Focal Cortical Atrophy Syndromes

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The topography of Alzheimer’s disease (AD) and its effects on language, perception, and praxis are briefly reviewed as background to the focal cortical atrophy syndromes, including primary progressive aphasia (PPA), posterior cortical atrophy (PCA), and corticobasal degeneration (CBD). Simplistically speaking, there are two main pathological and neuroimaging phenotypes associated with these syndromes. One is frontotemporal degeneration (FTD), a nonspecific spongiform degeneration, with gliosis and neuronal loss, sometimes with Pick cells and bodies, which is usually selective for frontal and anterior temporal cortex. The other is Alzheimer’s disease, in which amyloid plaques and neurofibrillary tangles initially develop in the hippocampal region, and spread to the lateral temporal and parietal neocortex and then to the frontal cortex. In the case of PPA, left perisylvian dysfunction is usually evident at presentation clinically and on neuroimaging. Nonfluent progressive aphasia tends to progress anteriorly and is usually associated with FTD. In fluent progressive aphasia, the pathology may progress anteriorly due to FTD or posteriorly, reflecting AD. In PCA, the visual association cortex is targeted bilaterally, often more so on the right, and the pathology is usually indicative of AD. CBD is an asymmetric akinetic–rigid syndrome associated with apraxia, in which swollen achromatic neurons are present in the frontoparietal cortex and substantia nigra on light microscopy, suggesting to some that it may fall within the spectrum of FTD and Pick’s disease. The application of new molecular biological techniques, however, suggest that CBD, FTD, and Pick’s Disease may be pathologically distinct. The clinico-pathological features of each syndrome are reviewed and compared to those typical for AD, and single photon emission computerized tomography scans representative for each are illustrated. © 1996 Academic Press, Inc.

1. INTRODUCTION

Just as sudden ablation of different regions in acute stroke can produce selective deficits in specific cognitive domains, such as language, memory,
or visuospatial abilities, it has become increasingly apparent over the past decade that focal cognitive deficits can also arise from slower degenerative processes which can selectively affect particular brain regions. The etiology of the focal cortical atrophy syndromes, also referred to as focal dementias or lobar atrophies, is unknown. Another term proposed for these syndromes is "asymmetrical cortical degeneration" since they are not always confined to a single lobe (Caselli, Jack, Peterson, Wahner, & Yanagihara, 1992; Caselli & Jack, 1992). Whatever the etiology, the resulting cognitive profile reflects the disease topography. The cognitive deficits may remain isolated for many years, but in later stages a more global dementia often supervenes. The clinical manifestations usually first appear in the presenium around age 60 and follow a 5- to 10-year course. A major impetus to the recognition and characterization of these syndromes was the influential paper describing six cases of progressive aphasia, published by Mesulam in 1982. Awareness of the syndromes has been further stimulated by advances in neuroimaging, particularly functional imaging with positron emission tomography (PET) or single photon emission computerized tomography (SPECT), which can reveal focal reductions in blood flow or metabolism even when structural imaging is uninformative.

The existence of these syndromes has made the differential diagnosis of Alzheimer's disease (AD) more challenging. AD is neurobehaviorally heterogeneous and atypical cases can present as focal cognitive deficits. Thus, AD enters the differential diagnosis for all these syndromes. On the one hand, patients who present with focal atrophy syndromes may turn out to have AD. On the other hand, patients who fit the clinical criteria for AD may have non-Alzheimer pathology. To gain some perspective on this confusing nosology, we will first review evidence for neuropsychological heterogeneity of AD and at the same time highlight the clinical and neuroimaging prototype in AD. Two other multifocal disorders, namely frontotemporal degeneration (FTD) (Gustafson, 1987; Neary, Snowden, Northern, & Goulding, 1988; Neary, 1990; Patterson & Hodges, 1992) and Lewy Body dementia (LBD) (McKeith, Perry, Fairbairn, Jabeen, & Perry, 1992), will also be briefly mentioned but are discussed more fully in other articles in this special issue. We will focus primarily on three focal cortical atrophy syndromes, namely primary progressive aphasia (PPA), posterior cortical atrophy (PCA), and corticobasal degeneration (CBD).

2. A BRIEF OVERVIEW OF ALZHEIMER'S DISEASE

2.1. Typical Behavioral Profile in AD

The neuropsychological deficits in typical cases of AD include memory loss, language impairment, and visuospatial dysfunction (Cummings, 1992). Noncognitive behavioral problems can also be present, including depression, delusions, and hallucinations (Cummings, 1992). In clinical–pathological
studies, the diagnostic accuracy of current criteria (McKhann, Drachman, & Fostein, 1984; Tierney, 1988; Boller, Lopez, & Moossy, 1989) varies from 64 to 87%, depending on the pathological criteria used. Atypical presentations are increasingly recognized and can make diagnosis difficult (Shuttleworth, 1984). A number of factors including age of onset, presence of family history, presence of extrapyramidal findings, degree of language impairment, behavioral aberrations, and comorbidity with cerebrovascular disease may all contribute to the resulting clinical profile and rate of progression (Friedland, Brun, & Budinger, 1985; Mayeux, Stern, & Spanton, 1985; Chang Chui, Lee Teng, Henderson, & Moy, 1985; Chang Chui, 1987; Drachman, O’Donnell, Lew, & Swearer, 1990). The typical course is gradual deterioration over 5–10 years but heterogeneity in the pattern and pace of deterioration has also been observed (Cummings, 1992; Haxby, Raffaele, Gillette, Schapiro, & Rapoport, 1992).

2.2 Topographical Pathology of AD

The cardinal histopathological findings in AD include loss of neurons and synaptic density, deposition of amyloid plaques, and neurofibrillary tangles (Braak & Braak, 1991). Molecular genetic abnormalities have been identified (Blass, 1993). Genes on chromosomes 14, 19, and 21 have been implicated in familial AD, and the presence of one or two alleles of apolipoprotein E4 has been shown to be an important risk factor for late-onset disease (Corder, Saunders, Strittmatter, Schmechel, Gaskell, Small, Roses, Haines, & Pericak-Vance, 1993). A cholinergic deficit is an invariant finding, with severe cell loss in the nucleus basalis of Meynert, but other neurotransmitters such as serotonin and noradrenaline and neuropeptides such as somatostatin are also decreased in many cases (Cummings, 1992; Blass, 1993). The etiology of the pathophysiological mechanisms underlying the disease remains obscure. For many decades, AD was considered the exemplar of diffuse brain disease, both neuropathologically and neuropsychologically, despite evidence to the contrary that it has regional accentuations. Since the 1980s, its regional selectivity has been increasingly recognized. In one autopsy series of Alzheimer patients in different stages of clinical severity, Brun and Englund (1981) measured cortical thickness and performed neuronal counts to elucidate the typical chronological evolution of the disease process. They suggested that the disease initially affects the amygdala and hippocampus, moves to the inferior temporal, superior, and inferior parietal regions and posterior cingulate, and later involves to the prefrontal region. A preference for association neocortex is evident with relative sparing of the somatosensory, motor, primary auditory, and visual cortices, and anterior cingulate region (Brun & Englund, 1981). A similar pattern was also described based on distribution of amyloid plaques and neurofibrillary tangles (Braak & Braak, 1991).
2.3. Imaging in AD

Structural imaging in AD generally shows global cortical atrophy, including hippocampal atrophy (Scheltens, 1993). Functional imaging studies with PET and SPECT have confirmed, in vivo, the predilection for association cortex and typically show biparietal–temporal perfusion deficits early on in the disease with involvement of the dorsolateral frontal region as the disease advances (Jagust, Reed, Seab, Kramer, & Budinger, 1989) (see Fig. 1). Asymmetries in perfusion or metabolism are not uncommon and frequently correspond to the neuropsychological profile (Foster, Chase, Mansi, Brooks, Fedio, Patronas, & DiChiro, 1984; Martin, Brouwers, Lalonde, Cox, Teleska, Fedio, Foster, & Chase, 1986) (see Fig. 5).

2.4. Lewy Body Disease (LBD)

Before discussing neuropsychological heterogeneity in AD, one relatively new entity needs to be mentioned because it can frequently overlap clinically
and pathologically with AD, namely diffuse cortical Lewy Body disease. Lewy bodies are proteinaceous structures with a central core and radiating filaments previously thought to be present primarily in the substantia nigra of patients with idiopathic Parkinson’s disease (PD) (Gibb, Luthert, Janota, & Lantos, 1989). With the advent of newer histopathological techniques, however, notably antiubiquitin methods, it has become clear that Lewy bodies are frequently present in the cortex as well. In a series of 93 dementia cases over age 70, 20% were attributed to diffuse cortical Lewy Body disease in the absence of Alzheimer changes (Perry, Irving, Blessed, Fairbairn, & Perry, 1990). In 100 pathologically verified cases of PD, 34% had a clinical history of dementia (Hughes, Daniel, Blankson, & Lees, 1993). The etiology in 29% was AD and, in 6%, vascular disease. Ten percent had cortical Lewy Body disease and 16% had plentiful Lewy bodies but did not meet criteria for the disease. Fifty-five percent had no obvious cause. In 36 autopsy-confirmed Alzheimer cases, on the other hand, 13 had diffuse Lewy Body disease, leading these authors to propose that Lewy Body disease was a variant of AD (Hansen, Salmon, Galasko, Masliah, Katzman, Detersea, Thal, Pay, Hofstetter, Klauber, Rice, Butters, & Alford, 1990). Others claim that LBD is a clinically distinct entity characterized by gait impairment and dementia with a fluctuating course, often with agitation, hallucinations, and delusions. EEG shows posterior slowing sometimes with frontal bursts (Morris, Cole, Banker, & Wright, 1984; McKeith et al., 1992; McKeith, Fairbairn, Bothwell, Moore, Ferrier, Thompson, & Perry, 1994). Pathologically, the Lewy bodies are most prevalent in the temporal region and, unlike Alzheimer’s disease, which affects the CA1 sector of the hippocampus, Lewy body disease primarily affects the CA2–3 sectors (Dickson, Ruan, Crystal, Mack, Davies, Kressy, & Yen, 1991). This is often associated with diffuse senile plaques which are Alz-50 negative, but there are a few neurofibrillary tangles. Neurochemically, LBD is associated with a severe cholinergic deficit.

