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Review Article

Subcortical Dementia

Neuropsychology, Neuropsychiatry, and Pathophysiology

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Subcortical dementia refers to a clinical syndrome characterised by slowing of cognition, memory disturbances, difficulty with complex intellectual tasks such as strategy generation and problem solving, visuospatial abnormalities, and disturbances of mood and affect. The syndrome was first described by Kinnier Wilson, but further progress in development of the concept has occurred only within the past ten years. Subcortical dementia occurs in degenerative extrapyramidal disorders and has also been identified in inflammatory, infectious, and vascular conditions. Histologic, metabolic, and neurochemical investigations implicate dysfunction primarily of subcortical neurotransmitter systems and subcortical structures or subcortical–frontal connections in the genesis of the syndrome. Subcortical dementia contrasts neuropsychologically and anatomically with disorders such as dementia of the Alzheimer type that affect primarily the cerebral cortex. The clinical characteristics of subcortical dementia reflect the interruption of fundamental functions (motivation, mood, timing, arousal) mediated by phylogenetically and ontogenetically early maturing structures.

Dementia is an acquired persistent impairment in intellectual function involving several domains of mental abilities and resulting from brain dysfunction (Cummings & Benson, 1983). Dementia was once regarded as a unitary disorder of brain failure with homogeneous mental status alterations, but recent studies of intellectual changes in specific disease processes reveal that dementia has variable manifestations and that the nature of the cognitive and behavioural alterations can be correlated with the distribution and severity of brain pathology. Preliminary investigations have demonstrated two principal patterns of neuropsychological deterioration within the dementias: 1) a cortical pattern with intellectual decline including loss of such abilities as language, learning, perception, calculation, and praxis and manifested by aphasia, amnesia, agnosia, acalculia, and apraxia; and 2) a subcortical pattern resulting from disturbances of functions such as motivation, mood, attention, and arousal evidenced by psychomotor slowing, memory impairment, affective and emotional disorders, and difficulties with strategy formation and problem solving. Anatomically, the cortical pattern is produced by diseases involving primarily, but not exclusively, the association cortex of the cerebral hemispheres and the medial temporal lobes, whereas the subcortical pattern occurs in disorders with predominant involvement of basal ganglia, thalamus, and brainstem structures (Albert *et al*, 1974; McHugh & Folstein, 1975; Albert, 1978; Cummings & Benson, 1983, 1984). Alzheimer's disease and Pick's disease are examples of cortical dementing processes; the dementia syndromes associated with the extrapyramidal disorders (Huntington's disease, Parkinson's disease, progressive supranuclear palsy, etc.) exemplify the subcortical pattern of intellectual impairment.

The relationship of dementia to cortical dysfunction is widely known and accepted, whereas the correlation between subcortical pathological involvement and dementia is more controversial. This review will present the available information regarding subcortical dementia and the contribution of subcortical structures to human intellectual and emotional function. A brief history of the idea of subcortical dementia will be presented first; followed by a discussion of the neuropsychological and neuropsychiatric characteristics of subcortical dementia; finally the pathology, pathophysiology, and possible mechanisms of subcortical dementia are described.

History of subcortical dementia

Subcortical dementia was first described by S. A. K. Wilson in 1912. In the course of describing the

disease that came to bear his name, Wilson commented on the "psychical symptoms" and noted that in contrast to "senile dementia" and dementia paralytica, his patients had no evidence of agnosia or apraxia, and memory and comprehension deficits were less severe. They manifested "narrowing of the mental horizon" manifested by a diminished capacity to store and retain mental impressions, and they evidenced "facility, docility, and childishness" with lack of insight and poor judgment. He observed that the symptoms closely resembled those occurring in Huntington's disease and Parkinson's disease. At autopsy, Wilson's patients had severe pathological changes in the lenticular nucleus and globus pallidus; the cerebral cortical structures were preserved. Thus, in addition to establishing the relationship between an extrapyramidal movement disorder and disease of the basal ganglia, Wilson must also be credited with the first description of a syndrome now recognised as subcortical dementia and with demonstration of its association with basal ganglionic dysfunction.

