already been mentioned. It is an extremely rare condition, described in both the USA (in a family of German origin) and Japan, of widespread vascular amyloid in multiple organs, vitreous amyloid (also of vascular origin) and severe leptomeningeal amyloid deposition. In the brain, however, only meningeal vessels show amyloid in their walls, and parenchymal CAA is rarely seen. The size range of vessels affected is, however, similar to that noted in CAA, and full-thickness amyloid is seen in the walls of the meningeal microvasculature. The adventitia of some larger meningeal arteries (e.g., the middle cerebral artery) is sometimes affected, indirectly producing fibrointimal thickening and occlusion. The patients thus develop cerebral infarcts rather than hemorrhage. Since AD changes are lacking in the brains examined at necropsy, the observed dementia is likely of the multi-infarct type.

Of more direct interest in providing insights into CAA-associated ICH is the syndrome of familial ICH identified in Iceland and the Netherlands. In several well-defined kindreds, ICH caused by CAA has been seen in many generations at a young age (as early as the third decade in the Icelandic form, the fifth and sixth decades in the Dutch variant). Inheritance of the condition is by autosomal dominant transmission with high penetrance. The cause of the hemorrhages, which are often multiple, has been established as CAA by careful necropsy studies. CAA is seen in the absence of systemic amyloid and in the absence of AD.
changes. In the Dutch kindred, cerebral infarcts have also been common.\textsuperscript{147} Published micrographs indicate that the morphology of individual microvessels involved by CAA in these individuals is identical to that in age-related CAA. Details of the topography and morphology of the microangiopathy have recently been presented.\textsuperscript{149-152} In general the CAA seems to be very extensive in affected brains, especially in the Icelandic variant, involving structures (cerebellum, brainstem) usually spared in age-related CAA.\textsuperscript{15}

The Icelandic form of CAA has been subjected to detailed immunologic study, with the result that immune dysfunction has been implicated in its etiology,\textsuperscript{153} and the amyloid has been shown to be composed of a neuroendocrine protein similar to \(\gamma\)-trace,\textsuperscript{154} which is clearly different from the protein seen in age-related CAA.\textsuperscript{15} Abnormal cerebrospinal fluid (CSF) metabolism of \(\gamma\)-trace protein has been implicated as the basic defect in this disorder,\textsuperscript{155} and measurement of this peptide in the CSF has been suggested to have diagnostic value in family members at risk for brain hemorrhage.

Finally, several reports from the United Kingdom\textsuperscript{196-199} have documented a degenerative condition with autosomal dominant inheritance characterized by progressive dementia and spastic paralysis, with or without encephalic hemorrhage. Autopsy study has shown severe disseminated CAA involving the brain and spinal cord, with hemorrhages and infarcts and amyloid-containing plaques, especially within the cerebellum and hippocampus. One report\textsuperscript{198} has suggested this is a variant of AD. Similar AD "variants" have been reported from Germany.\textsuperscript{199}

CAA, Brain Aging, and Alzheimer's Disease

CAA increases in extent and severity in the human brain as a function of age\textsuperscript{16} and is only one of numerous morphologic, physiologic, and biochemical parameters to show age-related change.\textsuperscript{161,162} Other types (e.g., visceral) of amyloid accumulate in the human with aging.\textsuperscript{163,164} Though CAA appears to be most severe in AD and SDAT\textsuperscript{160-162} and occurs in as many as 92\% of affected brains,\textsuperscript{166-171} it clearly is found in elderly brains in the absence of Alzheimer changes, despite claims to the contrary.\textsuperscript{168} This should not be surprising in view of the fact that other hallmarks of AD (e.g., neurofibrillary tangles, senile plaques) are found in aged brains but are quantitatively accentuated in AD.\textsuperscript{164,172-174} An important caveat is that severe CAA, often producing brain hemorrhage, may occur without any of the microscopic features of AD or SDAT in a given brain.\textsuperscript{29}

Theories on the key pathogenetic events in the causation of AD currently abound,\textsuperscript{175-184} and one view is that AD should be considered a form of "multiple cerebral amyloidosis."\textsuperscript{185,186} Yet the precise significance of CAA in this conceptual framework remains to be determined. If one accepts the premise that the cognitive deficits in AD or SDAT result from histopathologic alterations primarily in the hippocampal formation,\textsuperscript{187-191} it is puzzling that this cortical structure is relatively spared by the microvascular lesion of CAA, even in otherwise severe cases.\textsuperscript{14,170,192} Though in brains from AD patients senile plaques with amyloid cores are often seen in close proximity to CAA-affected microvessels,\textsuperscript{193,194} plaques may occur in the absence of vascular amyloid and CAA may occur without senile plaques.\textsuperscript{195} Some detailed histomorphometric investigations have shown a significant correlation between the presence of CAA and senile plaques, despite the finding that the amount of vascular amyloid fails to correlate with the severity of observed dementia.\textsuperscript{196} Similar meticulous analysis of the topography of CAA in relation to senile plaques in the calcarine cortex shows 1) a different distribution within the cortex of the microvascular lesions in normal aging and AD, and 2) a significantly greater density of plaques overall in AD cases without CAA (MA Bell, MJ Ball; personal communication).