In 1992, based on a comparison of 21 cases of pathologically confirmed Lewy Body disease and 37 Alzheimer’s disease cases, McKeith et al. proposed operational criteria for the diagnosis of LBD (McKeith et al., 1992). These include a fluctuating cognitive impairment, marked by episodic confusion with lucid intervals, persisting over a long period of time (weeks to months). At least one of the following were additionally required: visual and auditory hallucinations often accompanied by paranoid delusions, mild spontaneous extrapyramidal features with exaggerated adverse reactions to standard doses of neuroleptics, and repeated unexplained falls and/or transient clouding or loss of consciousness. The operational criteria assume exclusion of underlying systemic illness or structural brain lesions. The validity and reliability of these criteria have recently been verified (McKeith et al., 1994), but the nosological overlap with both Parkinson’s dementia and Alzheimer’s disease remains unresolved.
In one of the first detailed studies on neuropsychological heterogeneity in AD, Martin et al. (1986) identified three subgroups in 25 patients who met criteria for probable AD based on factor analysis of performance on standardized neuropsychological tests. In particular, they found nine subjects who showed significant impairment in language tasks with relative preservation in visuospatial function and eight who showed the opposite dissociation, while the remaining majority had comparable impairments in both domains. All patients had memory impairments as required by the NINCDS-ARDA criteria (McKhann et al., 1984). Subjects with greater language dysfunction showed more hypometabolism on PET in the left parietotemporal region and those with greater impairment of visuospatial function showed more right parietotemporal hypometabolism (Martin et al., 1986). Patients continued to show these patterns over a 1-year follow-up (Martin et al., 1986). The authors argued that these heterogeneous patterns reflect differences in the location of the initial pathology and of the progression of AD through the cortex. They suggested that while the disease is selective for certain regions and neurochemical systems, there is some variability in how this is expressed so that the target regions are not invariably damaged in everyone at a given point in time (Martin et al., 1986).

In an unselected series of 86 patients with probable AD and 92 elderly controls, Becker, Huff, Nebes, Holland, and Boller, (1988) similarly found focal cognitive syndromes in 17% of the AD subjects. Eleven subjects had impaired language with relatively intact visuoconstructional abilities and four had the opposite dissociation. Unlike some series, these authors found no correlation between demographic characteristics and patterns of deficit at initial evaluation, and no differences in rate of progression. However, in the language-impaired group, they suggested that there are two distinct neuropsychological abnormalities, one reflecting lexical–semantic impairment, unrelated to onset or progression of symptoms, and another based on syntactic impairments associated with earlier onset and more rapid progression (Becker et al., 1988). While the patients reported in this series met the clinical criteria for probable AD and therefore had memory impairments, it does not seem surprising that some cases of AD can present with isolated focal neuropsychological deficits. There has even been an autopsy-confirmed report of progressive hemiparesis showing typical Alzheimer’s pathology in the sensory motor cortex; this case, however, would not meet the clinical criteria for AD (Jagust, Davies, Janice, Borcich, & Reed, 1990).

In summary, a minority of AD subjects can masquerade as focal cortical atrophy syndromes. In the following sections, we will further elaborate on three such “focal” AD presentations, which include prominent breakdown in language, visuoperceptual functions, or praxis, to compare and contrast
them to focal progressive syndromes that can be associated with non-Alzheimer pathology.

3. PROGRESSIVE APHASIA

3.1. Language Breakdown in Alzheimer’s Disease

The frequency and severity of language disturbance in AD varies with both individual factors and stage of progression of the underlying disease (Appell, Kertesz, & Fisman, 1982). Thus Kertesz, Appell, and Fisman (1986) reported prominent language dysfunction in 10% of subjects seen routinely in an AD clinic. In a study of 150 AD subjects, 12% of early AD patients had aphasia and the frequency increased with severity, as judged by a structured interview (Faber-Langendoen, Morris, Knesevich, Labarge, Miller, & Berg, 1988). Thus, language dissolution was evident in 30% of mild, 82% of moderate, and 100% of severe AD subjects. The aphasic subjects had earlier onset and progressed more quickly. In an autopsy-confirmed series of 28 AD subjects, 85% had aphasia at the initial presentation. In 10% language disturbance was particularly prominent, and in 10% visuospatial deficits predominated (Price, Gurvit, Weintraub, Geula, Leimkuhler, & Mesulam, 1993). Thus, both autopsy and clinical series seem to suggest that aphasia is common in AD, particularly in the more advanced stages, and that it may be a predominant finding in 10%.

The language disturbance in AD has been characterized as a fluent aphasia which begins with anomia and progresses as auditory comprehension deteriorates into a performance pattern reminiscent of transcortical sensory aphasia or Wernicke’s aphasia, as classically described in patients with focal brain damage, depending on the degree of retention of repetition skills (Appell et al., 1982; Bayles, 1982; Cummings, Benson, Hill, & Read, 1985; Hier, Hagenlocker, & Shindler, 1985; Kertesz et al., 1986). Because of the concomitant cognitive deficits, some researchers avoid the term “aphasia” altogether in AD reserving it for focal lesions of the perisylvian language cortex. Nonfluent aphasia is distinctly unusual until an advanced stage is reached, at which time subjects become essentially mute. Morphosyntactic elements appear to be relatively preserved until late, while semantic breakdown progresses steadily through the course of the disease. The nature of the semantic breakdown in AD has been explored in several single-case or small group studies, to which the reader is referred (Schwartz, Oscar, Marin, & Saffran, 1979; Shuttleworth & Huber, 1988; Schwartz & Chawluk, 1990; Bayles, Tomoeda, & Trosset, 1990; Chertkow & Bub, 1990; Funnell & Hodges, 1991).

The demographic and prognostic implications of language breakdown in AD has also been subject to numerous studies with conflicting results. Several investigators suggest that aphasia is more prominent in younger-onset disease (Knesevich, Toro, Morris, & Labarge, 1984; Chang Chui et al., 1985;
Farber-Langendoen et al., 1988; Seltzer & Sherwin, 1993), but others do not agree (Kaszniak, Fox, Gandell, Garron, Huckman, & Ramsey, 1978; Berg, Danziger, Storandt, Cohen, Gado, Hughes, Knesevich, & Botwinick, 1984; Selnes, Carson, Rovner, & Gordon, 1988; Boller, Becker, Holland, Forbes, Hood, & McGonigle-Gibson, 1991; Bayles, 1991; Lawlor, Ryan, Schmeidler, Mohs, & Davis, 1994). One study suggests that, when severity is taken into account, aphasia is more prominent in later, than early-onset disease (Bayles, 1991). In several studies aphasia is a significant prognostic factor for morbidity and mortality, predicting poorer survival and faster deterioration to the level of dependency (Kaszniak et al. 1978; Knesevich et al., 1984; Heyman, Wilkinson, Hurwitz, Helms, Haynes, Utley, & Gwyther, 1987; Hier, Hagenlocker, & Shindler, 1985; Hier, Warach, Gorelich, & Thomas, 1989). Some of these effects disappear if allowance is made for severity of dementia but, in a recent study of 145 AD subjects followed from 2 to 9 years, severe language disturbance predicted faster deterioration and earlier death, even when severity was taken into account (Bracco, Gallato, Grigoletto, Lippi, Lepore, Bino, Lazzaro, Carella, Piccolo, Pozzili, Giotto, & Amaducci, 1994).

Similarly, as will be clear from the contribution by Neary et al. in this special issue, language and communication skills are frequently affected in the dementia syndromes arising from frontal–temporal degeneration, including Pick’s disease (Gustafson, 1987; Neary et al., 1988; Neary, 1990; Snowden & Neary, 1993). In fact, as pointed out in recent reviews, the index cases of both Alzheimer and Pick had prominent aphasic disturbance (Poock & Luzzatti, 1988; Kertesz, Hudson, MacKenzie, & Munoz, 1994). Interest in language breakdown in both types of dementia seems to have waned in subsequent decades, however. The concept of AD as the quintessential diffuse cognitive disorder with widespread atrophy came to prevail and, for Pick’s disease, behavioral and personality change, including a disturbance of comportment, became widely accepted criteria for diagnosis.

In summary, language breakdown is a frequent early feature of AD and universal in the later stages. When severe, it reflects a more aggressive form of the disease. Speech output is usually fluent initially, with word finding difficulty and circumlocutory and empty speech, often with low information content. Language difficulty must be accompanied by a progressive memory disorder to meet current diagnostic criteria for AD, but it may occasionally dominate the clinical picture before episodic memory difficulty emerges, in which case the subject may be classified as having primary progressive aphasia (PPA). This term was introduced in 1982 by Mesulam and co-workers who described six cases of progressive language deficit in the absence of other dementing features and proposed the syndrome of PPA as a distinct clinical–pathological entity (Mesulam, 1982). Since this pivotal paper, there have been numerous subsequent case reports and reviews of this syndrome. A debate has ensued concerning the typical and associated features, its patho-
TABLE 1

Comparisons of Primary Progressive Aphasia and Definite Alzheimer’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Primary progressive aphasia ($N = 63$)</th>
<th>Definite Alzheimer’s disease ($N = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset ≥65</td>
<td>27%</td>
<td>70%</td>
</tr>
<tr>
<td>Onset &lt;65</td>
<td>73%</td>
<td>30%</td>
</tr>
<tr>
<td>Male</td>
<td>64%</td>
<td>35%</td>
</tr>
<tr>
<td>Female</td>
<td>36%</td>
<td>65%</td>
</tr>
<tr>
<td>Fluent</td>
<td>48%</td>
<td>100%</td>
</tr>
<tr>
<td>Nonfluent</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>AD pathology</td>
<td>31%</td>
<td>100%</td>
</tr>
<tr>
<td>Non-AD pathology</td>
<td>69%</td>
<td>0%</td>
</tr>
</tbody>
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Note. Adapted from Mesulam and Weintraub (1992).