After Wilson's initial contribution linking intellectual impairment to basal ganglia disorders, observations regarding dementia in patients with thalamic and basal ganglionic diseases continued to accumulate, but no systematic formulation of the relationship was attempted for approximately 60 years. In nearly simultaneous publications, Albert and colleagues (1974) and McHugh & Folstein (1975) called attention to the subcortical origin of the dementia of progressive supranuclear palsy (PSP) and Huntington's disease, respectively. Albert *et al* (1974) noted that patients with PSP typically exhibited forgetfulness, slowness of thought processes, alterations of mood and personality, and impaired ability to manipulate acquired knowledge. They emphasised the absence of cerebral cortical involvement in PSP and observed that similar behavioural alterations had been described in patients with other subcortical degenerative processes such as thalamic degeneration, olivopontocerebellar atrophy, and Parkinson's disease and that all these disorders failed to produce the aphasic, agnosic, and apractic deficits characteristic of dementias associated with cortical dysfunction. Similarly, McHugh & Folstein (1975) described abnormalities of problem solving, insight, judgement, abstraction, attention, concentration, and motivation in patients with Huntington's disease. They contrasted these deficits with the aphasia, alexia, apraxia, and agnosia of Alzheimer's disease and with the amnesia of the Wernicke-Korsakoff syndrome. Noting the prominence of subcortical degeneration in Huntington's disease and the relatively limited and variable cortical involvement, they suggested that the mental changes were a product of the subcortical pathological alterations.

In the past decade, the seminal observations of Albert *et al*, (1974) and McHugh & Folstein (1975) have been supported and extended. Among the extrapyramidal syndromes, subcortical dementia has been found in Parkinson's disease (Albert, 1978), idiopathic basal ganglia calcification (Cummings *et al*, 1983), and spinocerebellar degenerations (Hart *et al*, 1985) as well as PSP, Huntington's disease, and Wilson's disease. Thalamic degeneration, likewise, produces a similar pattern of intellectual deterioration (Stern, 1939; Schulman, 1957; Katz *et al*, 1984). Subcortical dementia has also been identified in non-degenerative disorders: infarction of the basal ganglia and thalamus produces the characteristic mental status syndrome (Cummings & Benson, 1983; Guberman & Stuss, 1983; Graff-Radford *et al*, 1984), and similar behavioural changes have been observed in patients with granulomatous and post-encephalitic involvement of the same region (Pilleri *et al*, 1981; Hier *et al*, 1983). Among metabolic conditions, the subcortical pattern of dementia has been identified in parathyroid dysfunction where basal ganglionic calcification is often prominent (Bachman & Albert, 1984). This aetiologically heterogeneous group of disorders shares a similar pattern of intellectual compromise and a common preferential involvement of subcortical grey matter structures.

Characteristics of subcortical dementia

Neuropsychological and neurobehavioural aspects

Dysfunction of subcortical structures results in abnormalities in speed of information processing, attention and concentration, memory, word list generation, abstraction and categorisation, judgement, problem resolution, strategy formulation, and visuospatial abilities. The dementia syndromes of Parkinson's disease and Huntington's disease have been studied most extensively and will be cited to provide examples of these deficits.

Speed of cognition

Slowness of central processing is a ubiquitous abnormality that contributes to many of the deficits of subcortical dementia. Originally considered a reflection of retardation of movement (bradykinesia), recent studies have shown a slowness of information processing (bradyphrenia) in excess of the motor system abnormalities. Evarts *et al* (1981) compared parkinsonian patients with aged controls

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matched for severity of motoric slowing and found that the Parkinson's disease patients had significantly slower reaction times indicative of slowed central operations. Wilson *et al* (1980) demonstrated that the speed of memory scanning is increased in elderly Parkinson's disease patients compared to elderly control subjects, and Horne (1971) showed that post-thalamotomy Parkinson's disease patients had normal reaction times for tasks with no response delay but were significantly slower than control subjects when the tests were made more complex by requiring a delay in response. Rafal *et al* (1984) failed to demonstrate a retardation of central processing in their patients, but they found that dopamine treatment improved performance on two complex reaction time tasks and did not facilitate simple reaction times, suggesting that abnormalities of dopaminergic function were contributing to response latencies of the more complicated procedures. Stern and colleagues (1984) found a significant relationship between reaction times and abnormalities of norepinephrine metabolism in Parkinson's disease patients.