Despite these data, immunocytochemical\textsuperscript{196,197} and biochemical evidence suggests that plaque amyloid, CAA amyloid, and possibly even neurofibrillary tangle proteins (in both AD and Down's syndrome) are identical. Characterization of the chemical composition of meningeal and parenchymal microvessels infiltrated by amyloid was described above in "Pathology."\textsuperscript{194-195} The resultant proteins show striking similarity (in terms of molecular weight and amino acid composition and sequence) to peptides isolated from amyloid cores of senile plaques\textsuperscript{198,199} and from neurofibrillary tangles.\textsuperscript{200} If this biochemical identity of the major proteins that form the microscopic substrate of AD is confirmed by subsequent studies, it leads to interesting hypotheses regarding the pathogenesis of AD and CAA, some of which were proposed before this recent evidence was available. One idea\textsuperscript{202} is that circulating amyloid precursor passes through injured cerebral capillary, i.e., bloodbrain barrier (BBB) walls, resulting in deposition of amyloid in the vessel walls as CAA and in the cortical parenchyma at the core of senile plaques. The precursor may be toxic, either in its original form or after processing by microvascular endothelium, to some neurons in such a way as to produce intracytoplasmic neurofibrillary tangles, and this neurotoxicity may also contribute to the neurite degeneration noted in senile plaques. It is emphasized that this intriguing scenario must be tempered with the knowledge that CAA can occur without AD, though the nature of the amyloid material has not been investigated in all such cases. It also evades the question of whether BBB injury is a cause of CAA, or results from it. Others have claimed that the diverse forms of cerebral amyloid have their origins in the brain.\textsuperscript{200}

Future Research

Since so much of the speculation on CAA and its role in AD and SDAT centers on the BBB,\textsuperscript{202} it is unfortunate that there has been a recent intensification of research effort aimed at understanding this structure.\textsuperscript{203-206} Though the barrier is situated at the cerebral capillary endothelium,\textsuperscript{207} there is evidence that arterio-
lar endothelium also has significant barrier properties. Therefore the size range of microvessels affected by CAA is the same as that which subserves BBB functions. Immunoctochemical evidence for BBB impairment in SDAT includes the presence of serum proteins in the neuropil of affected brains and the previously described finding of such proteins in CAA microvessels. $B_B$ permeability does not, however, appear to change as a simple function of aging in rodents. Morphometric assessment of the human BBB as a function of age shows no morphological substrate for increased nonspecific BBB permeability in the aging brain, no age-related alteration of the endothelial mitochondrial population, and progressive thinning restricted to white matter capillaries secondary to loss of both pericytes and endothelial cytoplasm.

Given that CAA is especially severe in AD and SDAT, it is of interest that a structure known to exert major controls on BBB integrity and cerebral blood flow, i.e., the locus ceruleus, is consistently affected in SDAT. Pigmented locus ceruleus neurons undergo marked depletion in SDAT as compared to age-matched controls, and remaining cells show a 30% reduction in nucleolar volume, implying decreased ribosomal RNA synthesis in these cells. The locus ceruleus has also been shown to lose neurons in (small numbers of) patients with Down’s syndrome and dementia pugilistica, conditions in which CAA is seen. A direct quantitative comparison of CAA torophy and severity with pathology in the locus cereuleus in similarly affected brains might thus prove rewarding. Experimental work examining cerebral microvascular permeability after the locus ceruleus has been lesioned may also be relevant.

The ability to isolate cerebral microvessels from several species including man and to culture the derived cells will allow for direct study of the cerebral microvasculature and some BBB properties. Understanding how isolated microvascular endothelium and smooth muscle in vitro respond to growth factors, take up and metabolize substrates, interact with one another, and deal with sublethal injury may provide insights into CAA and other forms of cerebral microangiopathy.

The animal model of scrapie, in which both parenchymal and vascular amyloid are found, provides a system in which an infectious agent produces amyloid. Cerebrovascular amyloid may be quite severe in scrapie-affected sheep and of great interest is the finding of abnormal BBB permeability in scrapie-infected mice. A particularly interesting recent discovery is that the amyloid associated with AD (including CAA) has similar amino acid composition (but not sequence) to the scrapie-associated fibril. Finally, it will be of interest to ascertain if mechanisms thought to be important in the pathogenesis of systemic amyloidosis play a part in CAA.

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