3.2. Primary Progressive Aphasia

3.2a. Clinical features. In a brief historical review, Poeck and Luzzatti (1988) noted that of 19 historical cases of cortical degeneration with prominent language dysfunction, only 6 (3 males and 3 females) had language dysfunction as the only feature (see also Luzzatti & Poeck (1991)). The age of onset was presenile, except for Pick’s original case (age 69) and the mean duration of focal language dysfunction was 2.8 years. All of these cases had a fluent aphasia related to circumscribed atrophy in the temporal region at autopsy, in keeping with Pick’s disease. In the first modern case report of progressive aphasia, albeit in a patient who also had a mild change in comportment, Pick’s disease was confirmed at autopsy (Wechsler, 1977; Wechsler, Verity, Rosenschein, Fried, & Scheibel, 1982).

In five of six of Mesulam’s original cases, the course began with word-finding difficulty and advanced to what he called “logopenic” fluent speech in four of five patients (Mesulam & Weintraub, 1992). Logopenia was the term Mesulam used to characterize a speech output marked by hesitant word-finding difficulty causing reduced speech rate, in the presence of normal phrase length and grammar. Comprehension impairment developed in three of five cases. In subsequent editorials and a report of four additional cases followed longitudinally, Mesulam and Weintraub demonstrated the relative preservation of other cognitive functions in PPA and highlighted the differences from AD (see Table 1) (Mesulam, 1987; Weintraub, Rubin, & Mesulam, 1990; Mesulam & Weintraub, 1992). They pointed out that logopenic speech is unusual in AD and that phonemic paraphasias are more common in PPA (62%) than in AD (8%), in which semantic substitutions predominate (Mesulam & Weintraub, 1992). Loss of memory, poor insight, and deteriora-
tion in activities of daily living (ADL) also distinguish AD from PPA subjects. These authors proposed operational criteria for the provisional diagnosis of PPA: progressive worsening of language, in the absence of other cognitive deficits, for 2 years or longer, with relatively intact independence in ADL (Mesulam, 1987; Mesulam & Weintraub, 1992). They further emphasized the relative preservation of episodic memory, spatial skills, insight, and comportment early in the course, but did not preclude progression at a later stage to a more generalized dementing illness.

In reviewing the literature on PPA between 1982 and 1992, Mesulam and Weintraub (1992) found 63 cases who met these operational criteria and tabulated their characteristics. Age of onset was in the presenium in 46 of 63 cases (mean age 60 ± 0.8, range 40–75). Males were more commonly affected than females (40 males:23 females). The mean duration of the “pure” aphasic syndrome was 5.2 ± 2.8 years and, in six patients, this phase lasted 10 years. Focal neurological signs (for example right hyperreflexia) were present in 17%. In terms of the language profile, anomia was the commonest presenting disturbance; 44% had a nonfluent aphasia and the remainder had fluent output, but often with logopenic speech, as described above. On neuroimaging utilizing CT or MRI and/or PET or SPECT, a left perisylvian abnormality was noted in 45 of the 63 subjects (65%) (Mesulam & Weintraub, 1992). The pathological features are described below.

If one includes all neurodegenerative cases presenting with either aphasia or predominant aphasia since the report of Wechsler in 1977, altogether 161 cases have been reported, 95 of which would meet the Mesulam–Weintraub criteria. In the additional 32 cases who met these criteria published since

1 The only exception was a 17-year-old girl with progressive word deafness which progressed for 4 years and stabilized after 10 years of follow-up. Recently, the author had the opportunity to see this patient, who was able to obtain a B.Sc. degree and currently works as a biochemist in a government lab. Her deficit, which began as word deafness, has slowly progressed to complete deafness without significant deterioration of language. An unusual primary auditory-vestibular degenerative process is postulated. Thus, both her age and subsequent course suggest that she does not conform to the prototype of PPA.

2 The additional cases not included in the Mesulam and Weintraub paper listed in chronological order are: (Cole, Wright, & Banker, 1979; Morris, Cole, Banker, & Wright, 1984; Gordon & Selnes, 1984; Holland, McBurney, Moosy, & Reimnuth, 1985; Shuttleworth, Yates, & Paltan-Ortiz, 1985; Munoz-Garcia & Ludwin, 1986; Salmon, Sadzot, Marquet, Dive, & Franck, 1989; Mandell, Alexander, & Carpenter, 1989; Sapin, Anderson, & Pulaski, 1989; Lippa, Smith, & Fontneau, 1990; Craenhals, Raison-Van Ruymbeke, Rectem, Seron, & Laterre, 1990; Hodges, Patterson, Oxbury, & Funnell, 1992; Caselli, Jack, Peterson, Wahrner, & Yanagihara, 1992; Beland & Ska, 1992; Hodges, Patterson, Oxbury, & Funnell, 1992; Caselli, Windebank, Petersen, Komori, Parisi, Okazaki, Kokmen, Iverson, Di Napoli, Graff-Radford, & Stein, 1993; Chiachio, Grossi, Stanzione, & Trojan, 1993; Cohen, Benoit, Van Eechhou, Ducarne, & Brunet, 1993; Snowden & Neary, 1993; Kirk & Ang, 1993; Karbe, Kertesz, & Polk, 1993; Hodges, Patterson, & Tyler, 1994; Kertesz, Hudson, MacKenzie, & Munoz, 1994; Victoroff, Ross, Benson, Verity, & Vinters, 1994). Included in their tabulation are the following reports in chronological order: (Mesulam, 1982; Heath, Kennedy, & Kapur, 1983; Assal, Favre, & Regli, 1984; Pogacar & Williams, 1984; Kirshner, Webb, Kelly, & Wells, 1984;
1992, the average age remains 59 and there are slightly more females than males (18 females: 14 males). The mean duration of the aphasic syndrome remains unchanged at 5 years, and nonfluent aphasia predominates (19 nonfluent and 13 fluent cases). Thus, apart from a more equal gender distribution these additional cases conform to the initial literature sample reviewed by Mesulam and Weintraub (1992).

To assess the generalizability of these literature cases, the current author reviewed 27 cases (17 male, 10 female) of progressive aphasia consecutively referred to her behavioural neurology clinic over the past few years. The average age of the onset was 59.8 years (range 49–76) and average duration of illness when first seen was 5 years (range 1–10). Nineteen had nonfluent and 8 had fluent aphasia, 3 of whom were anomic. Sixteen patients met the Mesulam–Weintraub criteria of 2 years of isolated aphasia. The average age and duration were similar to the overall group and 11/16 had nonfluent speech. Only 6 of the total group had focal atrophy on CT or MRI, but HmPAO SPECT was abnormal in all. Bilateral hypoperfusion was noted in 11 (6 frontotemporal, 5 parietal–temporal) and 14 showed perisylvian hypoperfusion on the left.

3.2b. Associated symptoms and the question of dementia. Although most case studies of PPA have concentrated on the primary language characteristics and performance on standardized neuropsychological tests, a few studies have looked more closely at deficits that could be expected to be associated with aphasia based on the study of focal lesions, including verbal and limb


1 Recent cases since 1992 not previously tabulated include, in chronological order: (Sinforniana, Mauri, Sances, & Martelli, 1992; Caselli, Jack, Peterson, Wahner, & Yanagihara, 1992; Beland & Ska, 1992; Hodges, Patterson, Oxbury, & Funnell, 1992; Caselli, Windebank, Petersen, Komori, Parisi, Okazaki, Kokmen, Iverson, Di Napoli, Graff-Radford, & Stein, 1993; Chiaccchio, Grossi, Stanzione, & Trojano, 1993; Cohne, Benoit, Van Eeckhout, Ducarne, & Brunet, 1993; Snowden & Neary, 1993; Kirk & Ang, 1993; Karbe, Kertesz, & Polk, 1993; Hodges, Patterson, & Tyler, 1994; Kertesz, Hudson, MacKenzie, & Munoz, 1994; Victoroff, Ross, Benson, Verity, & Vinters, 1994).
apraxia (Tyrrell, Kartsounis, Frackowiak, Findley, & Rossor, 1991; Be- 
In two subjects, gesture was initially used to compensate for progressive 
difficulty in communication, but praxis was gradually lost as the speech 
deficit progressed over 2 to 3 years (Northern, Hopcutt, & Griffiths, 1990; 
Beland & Ska, 1992). Standardized praxis testing has been used in only a 
few patients with PPA (Kempler, Metter, Riege, Jackson, Benson, & Hanson, 
1990; Tyrrell et al., 1991; Karbe, Kertesz, & Polk, 1993); one subject showed 
only mild impairment initially and one was moderately impaired; on re-
testing, the mildly impaired patient had become severely apraxic and the one 
with moderate impairment progressed only slightly (Kempler et al., 1990). 
Another patient developed swallowing difficulty attributed to oral apraxia 3 
years after aphasia onset (Fuh, Liao, Wang, & Lin, 1994). Generally speak-
ing, praxis has not been well studied in this group of patients, but more 
problems in production of skilled movements than in the conceptual system 
for actions might be anticipated from the topography of the disease (see 
Sections 3.2d and 5.1).

Other deficits associated with PPA have included acalculia (Kempler et 
al., 1990) and loss of analytic musical skills (Polk & Kertesz, 1993). An 
intriguing observation noted by Mesulam and Weintraub in their sample of 
10 cases, was that four of nine cases, in whom the information was available, 
had a history of early learning disability as compared to 0/10 patients with 
AD and 0/11 age-matched controls (Weintraub et al., 1990). The first-degree 
relatives of these subjects revealed a 24% frequency of learning disability 
compared to 3% in AD and 2% in control subjects, raising the possibility of 
a genetic or acquired vulnerability of the left hemisphere language network in 
these subjects. This is the only report of such a relationship and certainly 
warrants confirmation.