Slowing, unrelated to motor disturbances, has also been noted in patients with Huntington's disease and PSP (Rafal & Grimm, 1981; Brouwers *et al*, 1984).

Attention and concentration

Attention, concentration, and vigilance may also be disturbed by dysfunction of subcortical mechanisms. Parkinson's disease patients may manifest abnormalities on tests of concentration including digit span, digit symbol, trail making tests, and serial cancellation tasks (Reitan & Boll, 1971; Pirozzolo *et al*, 1982), and patients with left-unilateral Parkinsonism exhibit disturbances of visual attention and cancellation (Villardita *et al*, 1983). McHugh & Folstein (1975) emphasized that Huntington's disease patients had abnormalities of attention and concentration that contributed to their memory and cognitive deficits.

Memory

Memory disturbances are a cardinal feature of subcortical dementia but have been only partially characterised and contrasted with memory abnormalities in cortical dementing illnesses. While remaining oriented and performing adequately on simple memory tests, Parkinson's disease patients explored with more detailed testing manifest abnormalities in visual memory, learning of superspan word lists, logical memory, paired associate learning, tactile memory, and recall of remote personal and sociopolitical information (Warburton, 1967; Reitan & Boll, 1971; Pirozzolo *et al*, 1982; Freedman *et al*, 1984; Globus *et al*, 1985). The deficits in recall of new information are partially aided by cues and by choice recognition manoeuvers suggesting a greater deficit in recollection of stored information than of encoding new material (Tweedy *et al*, 1982). Impaired recall of remote information is equally severe for all decades of the patient's life; the temporal gradient characteristic of Korsakoff's syndrome is lacking (Freedman *et al*, 1984). A relationship between altered catecholamine function and memory impairment in Parkinson's disease is suggested by the correlation between memory performance and cerebrospinal fluid catecholamine metabolite ratio (Mann *et al*, 1983) and the observation that verbal memory performance improves following levodopa administration (Marsh *et al*, 1971; Halgin *et al*, 1977).

Memory disturbances in Huntington's disease resemble those of Parkinson's disease. Impaired performance in tests of recent memory are among the earliest detectable abnormalities of Huntington's disease patients, and analysis of the recall deficits suggests disturbances in both encoding and retrieval (Caine *et al*, 1977; Butters *et al*, 1978). Compared with Korsakoff's syndrome, patients with Huntington's disease show no improvement with reduced proactive interference but are significantly aided by using recognition as opposed to recall paradigms (Butters *et al*, 1976; Martone *et al*, 1984). Like Parkinson's disease patients, those with Huntington's disease have remote memory deficits involving all decades (Albert *et al*, 1981). There is a significant correlation between the severity of memory abnormalities and the extent of caudate atrophy seen on computerised tomographic (CT) scans of the head of Huntington's disease patients (Sax *et al*, 1983).

Memory abnormalities have not been as well studied in other subcortical dementing disorders, but slowed memory scanning is evident in patients with Friedreich's ataxia, and memory is impaired in PSP (Albert *et al*, 1974; Davis *et al*, 1985; Hart *et al*, 1985).