Most case reports of PPA have used conventional neuropsychological tests 
and aphasia batteries to study the affected individuals. More recently, how-
ever, an information-processing approach has been used to explore the nature 
of the language dissolution in PPA in more detail (Schwartz & Chawluk, 
1990; Hodges, Patterson, Oxbury, & Funnell, 1992; Patterson & Hodges, 
1992; Hodges, Patterson, & Tyler, 1994; Graham, Hodges, & Patterson, 
1994; Breedin, Saffran, & Coslett, 1994). Surface dyslexia has been reported, 
in which words with regular spelling can be correctly pronounced even 
though the word is not understood, and irregular words are phonetically de-
coded (Patterson & Hodges, 1992; Chiacchio, Grossi, Stanzione, & Trojano, 
1993; Parkin, 1993; Graham, Hodges, & Patterson, 1994). Other studies have 
focused on the semantic breakdown in some subjects with PPA in whom 
word-meaning is lost relatively early in the course of the disease (Snowden, 
Neary, Mann, Goulding, & Testa, 1992; Hodges, Patterson, Oxbury, & Fun-
nell, 1992; Snowden & Neary, 1993; Neary, Snowden, & Mann, 1993b; 
Hodges, Patterson, & Tyler, 1994; Breedin, Saffran, & Coslett, 1994). In
these subjects, a lexical semantic deficit is found to be associated with impaired understanding of the meaning of objects and depicted events. In one case report, meaning for concrete items was lost with relative sparing of abstract nouns and verbs (Breedin et al., 1994). Since the loss of semantic memory can extend beyond word comprehension to object recognition, the term ‘semantic dementia’ has been proposed because the deficit embraces visual object processing as well as language (Schwartz & Chawluk, 1990; Hodges, Patterson, Oxbury, & Funnell, 1992; Hodges, Patterson, & Tyler, 1994). This syndrome afflicts PPA patients who present with fluent speech and comprehension disturbance and is associated with bilateral anterior temporal atrophy (Snowden, Neary, Mann, Goulding, & Testa, 1992; Snowden & Neary, 1993; Neary, Snowden, & Mann, 1993b; Breedin et al., 1994). Appropriate testing is required to elicit these deficits, which may not be apparent on conventional aphasia tests.

Although, strictly speaking, the loss of visual object knowledge implies a cognitive deficit not confined to language, the term dementia by current criteria implies impairment in episodic memory, which is usually not observed, at least not in the early stages of PPA. Thus, the term aphasia rather than dementia still seems appropriate for most cases of PPA, at least in the initial stages. Nevertheless, the controversy continues as to whether PPA is a clinically distinct entity as proposed by Mesulam and Weintraub (see Table 1) or is only the prodromal stage of a more generalized dementing illness (Mesulam, 1982; Weintraub et al., 1990; Mesulam & Weintraub, 1992; Tranel, 1992). Some authors, based on autopsy findings, have argued that PPA represents an atypical form of AD, claiming that comprehensive, standardized neuropsychological testing reveals more widespread deficits than language dysfunction, when these are adequately tested (Foster & Chase, 1983; Gordon & Selnes, 1984; Poeck & Luzzatti, 1988; Green, Morris, Sandson, McKeel, & Miller, 1990; Feher, Doody, Whitehead, & Pirozzolo, 1991). The difficulty, however, continues to be that significant aphasia, especially impaired comprehension, often precludes standardized, in-depth neuropsychological testing. Direct patient observation and history from caretakers concerning competence in ADL, social interactions and comportment, supplemented when possible by nonverbal neuropsychological tests, are necessary to infer retention of nonverbal intellectual abilities. In the cases so far reported, approximately half of the subjects developed dementia at some point in their course. Perhaps all PPA patients if followed long enough will become demented. Neary, Snowden, and the Manchester group argue that the majority of cases pathologically belong to the frontotemporal degenerations (Snowden, Neary, Mann, Goulding, & Testa, 1992; Snowden & Neary, 1993; Neary, Snowden, & Mann, 1993b). As we will discuss now, there is neuroimaging and pathological support for all these apparently contradictory claims.

3.2c. Brain correlates in PPA: Neuroimaging. Asymmetric left perisylvian atrophy was noted in five of Mesulam’s original cases of PPA (Mesu-
HmPAO SPECT shows anterior temporal-inferior frontal hypoperfusion more marked on the left in a patient with nonfluent Primary Progressive Aphasia.

Subsequent case reports have confirmed this finding, which is best depicted on MRI particularly in the coronal or sagittal plane, as amply demonstrated by the study by Caselli et al. (1992) and illustrated in Figs. 2 and 3. Left anterior temporal and inferior frontal atrophy as well as bilateral temporal and frontal atrophy have been reported (Scheltens, Hazenberg, Lindeboom, Valk, & Wolters, 1990; Neary et al., 1993b; Snowden & Neary, 1993; Scheltens, Ravid, & Kamphorst, 1994). Even when atrophy is not seen clearly on the structural images, functional focal left hemisphere deficits are routinely seen on PET or SPECT imaging. The common finding is left temporal hypoperfusion with variable extension (Fig. 2) to other hemispheric regions, including frontal and parietal areas (Caselli, Jack, Peterson, Wahner, & Yanagihara, 1993; Chawluk, Mesulam, Hurtig, Kushner, Weintraub, Saykin, Rubin, Alavi, & Reivich, 1986; Salmon, Sadzot, Maquet, Dive, & Franck, 1989; Kushner, 1989; Delecluse, Andersen, Waldemar, Thomsen, Kjaer, Lassen, & Postiglione, 1990; Kempler et al., 1990; Graff-Radford, Damasio, Hyman, Hart, Tranel, Damasio, Van Hoesen, & Rezai, 1990; Tyrrell, Warrington, Frackowiak, & Rossor, 1990; Parkin, 1993). Bitemporal and bifrontal perfusion deficits have also been reported (Goulding, Northern, Snowden, MacDermott, & Neary, 1989; Sapin, Anderson, & Pulaski, 1989; McDaniel, Wagner, & Greenspan, 1991; Lee & Kramer, 1992;
Fig. 3. MR scan of patient in Fig. 2. (a) shows left temporal-inferior-frontal atrophy on $T_1$ weighted sagittal images. (B) shows left temporal-frontal atrophy on $T_2$ weighted coronal view (with the left brain on the right side of the image).
FOCAL CORTICAL ATROPHY SYNDROMES

Snowden & Neary, 1993; Neary et al., 1993a). A typical case of PPA is shown in Figs. 2 and 3, in contrast with the asymmetric parietotemporal perfusion deficits seen in a patient who has prominent aphasic disturbances, but also meets clinical criteria for AD (Fig. 5a).

3.2d. Brain correlates in PPA: Pathology. The pathological substrate of cases of PPA has varied considerably. Rapidly progressive cases have been associated with Creutzfeldt–Jakob disease (Shuttleworth, Yates, & Paltan-Ortiz, 1985; Mandell, Alexander, & Carpenter, 1989; Kirk & Ang, 1993; Victoroff, Ross, Benson, Verity, & Vinters, 1994), progressive multifocal leukoencephalopathy (Llewelyn, Valentine, Bradley, King, & Gross, 1990), and motor neuron disease (Cambier, Masson, Dairou, & Henin, 1981; Casselli, Windebank, Petersen, Komori, Parisi, Okazaki, Kokmen, Iverson, Di Napoli, Graff-Radford, & Stein, 1993). One case revealed swollen achromatic neurons in the neocortex and neuronal loss in the substantia nigra, typical of CBD (Lippa, Cohen, Smith, & Drachman, 1991). Pathological changes consistent with Pick’s disease have also been reported (Wechsler, Verity, Rosenschein, Fried, & Scheibel, 1982; Holland, McBurney, Moossy, & Reinmuth, 1985; Graff-Radford et al., 1990) and some patients have shown AD at autopsy (Pogacar & Williams, 1984; Morris et al., 1984; Benson & Zaias, 1991). In one family with PPA, profuse neuritic plaques, Lewy bodies, and neuronal loss in the substantia nigra as well as spongiform degeneration in superficial cortical layers was seen in the context of asymmetrical focal cerebral atrophy, leading the authors to postulate a Pick/Alzheimer spectrum of cortical neuronal degeneration (Morris et al., 1984). PPA has also been seen in association with neuronal intranuclear hyaline inclusion bodies (Munoz-Garcia & Ludwin, 1986). In the only neurochemical study to date, the patient pathologically had Pick’s disease; a cholinergic deficit was not evident but somatostatin levels were exceptionally low (Mehler, Horoupian, Davies, & Dickson, 1987; Mehler & Korey, 1988).

The most common pathological finding in PPA was first reported by Kirshner, who studied two patients dying after 10 years of progressive aphasia without generalized dementia (Kirshner, Webb, Kelly, & Wells, 1984; Kirshner, Tanridag, Thurman, & Whetsell, Jr., 1987). Gliosis and spongiform degeneration were seen, primarily in layer two of the left inferior frontal and temporal cortex. Intra- and extracellular vacuolization was noted. One patient developed motor neuron disease. These pathological findings are similar to ‘‘dementia lacking distinctive histological’’ features (DLDH) reported in 14 of 460 dementia autopsies by Knoepp and colleagues in 1990 (Knoepp, Mastri, Frey, Sung, & Rustan, 1990). The psychometric features and distribution were compatible with a frontal lobe dementia, although subcortical structures such as the striatum, substantia nigra, and the medial thalamus were also involved. The age of onset was <70 years, 50% had a family history of dementia, and the course of illness ran 2–7 years (Knoepp et al., 1990).
In the 40 cases of PPA reported with pathological correlations since 1977, this nonspecific neuronal loss, gliosis, and spongiform change in the frontal and temporal regions usually more evident in the left hemisphere, accounted for almost half of the cases. The frequency of different pathologies, including all cases with predominant language disorder, irrespective of other cognitive features, was as follows: nonspecific spongiform change, 19 (Kirshner et al., 1987; Mehler et al., 1987; Kobayashi, Kurachi, Gyoubu, Fukutani, Inao, Nakamura, & Yamaguchi, 1990; Green et al., 1990; Snowden et al., 1992; Caselli et al., 1993; Karbe et al., 1993; Neary et al., 1993a,b; Scheltens et al., 1994; Kertesz et al., 1994); Pick’s disease, 10 (Wechsler et al., 1982; Holland et al., 1985; Graff-Radford et al., 1990); Alzheimer’s Disease: 5 (Pogacar & Williams, 1984; Morris et al., 1984; Benson & Zaias, 1991); Creutzfeldt-Jakob disease, 4 (Shuttleworth, Yates, & Paltan-Ortiz, 1985; Mandell, Alexander, & Carpenter, 1989; Kirk & Ang, 1993; Victoroff, Ross, Benson, Verity, & Vinters, 1994); other (swollen neurons or hyaline inclusions), 2 (Lippa, Cohen, Smith, & Drachman, 1991; Munoz-Garcia & Ludwin, 1986). Pathologically, there was a resemblance between some cases labeled as Creutzfeldt–Jakob disease and nonspecific spongiform change, raising the possibility that these patients did not have prion disease.

The fact that spongiform degeneration, gliosis, and neuronal loss are the most common pathological findings in FTD has lead Snowden, Neary, and colleagues in Manchester to suggest that PPA is a left-hemisphere variant of FTD (Neary et al., 1993b; Snowden & Neary, 1993). These authors argue that the clinical phenotype of FTD will vary depending on the brain region primarily affected. If bifrontal degeneration is present early in the course, alterations in personality and social conduct with loss of insight occur (see Fig. 4). With progression, two different clinical profiles develop, one marked by apathy and the other by restlessness, disinhibition, and inappropriate affect. In bifrontal FTD, speech becomes increasingly laconic with stereotypes, echolalia, and eventually mutism. In some of these patients, there may be associated motor neuron disease, implicating disease in the precentral cortex and anterior horn cells of the brainstem and spinal cord. Balloon cells, typical of Pick’s disease, and Pick inclusion bodies may also be seen. These authors postulate that FTD encompasses a pathological spectrum which includes the Pick’s variant. Pick cells and bodies, considered to be pathognomonic of Pick’s disease, may represent an early or even late stage of a common disorder (see also Tissot, Constantinidis, & Richard (1985) and Hulette & Crain (1992)).

When asymmetric FTD is present, the clinical phenotype reflects the side of greater impairment. With right hemisphere predominance, behavioral aberrations, sometimes with psychotic delusions, and depression can develop (Neary et al., 1993b). If left-sided degeneration predominates, the clinical syndrome of PPA is seen, which can be subdivided into three clinical profiles (Snowden et al., 1992; Snowden & Neary, 1993). In one constellation, primary progressive nonfluent aphasia, nonfluent speech output with anomia,
phonemic paraphasias, impaired repetition, and relative preservation of comprehension is present, with deterioration in conduct later in the course of the disease as bifrontal degeneration supervenes. This aphasic profile corresponds to the PPA prototype described by Weintraub and Mesulam (1990). In the second profile, primary progressive fluent aphasia, speech is fluent with preserved repetition, semantic substitutions, and severely impaired comprehension, often with surface alexia and surface agraphia in which oral reading and writing of regular words is preserved, but without comprehension of word meaning. These are the patients whose semantic loss also extends to visual object knowledge, labeled “semantic dementia” (Hodges et al., 1992). These patients show bitemporal atrophy initially and may evolve anteriorly to involve the frontal lobes if they survive long enough. The third clinical profile, which would fall into the nonfluent aphasia group, is characterized by a mixed form of aphasia with both nonfluent speech and severe comprehension disturbance, often with apathy and personality change at the same time. SPECT images show predominant left perisylvian compromise (Snowden & Neary, 1993).

One recent study of three patients with PPA revealed achromatic balloon cells in all cases, with reactivity to tau protein in the perikarya detected by
immunohistochemical methods (Kertesz et al., 1994). One patient also had agyrophilic inclusions typical of Pick’s disease. In two cases, the hippocampus was conspicuously spared, which is atypical in Pick’s disease. Spongiform degeneration with vacuolization was seen in cortical layers 2 and 3 in two of the cases and throughout the cortex in the third case. The authors argue that the tau-reactive neurofilamentary changes in the balloon cells may be a transitional form of the Pick body and postulate the many cases of PPA have a common pathological substrate within the spectrum of Pick’s disease. They suggest that CBD may be a variant of this as well (Kertesz et al., 1994). Scheltens and colleagues followed a 59-year-old patient for 13 years with a mixed aphasic disorder and behavioural charges late in the course (Scheltens, Hazenberg, Lindeboom, Valk, & Wolters, 1990). Bitemporal atrophy was noted on MR and nonspecific cortical degeneration with neuronal loss was seen at autopsy, particularly in the parietal and temporal cortex. Alz-50 positive neurons were present and exhibited granular or diffuse cytoplasmic staining, again indicative of tau reactivity (Scheltens, Ravid, & Kamphorst, 1994). Characteristic changes of Pick’s disease were confined primarily to the left hippocampal and parahippocampal region and the left anterior temporal region, were identified in another patient whose primary symptom was progressive anamia (Graff-Radford et al., 1990). This contrasted with an earlier case of Pick’s disease in which loss of oral comprehension paralleled phonemic and morphologic speech impairment. In this patient the affected regions primarily included the superior temporal area with sparing of the anterior temporal pole and hippocampus (Holland, McBurney, Moosy, & Reinmuth, 1985). Together these two well-documented cases point to an important role for the left anterior and medial temporal region in the learning and retrieval of verbal lexical items (Graff-Radford et al., 1990) and indicate the circumscribed topography that can sometimes be seen in Pick’s disease.

Kertesz and colleagues (1994) summed up the literature by suggesting that PPA with nonfluent aphasia typically shows changes consistent with Pick’s complex disease ranging from nonspecific spongiform degeneration to Pick bodies and Pick cells (Tissot et al., 1985; Hulette & Crain, 1992). Patients presenting with fluent anomic aphasia may show either similar pathological changes or can represent an early asymmetric presentation of AD. This opinion is convergent with that of the Manchester group (Neary et al., 1993b; Snowden & Neary, 1993) who see FTD as part of the spectrum of Pick’s disease and regard PPA as a left-hemisphere variant of this disorder. This view is also potentially reconcilable with Mesulam and Weintraub’s original argument that PPA is a clinically distinct entity (Mesulam, 1982; Weintraub et al., 1990; Mesulam & Weintraub, 1992). These latter authors were primarily concerned with distinguishing PPA from AD and Pick’s disease. Nevertheless, whether FTD with spongiform change and neuronal loss and Pick’s disease represent a spectrum of the same disease or different pathological etiologies remains unsettled.
3.2e. Summary: Primary progressive fluent and nonfluent aphasia. The reality may be that PPA may be a variant of either AD or FTD, in which disease initiation occurs in the left perisylvian cortex. As the disease progresses, it can spread anteriorly or bilaterally into the anterior frontal region and as it does so, personality and behavioral changes will supervene. Autopsy will usually show the pathological changes of FTD, sometimes with Pick cells and bodies. The clinical syndrome may present as primary progressive nonfluent or fluent aphasia depending on the relative degree of temporal and frontal involvement. When the left perisylvian disease spreads posteriorly and bilaterally, memory loss and visuospatial disorientation may develop and Alzheimer pathology is likely at autopsy (see Fig. 5a). The initial language profile is usually a fluent aphasia, progressing to mutism in the terminal stages. It is notable that fluent aphasia can result from either FTD or AD, whereas nonfluent progressive aphasia usually will be caused by FTD. Importantly, these progressive patterns of invasion can be captured by serial

Fig. 5. (a) The transaxial images in the upper left and right show the HmPAO SPECT of a patient with probable Alzheimer’s Disease with prominent fluent aphasia. Note perfusion deficit in the left temporal-parietal region on the left of the brain (right side of image) extending anteriorly to the frontal region. (b) Transaxial images show opposite pattern of hypoperfusion more marked in the right parietal-temporal region on HmPAO axial SPECT images of a patient with probable Alzheimer’s Disease with prominent visual-spatial disorientation and visuoconstructive apraxia.
functional imaging, such as SPECT, allowing the clinician to anticipate and explicate the clinical course in an individual subject.

4. POSTERIOR CORTICAL ATROPHY

Not surprisingly, just as progressive dissolution of language function can be caused by neurodegenerative diseases affecting the left perisylvian language cortex, progressive visuoperceptual disorders can also arise from degenerative diseases affecting the visual association cortex (Bender & Feldman, 1972; Marin, 1987; Hof, Bouras, Constantinidis, & Morrison, 1990; Saffran, Fitzpatrick-Desalme, & Coslett, 1990). Although first described in the early years of this century by some of the same observers who reported progressive aphasia, these disorders have only recently come under scrutiny. For historical accounts, see Bender & Feldman (1972), Marin (1987), Hof et al. (1990), Saffran et al. (1990), and Coslett and Saffran (1996). Once again, the debate has arisen as to whether the patients have an atypical form of AD or represent a distinctive clinico-pathological entity. In order to evaluate this debate, it is first necessary to review what is known about the visuoperceptual deficits in AD.