Visuospatial abilities

Visuospatial deficits not attributable to motor system abnormalities including visual discrimination, visual organisation, spatial orientation, drawing, angle perception, and rotational task disturbances have been identified in patients with Parkinson's disease (Mortimer *et al*, 1982; Pirozzolo *et al*, 1982; Boller *et al*, 1984; Globus *et al*, 1985). Parkinsonian patients also have difficulty judging vertical and horizontal

axes visually and with regard to their own posture when vision is obscured (Proctor *et al*, 1964; Danta & Hilton, 1975). Gainotti *et al* (1980) compared patients with Parkinson's disease, Huntington's disease, and Alzheimer's disease and found the latter to be significantly more impaired on tests requiring copying of designs. In another study comparing patients with cortical and subcortical dementias, Brouwers *et al* (1984) demonstrated that Alzheimer's disease patients had more difficulty with reproduction of constructional models, whereas Huntington's disease patients had greater impairment on a road map test. Kimura *et al* (1981) found that patients with PSP manifest abnormalities on tasks involving visual search or visual scanning abilities.

Cognition

Patients with Parkinson's disease also suffer from a variety of cognitive deficits. Category naming (verbal fluency, number of members of a specified category named in one minute) is diminished in many parkinsonian patients (Matison *et al*, 1982; Lees & Smith, 1983). They may also exhibit abnormalities on the similarities subtest of the Wechsler Adult Intelligence Scale (WAIS) and have difficulty shifting set on tasks requiring abstraction and categorisation (Talland & Schwab, 1964; Reitan & Ball, 1971; Lees & Smith, 1983; Globus *et al*, 1985). The latter deficit is partially reversible with levodopa therapy, supporting a relation with the underlying dopamine deficiency (Bowen *et al*, 1975).

Huntington's disease patients exhibit a similar pattern of cognitive deficits. Category naming is impaired early in the course of the disease, and subtests of the WAIS dependent on abstraction and concept manipulation are performed poorly (Boll *et al*, 1974; Butters *et al*, 1978; Josiassen *et al*, 1982).

The cognitive deficits of PSP similarly include poor abstraction, difficulty shifting sets, and poor manipulation of information (Rafal & Grimm, 1981; Maher *et al*, 1985). The cognitive deficits of the spinocerebellar degenerations have not been well studied but appear to resemble those of other subcortical dementias and lack the features indicative of cortical dysfunction (Carter & Sukavajana, 1956; Chandler & Debin, 1956; Cummings & Benson, 1983; Trauner, 1985). Similarly, the cognitive abnormalities of idiopathic basal ganglia calcification and Wilson's disease share the characteristics of subcortical dementia (Knehr & Bearn, 1956; Cummings *et al*, 1983).

Language

Compared with other areas of neuropsychological function, language is largely spared in the subcortical dementias. In Parkinson's disease, Huntington's disease, and PSP patients perform normally or manifest mild deficits in picture and object naming, but they lack the more severe disturbances of comprehension and the paraphasic abnormalities characteristic of the cortical dementias (Butters *et al*, 1978; Matison *et al*, 1982; Bayles & Tomoeda, 1983; Cummings *et al*, 1985; Globus *et al*, 1985; Maher *et al*, 1985). The few studies of Wilson's disease reveal relative preservation of vocabulary, whereas abstraction and conceptualisation abilities are compromised (Knehr & Bearn, 1956; Goldstein *et al*, 1968).

Summary and contrast with cortical dementias

Analysis of the neuropsychological profile of subcortical dementia allows the pattern of intellectual disturbances to be contrasted with the abnormalities manifested by patients with dementias involving predominantly the cerebral cortex (Table I). Subcortical dementias are characterized by psychomotor retardation, whereas the cortical dementias manifest normal psychomotor speed throughout most of the clinical course (Cummings & Benson, 1986). Memory disturbances are present in both cortical and subcortical dementias, but subcortical disorders have a prominent recall deficits and are benefited by clues and recognition tasks whereas the memory abnormalities in cortical dementias are a product of encoding failure and are aided little by recall facilitation strategies. Language abnormalities provide the most readily observable distinctions between cortical and subcortical dementias: subcortical conditions manifest no abnormalities or have mild impairments of confrontation naming and auditory comprehension, whereas cortical dementias evidence fluent paraphasic verbal output with severe anomia and moderate to severely impaired language comprehension (Cummings & Benson, 1983; Cummings *et al*, 1985). Visuospatial abilities are abnormal in both cortical and subcortical dementias. Alzheimer's disease patients have greater difficulty performing constructional tasks, and patients with subcortical dementias are more impaired on tests involving egocentric spatial operations such as map reading and judgement of vertical and horizontal axes (Proctor *et al*, 1964; Danta & Hilton, 1975; Boller *et al*, 1984; Brouwers *et al*, 1984). Abnormalities of abstraction and categorisation are present in both cortical and subcortical dementias