4.1 Visuoperceptual Deficits in AD

Visuoperceptual processing deficits constitute part of the symptom complex of AD along with language and memory dysfunction. As discussed above, a subgroup with particular impairment on visuоconstructive tasks emerged from the factor analysis of neuropsychological tests performed in the group of AD patients studied by Martin et al. (1986). Visuоconstructive impairment corresponded to greater right parietal hypometabolism on PET studies (Foster et al., 1984; Martin et al., 1986) (also see Fig. 5b). In 1986, DeRenzi described two patients who presented with predominant visuospatial deficits in the absence of any significant loss of memory, insight, or judgment (DeRenzi, 1986). This author, along with Benson and colleagues, based on five additional cases, postulated a separate clinical entity, distinct from AD, for which the term posterior cortical atrophy, or primary posterior dementia, was proposed (DeRenzi, 1986; Benson, Davis, & Snyder, 1988) (see Table 2).

The visuoperceptual deficits described in AD include impairment on visuоconstructive tasks, environmental or topographical agnosia, and object and face agnosia (Saffran et al., 1990; Cummings, 1992; Kaskie & Storandt, 1995). Current cognitive models of object recognition and spatial orientation postulate several stages in the processing of visual information beginning with feature extraction, which occurs in parallel in the peristriate cortex and involves basic visual attributes such as color, orientation, and motion (Marin, 1987; Saffran et al., 1990; Thaiss & DeBleser, 1992). Feature information is combined automatically at an early stage of visual processing by the operation of selective attention. Spatial location information is transmitted along
### TABLE 2
Differential Diagnosis of Cortical Dementias

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer’s disease</th>
<th>Pick’s disease</th>
<th>Posterior cortical atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnesia</td>
<td>Early</td>
<td>Late</td>
<td>Late</td>
</tr>
<tr>
<td>Constructional disturbance</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Environmental agnosia</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Visual Agnosia</td>
<td>Late</td>
<td>Unusual</td>
<td>Early</td>
</tr>
<tr>
<td>Acalculia</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Anomia</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
</tr>
<tr>
<td>Alexia</td>
<td>Moderately late</td>
<td>Moderately late</td>
<td>Early</td>
</tr>
<tr>
<td>Agraphia</td>
<td>Moderately late</td>
<td>Moderately late</td>
<td>Early</td>
</tr>
<tr>
<td>Gerstmann’s syndrome</td>
<td>Moderately late</td>
<td>Late</td>
<td>Relatively early</td>
</tr>
<tr>
<td>Balint’s syndrome</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Kluver–Bucy syndrome</td>
<td>Absent or late</td>
<td>Early</td>
<td>Absent</td>
</tr>
<tr>
<td>Loss of insight</td>
<td>Early</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Behavioral response</td>
<td>Unconcerned</td>
<td>Disinhibited</td>
<td>Appropriately concerned</td>
</tr>
<tr>
<td>Pathology</td>
<td>Neuritic plaques and tangles; neuronal loss</td>
<td>Neuronal loss, gliosis, spongiform degeneration; Pick cells and Pick bodies</td>
<td>Neuritic plaques, tangles, and neuronal loss are most commonly observed.</td>
</tr>
</tbody>
</table>

*Note.* Adapted from Benson et al., 1988.
a dorsal occipitoparietal pathway and visual form information is transmitted along a ventral occipitotemporal pathway (Goodale & Milner, 1992). A viewer-centered or egocentric spatial mapping of location information is constructed and an abstract representation of shape, called a ‘structural description,’ is derived to allow comparison to stored representations in the act of object recognition. Binding of spatial and object attributes is considered necessary for conscious perception. Problems can arise in any stage of this processing or in the transfer of information from one stage to the other. Both top-down and bottom-up information transfer occurs. Traditionally, AD was believed to spare the primary visual and even visual association cortex and target multimodal association cortex in the superior temporoparietal and dorsolateral frontal regions (Brun & Englund, 1981). This was in keeping with one study which found no difference in visual acuity or spatial frequency contrast sensitivity in AD subjects compared to age-matched controls; in a pattern-masking task, the AD subjects showed more interference and longer temporal effects, suggesting that their perceptual problems arose at a later stage of processing (Schlotterer, Moscovitch, & Crapper-McLachlan, 1983). Evidence has emerged more recently, however, which suggests that visual system impairments can occur at a more peripheral level in AD subjects (Sadun, Borchert, De Vita, Hinton, & Bassi, 1987).

Histopathological evidence of degeneration in the optic nerve and retina has been documented (Hinton, 1988) and one report estimated of 30–60% drop-out of fibers in the optic nerve in AD subjects despite minimal clinical evidence of primary visual impairment in AD subjects (Sadun & Bassi, 1987). Another study demonstrated elevated contrast sensitivity at all frequencies in 15 AD subjects compared to that seen in age-matched controls (Nissen, Corkin, Buananno, Growdon, Wray, & Bauer, 1985). One subject with a severe perceptual impairment, including face and object agnosia and alexia, showed marked reduction in contrast sensitivity to low and intermediate frequencies, suggesting an important role for low spatial frequencies in object and face recognition (Nissen et al., 1985). In five patients with probable AD in whom visual complaints such as reading difficulty and spatial disorientation were prominent, a number of primary visual deficits were documented including decreased contrast sensitivity, impaired color perception, reduced visual acuity, abnormal visual evoked potentials, and prolonged latency in the initiation of saccades, with more deficits occurring in patients with more severe cognitive decline. The authors speculated that large fiber projections from the retinal ganglion cells to the superior colliculus, which play an important role in the control of eye movements and orientation, are involved in AD (Sadun et al., 1987).

In a study of 30 community-dwelling AD subjects, 13 (43%) had complex visual deficits. Visual acuity and color perception were preserved in these subjects, but there were clear impairments in the visual evaluation of objects, face, spatial location, and complex figures (Mendez & Zander, 1991). All 30 AD subjects had problems in figure–ground perception; 57% had agnosia
and 6% had Balint’s syndrome, which was associated with the most impaired performance on the complex visual tasks. Balint’s syndrome consists of “sticky fixation” with difficulty moving eyes toward an intended target, impaired eye–hand coordination in reaching toward a target, and simultanagnosia, and inability to process more than one visual object in an array at a time (Hof, Bouras, Constantinidis, & Morrison, 1989; Hof et al., 1990; Hof, Archin, Osman, Dougherty, Wells, Bouras, & Morrison, 1993). A more recent study revealed deficits on visual form discrimination even in early AD (Kaskie & Storandt, 1995). In a retrospective survey of 2500 autopsies in a psychogeriatric hospital over a 60-year period, 8 AD patients had Balint’s syndrome documented clinically (Hof, et al., 1990). In these cases, Brodmann areas 17, 18, and 19 and the posterior parietal region had two to three times the concentration of plaques and tangles than would be seen in these areas in typical AD. A PET study of 5 AD subjects with major visual complaints, compared to 3 without such impairments, revealed normal metabolism in the visual cortex with decrease in the visual association cortex and inferior parietal lobule in the visually impaired subjects, providing in vivo collaboration of this visual variant of AD (Kiyosawa, Bosley, Chawluk, Jamieson, Schatz, Savino, Sergott, Reivich, & Alavi, 1989) (see Fig. 5b).

4.2 Primary Posterior Cortical Atrophy

The above studies suggest that there is a subgroup of AD subjects with prominent visual complaints who have preferential involvement of the visual association areas. As mentioned above, however, some patients do not fit the diagnostic criteria for probable AD because they present with visuoperceptual difficulties in the apparent absence of other signs of AD such as poor memory, insight, or judgment (DeRenzi, 1986; Benson et al., 1988). Some skeptics have pointed out that mild memory difficulty has been present in many of these cases (Feher et al., 1986) and, frequently, the severe visual impairments make formal neuropsychological testing difficult (Benson et al., 1988; Snowden et al., 1992). Nevertheless, there has been a series of individual case reports describing relatively isolated, progressive visuoperceptual deficits. Symptoms have included object and/or facial agnosia, elements of Balint’s syndrome, topographical disorientation or spatialagnosia, spelling alexia, Riddoch’s phenomenon, in which objects disappear from view unless the head is moved, an inability to see large objects while small items can be recognized, and other problems in the focusing of visual attention. Visual extinction and eventually full field defects can also evolve and, interestingly, are often more frequent in the left hemifield. Visuoconstructive difficulties are prevalent in drawing to copy or to command (Celsis, Aigneil, Puel, Rascal, & Vergnes, 1987; Mehler & Korey, 1988; McDaniel, Wagner, & Greenspan, 1991; Berthier, Starkstein, Sevlever, & Taratuto, 1991; Levine, Lee, & Fisher, 1993). A large discrepancy in verbal and performance IQ is frequently apparent (Benson, Davis, & Snyder, 1988). Although many of
Fig. 6. HmPAO SPECT shows bilateral parietal–occipital hypoperfusion in a 64 year old woman with an 8 year history of progressive visuoperceptual defect starting with loss of stereoscopic vision and motion perception and progressing to prosopagnosia, visual agnosia, alexia, and Balint’s syndrome. At the time of this scan she was severely visually disabled.

these patients are likely an atypical variant of AD, they have attracted attention because of the prominence of their visuoperceptive deficits.

As with PPA, the onset of PCA, based on reports over the past 10 years, is presenile with an average age of 59.8 (range 45–68). Imaging may show parieto-occipital atrophy on CT or MR and parieto-occipital hypoperfusion is usually evident on functional imaging (Caselli et al., 1992; Attig, Jacquay, Uytdenhoef, & Roland, 1993) (see Fig. 6.) The hypofunction is often asymmetrical, being more marked on the right. Of the 38 cases so far reported, only 8 have had tissue diagnosis (6 autopsy and 2 biopsies) (Crystal, Horoupian, Katzman, & Jokowitz, 1982; Cogan, 1985; Berthier et al., 1991; Hof, Archin, Osman, Dougherty, Wells, Bouras, & Morrison, 1993; Victoroff, Ross, Benson, Verity, & Vinters, 1994). Of these 8, AD accounted for 6 and the 7th showed nonspecific spongiform change with gliosis. One other case developed periodic complexes on EEG and myoclonus and followed a rapid course. Creutzfeld–Jakob disease was confirmed at autopsy (Victoroff et al., 1994). The pathological differential, therefore, is similar to PPA, but in the PCA cases so far reported, AD has predominated.

Unfortunately, case reports vary with respect to the completeness of the patient evaluation on both standardized neuropsychological and ophthalmol-
logical assessments in PCA. An information-processing approach has been applied to some case studies (Taylor & Warrington, 1971; Saffran et al., 1990; Thaiss & DeBlaser, 1992; Stark, Coslett, & Saffran, 1996; Saffran & Coslett, 1996; Coslett & Saffran, 1996). For example, the performance of two patients with visual attention impairments has been investigated on automatic and effortful visual search paradigms (Treisman & Souther, 1985; Saffran et al., 1990; Coslett & Saffran, 1996). One patient with simultanagnosia had no difficulty identifying single objects, but could not process more than one object at a time. On the automatic visual search paradigm, single features were detected without difficulty, but conjoint feature detection could not be accomplished at all. Another subject, who had a more severe impairment including visual agnosia, could read small print but not large (Saffran et al., 1990). A recently reported patient had no difficulty with object recognition or complex visual arrays, but was unable to navigate her environment or to place her body correctly in space, for example when sitting on a chair or lying down in bed. The authors argued that she has a defect in egocentric mapping, which means she cannot successfully relate her body spatially to her environment (Stark, Coslett, & Saffran, 1996). Another patient exhibited “attentional dyslexia” whereby letters migrated from one word into the next in two-word displays, a tendency which was mitigated if the words were physically dissimilar, for example a word in upper case juxtaposed to a word in lower case (Saffran & Coslett, 1996).

What is needed is more such careful study, using information processing models of visual perception in conjunction with neuroimaging and conventional neuropsychology to fully describe the associated cognitive deficits. Further autopsy studies are also required to see if clinical phenotypes are distinguishable in patients with AD at autopsy as opposed to spongiform degeneration. From the evidence so far, however, it seems clear that, unlike PPA, the majority of PCA cases will turn out to be atypical variants of AD.

5. PROGRESSIVE APRAXIA

5.1. Praxis in AD

Apraxia is another “cortical deficit” frequently encountered in AD. It increases in severity as the disease progresses (Edwards, Deuel, Baum, & Morris, 1991) and is present in 70–80% in the late stage (Sjogren, Sjogren, & Lindgren, 1952). It has been relatively understudied until recently, and the emphasis has been on relationships with overall indices of cognitive decline and language functions and on fractionation of praxis functions, which can be differentially affected in AD. Current models of praxis distinguish between a conceptual system that includes knowledge of tools and how to use them, and a production system containing knowledge of motor action programs and how to translate them into skilled movements (Ochipa, Rothi, & Heilman, 1992; De Renzi & Lucchelli, 1988). Ideomotor apraxia relates to the production system, resulting in spatial and temporal errors. Conceptual
apraxia leads to content errors and manifests as a problem in the use of single 
objects or in the sequential use of objects in complex motor acts (Ochipa et al., 1992). This is also referred to as ideational apraxia (De Renzi & Lucchelli, 1988). Ideomotor apraxia can be tested by showing object use to command and by imitating the required action demonstrated visually. Tests for conceptual apraxia include comprehension of gestures and demonstration of the use of tools, either as single objects or as multiple objects to be used in correct sequence.

One of the first group studies on apraxia in mild AD ($N = 18$), concluded that ideomotor apraxia was not an early feature and that it progressed slowly relative to other deficits (Della Sala, Lucchelli, & Spinnler, 1987). Some studies have found gestures to command and imitation equally affected in AD subjects (Rapcsak, Croswell, & Rubens, 1989; Foster, Chase, Patronas, Gillespie, & Fedio, 1986). However, Lucchelli and colleagues found imitation less impaired than pantomime in 56%, more impaired in 15% and equally affected in 28% of 32 AD subjects, who were compared to 30 controls (Lucchelli, Lopez, Faglioni, & Boller, 1993). In a PET study, Foster and colleagues found that imitation deficits correlated to visual–spatial defects and right parietal hypometabolism, while pantomime impairment correlated to language performance and left frontal and temporal hypometabolism (Foster et al., 1986). Kempler et al. noted parallel loss in both production and recognition of words and their gestures in AD subjects and postulated a common impairment in symbolic representation (Kempler, 1995). Ochipa and colleagues undertook a thorough investigation of conceptual apraxia in AD, by systematically assessing tool use, the association of tools with objects, and mechanical problem-solving in 32 AD subjects also evaluated on language skills and ideomotor apraxia. They found double dissociations on language performance and ideomotor and conceptual apraxia (Ochipa et al., 1992). Similar dissociations have been reported by other groups (Benke & Bacher, 1991; Lucchelli et al., 1993), supporting the concept of separate semantic systems for language and action and separate action conceptual and production systems (Ochipa et al., 1992).

### 5.2. Corticobasal Degeneration

Isolated progressive apraxia has been described in the absence of significant aphasia (Cambier et al., 1981; DeRenzi, 1986; Rapcsak, Ochipa, Roeltgen, & Roeltgen, 1988; Rapcsak, Ochipa, & Roeltgen, 1990). Generally this has been poorly characterized, but one case report described a severe production deficit for transitive gestures in the absence of conceptual apraxia (Rapcsak et al., 1990). When accompanied by an asymmetric akinetic–rigid syndrome, progressive apraxia is often part of the symptom complex called corticobasal degeneration (CBD) (Cambier et al., 1981; Riley, Lang, Lewis, Resch, Ashby, Hornykiewicz, & Black, 1990; Thompson & Marsden, 1992; Rinne, Lee, Thompson, & Marsden, 1994). CBD usually presents as an
akinetic-rigid syndrome related to subcortical pathology, as well as with parietal findings such as cortical sensory loss and ideomotor apraxia. It was first described by Rebeiz, Kolodny, and Richardson (1968) in three patients whose pathology was characterized by swollen achromatic neurons and gliosis in the frontal and parietal cortex, basal ganglia, and thalamus. In subsequent reports, the terms “corticodentonigral degeneration,” “corticobasal ganglionic degeneration,” and “neuronal achromasia” have all been used to denote this entity, which has a clinically distinctive phenotype. By 1990, 40 cases had been reported, 14 with pathological confirmation. In that compilation, which added 15 cases to the literature, the average age of onset was 60 with male predominance of 3:2 (Riley et al., 1990). The asymmetric onset involved the left arm in 12/15 cases. A mild dementia supervened in 4, aphasia was present in 3, and 11/15 had ideomotor apraxia. Recently, Rinne et al. (1994) summarized 36 cases, followed at Queen’s Square in London, 30 of whom had been seen over several years and 6 of whom had autopsies (Rinne et al., 1994). In this series, the average age at onset was 60.9 ± 9.7 with a range of 40–76. There were 20 females and 16 males and the average duration of illness for those who eventually died was 4–8 years; in those still being followed, it was 2–8 years. There was no familial incidence. Patients routinely underwent MR or CT scanning, EEG, and 26 had neuropsychological testing. A typical symptom complex included progressive asymmetric akinesia-rigidity with limb dystonia, bilateral ideomotor apraxia, focal myoclonus, supranuclear gaze palsies, and the alien limb phenomenon. (In the latter phenomenon, the affected arm elevates or carries out movements not intended by the individual). Gait difficulty and asymmetric sensory loss were also common (see Table 3). The extrapyramidal symptoms tended not to be responsive to treatment with L-dopa. Atypical cases have also been reported presenting with primary cognitive impairment (Bergeron, Pollanen, Weyer, Black, & Lang, 1996).

At initial presentation, the arm was the first limb affected in 64% with clumsiness and loss of dexterity (Rinne et al., 1994). The right and left arms were almost equally affected. Myoclonic jerking frequently accompanied the developing rigidity. Gait difficulty and/or leg stiffness was the next most common presenting sign (28%) and one patient presented with isolated speech difficulty, as was also described by Lang (1992). Oculomotor and eyelid apraxia frequently occurred and cortical sensory loss was common, as were pyramidal tract signs. Although in the majority of cases cognitive dysfunction was not prominent, a variety of cognitive impairments was noted, including frontal lobe dysfunction in two subjects, prominent behavioral aberration and personality change in one, and mild memory and visuospatial difficulties in others, in addition to the pervasive ideomotor apraxia (Rinne et al., 1994). In other case studies, particularly autopsy series, dementia has been a predominant characteristic, although details are usually lacking (Bergeron et al., 1996; Clark, Manz, White, Lehmann, Miller, & Coyle, 1986;
TABLE 3
Clinical Features of Corticobasal Degeneration in 64 Cases.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akinesia, rigidity</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>Postural instability</td>
<td>47</td>
<td>73</td>
</tr>
<tr>
<td>Postural-action tremor</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Limb Dystonia</td>
<td>43</td>
<td>67</td>
</tr>
<tr>
<td>Reflex Myoclonus</td>
<td>43</td>
<td>67</td>
</tr>
<tr>
<td>Other Dyskinesias</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Cerebral cortical signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory Loss</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>Apraxia</td>
<td>54</td>
<td>84</td>
</tr>
<tr>
<td>Alien Limb</td>
<td>30</td>
<td>47</td>
</tr>
<tr>
<td>Frontal Release Signs</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Dementia</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Aphasia</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Other manifestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>Babinski signs</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Impaired ocular motion</td>
<td>38</td>
<td>59</td>
</tr>
<tr>
<td>Impaired eyelid motion</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>34</td>
<td>53</td>
</tr>
</tbody>
</table>

Note. Based on summaries provided in Riley et al., 1990 and Rinne et al., 1994.

Lippa, Smith, & Fontneau, 1990; Rey, Tomer, Levin, Sanchez-Ramos, Bowen, & Bruce, 1995). Massman et al. (1994) compared 19 patients (14 female and 5 males) with CBD to 23 age- and severity-matched AD subjects (Massman, Kreiter, Jankovic, & Doody, 1994). They found less severe memory difficulty in CBD compared to AD, but the CBD subjects had higher depression scores, more severe motor impairment, and more difficulty in mental control and praxis. Performance was relatively better on tasks of abstraction and on attention, whereas the opposite was found in AD subjects. It is the relative preservation of memory in many CBD subjects and the frequent preservation of the language that has led to the common impression that dementia is unusual in this syndrome. The combination of dysarthria and severe apraxia make neuropsychological testing difficult to perform in CBD and the cognitive course of the disease has not been as well studied as has the focal motor symptomatology. One detailed study distinguished the myoclonus seen in CBD from other degenerative conditions such as AD on the basis of neurophysiological characteristics, suggesting that reflex myoclonus in CBD is based on the pathological enhancement of direct sensory input to the motor cortical areas (Thompson, Day, Rothwell, Brown, Britton, & Marsden, 1994).

The most striking and disabling neurocognitive deficit in CBD is apraxia
Fig. 7. HmPAO SPECT shows severe left frontal-parietal and right parietal hypoperfusion in a patient with probable corticobasal degeneration. He has an akinetic rigid syndrome, limb dystonia, and alien limb phenomenon in the right arm and severe apraxia. At time of this scan he had also developed a significant fluent aphasia.

(Leiguarda, Lees, Merello, Starstein, & Marsden, 1994). Preliminary studies suggest that ideomotor apraxia predominates in this condition, but conceptual apraxia has not been systematically studied. In one abstract report of six patients, ideomotor apraxia was found on pantomime and imitation and attributed to the supplementary motor area pathology characteristic in this disease. Gesture recognition was intact, but knowledge of tool use was not explored (Jacobs, Boston, Adair, Macauley, Gold, Gonzalez-Rothi, & Heilman, 1995). Given that the parietal lobe is prominently affected in this disorder, conceptual deficits would seem likely, if formally elicited.

5.2.a. Neuroimaging. Morphological imaging in CBD has been reported at times to show bilateral frontoparietal atrophy which is usually greater on the side opposite the dystonic limb (Rinne et al., 1994), but functional imaging has been more revealing (see Fig. 7). One PET study reported asymmetrical decrease in the thalamus and inferior parietal lobule contralateral to the affected limb in six CBD subjects in contrast to patients with hemi-Parkinson’s disease in whom no such abnormality was seen (Eidelberg, Dhaban, Moeller, Sidtis, Grinos, Strother, Cederbaum, Greene, Fahn, Powers, &
Rottenberg, 1991). In Parkinson’s disease (PD), in vivo labeling of presynaptic dopaminergic neurons with 6–18 F fluoro-dopa (6FD) has shown decreased uptake in the putamen contralateral to the symptomatic limbs (Nahmias, Garnett, Firnau, & Lang, 1995). In cerebral blood flow studies of PD with SPECT, biparietal and/or frontal hypoperfusion have been frequently reported, particularly in demented PD subjects (Pizzolato, Dam, Borsatto, Saïta, Da Col, Perlotto, Zanco, Ferlin, & Battistin, 1988; Sawada, Vdaka, Kameyama, Seriu, Nishinaka, Shindou, Kodama, Nishitani & Dkumiya, 1992). In contrast, other PET studies of CBD subjects have revealed decreased metabolism in the contralateral mediofrontal, sensorimotor, parietal, and superior temporal regions (Blin, Vidalinet, Phillon, Dubois, Feve, & Agid, 1992; Sawle, Brooks, Marsden, & Frackowiak, 1991). Decreased fluorodopa uptake has also been noted in the caudate, posterior putamen, and mediofrontal region in patients with CBD (Sawle et al., 1991).

5.2b. Pathology. At the time of this review, there have been 76 cases of CBD reported, 20 of whom have had autopsy confirmation. The pathognomonic finding in CBD is the presence of swollen achromatic neurons that resemble Pick’s cells except that they are preferentially distributed in the parietal and frontal regions and substantia nigra (Rebeiz et al., 1968; Gibb, Luthert, & Marsden, 1989; Riley et al., 1990; Rinne et al. 1994). Dopamine concentrations were profoundly reduced in the caudate and putamen by 98% and by 88% in the substantia nigra in the one neurochemical case report of CBD so far published (Riley et al. 1990). Clark et al. (1986) reported agyrophilic staining in the swollen achromatic neurons of two cases resembling the clinical phenotype of CBD and concluded that their cases had Pick’s disease. Case 9 of the Rinne et al. series presented with personality change and aberrant behavior, reminiscent of Pick’s disease but with histopathological distribution typical of CBD (Rinne et al., 1994). In some case reports of progressive apraxia in the absence of an asymmetric akinetic rigid syndrome, neuronal achromasia was the characteristic finding at autopsy (Cambier et al., 1981; Rinne et al., 1994). The possible overlap with Pick’s disease has been raised by several authors, but Pick bodies are absent and the distribution is quite different from typical Pick’s disease (Gibb et al., 1989; Riley et al., 1990; Rinne et al., 1994; Kertesz et al., 1994; Bergeron et al., 1996). The hippocampus is spared and parietal lobe preferentially involved, whereas Pick’s is a frontotemporal disease that frequently involves the hippocampus (Munoz-Garcia & Ludwin, 1984). Basophilic inclusion bodies (called corticobasal inclusions), including some which react with antineurofilament antibody have been reported in the substantia nigra in CBD and also occasionally in Pick’s disease (Gibb et al., 1989). In a clinicopathologic study of 32 patients with Pick’s disease, Tissot et al. (1985) noted that the clinical phenotype of personality change as well as behavior and language disorder, was usually associated with temporo-orbital lobar atrophy with swollen neurons and agyrophilic inclusion bodies, with minimal subcortical pathology (Tissot et al., 1985). Another group, however, showed extrapyramidal and pyramidal
findings with dysarthria corresponding to pathological changes in the dorso-lateral frontal and precentral gyri and basal ganglia. Pick bodies were not present but neuronal swellings were (Tissot et al., 1985). The latter group could be interpreted as having CBD. In conclusion, it may be that the CBD and Pick’s disease represent different expressions of a similar pathological process with a clinical phenotype reflecting the areas of the brain primarily involved. Immunohistochemical techniques, for example tau staining, may help to clarify this (Bergeron et al., 1996; Feaney, Mattiace, & Dickson, 1996). The typical distribution of changes including neuronal achromasia and gliosis is shown in Table 4.

### TABLE 4
Distribution of Main Pathological Findings in Eight Autopsy Cases of Corticobasal Degeneration

<table>
<thead>
<tr>
<th>Region</th>
<th>Gibb et al. (1989)</th>
<th>Rebeiz et al. (1968)</th>
<th>Riley et al. (1990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Frontal Pole</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Medial Frontal</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Precentral</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Postcentral</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Temporal Pole</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Temporal Gyri</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Striate</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lenticular nucleus</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Brain stem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticospinal tracts</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red nucleus</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periaqueductal grey area</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus basalis of meynert</td>
<td>0</td>
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<tr>
<td>Cerebellar cortex</td>
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<td>0</td>
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<tr>
<td>Dentate nucleus</td>
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<tr>
<td>Thalamus</td>
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<tr>
<td>Anterior</td>
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</tr>
<tr>
<td>Medial</td>
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<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>2</td>
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<td></td>
</tr>
</tbody>
</table>

*Note.* Adapted from Gibb et al., 1989 and Riley et al., 1990. Estimated degree of involvement: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
6. CONCLUSION

The focal cortical atrophy syndromes have been the subject of intense interest over the last decade. In part, they are a by-product of the new functional imaging era which allows focal dysfunction to be correlated in vivo with behavioral abnormalities. Altogether, there have been over 160 case reports of PPA, almost 40 reports of PCA, and 76 reports of CBD. The clinical characteristics and imaging parameters have been adequately delineated and it is apparent that they are more common than first thought. They are important syndromes to study and recognize, both from the point of view of health care planning and support of the patient and caretakers, and from the point of view of appropriate selection for drug intervention. What is now needed, however, is an integrated approach to case studies in which both standard neuropsychological and ADL measures are combined with individualized cognitive analysis in conjunction with structural and functional imaging and, wherever possible, eventual autopsy. More longitudinal studies are desirable, but with instruments that will allow continued assessment as the diseases progress and patients become less testable. Biological markers need to be examined and the neurochemical changes in frontotemporal degeneration requires elucidation.

In summary there are distinctive pathological phenotypes that manifest as focal progressive neurocognitive disorders. One disorder, FTD, consists of a nonspecific spongiform degeneration with gliosis and neuronal loss primarily affecting the frontal and/or temporal regions. Some cases will show Pick cells and/or Pick bodies. The other main disorder reveals amyloid plaques and neurofibrillary tangles typical of AD, usually most plentiful in the hippocampus, posterior parietal and temporal regions, although the frontal regions are affected as the disease progresses. In PPA, left perisylvian dysfunction is usually evident at presentation clinically and on neuroimaging. In patients with nonfluent aphasia the disease tends to progress anteriorly reflecting FTD. Fluent forms may either progress anteriorly, as result of a nonspecific frontotemporal degeneration or posteriorly reflecting AD. In PCA, the visual association cortex is targeted bilaterally, but often with greater involvement on the right and the common pathological substrate is AD. In CBD, the clinical phenotype is an asymmetric akinetic-rigid syndrome with apraxia; there is a frontoparietal and substantial nigra involvement on functional and receptor imaging, respectively. Pathologically, on light microscopy the disease appears to fall into the spectrum of Pick’s disease, but new immunohistochemical markers may help to distinguish these disease entities (Faney et al., 1996; Bergeron et al., 1996).

REFERENCES