TABLE I
Contrasting features of cortical and subcortical dementias

Characteristics	*Subcortical dementia*	*Cortical dementia*
Neuropsychological features		
Severity	Mild to moderate throughout most of the course	More severe deficits earlier in the disease course
Speed of cognition	Slowed	Normal
Memory		
Short term	Recall partially facilitated by clues and recognition tasks	Encoding deficit; aided little by clues
Remote recall	No temporal gradient	In early stages, temporal gradient may be present
Language	Normal or mild anomia	Anomia, comprehension deficit, paraphasia
Visuospatial skills	Impaired; poor manipulation of egocentric space (map reading, judgement of horizontal and vertical)	Impaired; poor model copying
Cognition	Poor abstraction and categorization	Impaired early; late untestable
Neuropsychiatric features		
Personality	Apathy, irritability	Indifference, occasional disinhibition
Depression	Common	Uncommon
Mania	Infrequent	Absent
Psychosis	Common in some disorders, may have complex delusions	Common; simple delusions
Motor system		
Speech	Dysarthria	No dysarthria
Posture	Flexed or extended	Normal (flexed late)
Gait	Hypokinetic or hyperkinetic	Normal (until late)
Speed	Slow	Normal (until late)
Adventitious movements	Tremor, chorea, dystonia	None or myoclonus
Tone	Abnormal (hypotonic in choreic disorders; hypertonia in parkinsonian conditions)	Normal early; rigid or gegenhalten in later stages
Topography of pathologic changes	Most intense changes in striatum and thalamus	Frontal and temporo-parieto-occipital association cortex and hippocampus most involved
Neurochemical changes	*Huntington's disease*: decreased GABA, angiotensin converting enzyme, substance P, cholecystokinin-like immunoreactivity, and CAT	*Alzheimer's disease*: decreased CAT, somatostatin, and norepinephrine
	Parkinson's disease: decreased dopamine, noradrenalin, serotonin, methionine-enkephalin, CAT neurotensin, bombesin, cholcystokinin-immunoreactivity, GABA	
	PSP: decreased dopamine, variable loss of CAT	
Aetiologic disorders	Degenerative extrapyramidal syndromes, subcortical infarctions; subcortical infectious, metabolic, and neoplastic conditions	Alzheimer's disease, Pick's disease

but are more severe in the former. Thus, psychomotor retardation is most characteristic of subcortical dementias and aphasia is most indicative of a cortical dementing disease; other neuropsychological abilities are affected by both cortical and subcortical conditions, but their effects within these domains are often qualitatively distinguishable.

Detection and characterisation of the subcortical dementias depends on utilising techniques sensitive to the intellectual consequences of subcortical dysfunction. Previous failures to establish differences between cortical and subcortical dementia utilised simple mental status questionnaires insensitive to the distinguishing features of the different patterns of intellectual deterioration (Mayeux *et al*, 1983). Future investigations of the intellectual deficits of subcortical dementias should focus on the differences between individual subcortical disorders (e.g. Parkinson's disease *vs* Huntington's disease), the relationships among the individual components of the dementia syndromes (e.g. association of the memory, visuospatial, and cognitive abnormalities), and comparative studies of cortical and subcortical dementias.

Neuropsychiatric aspects

In addition to intellectual impairments, abnormalities of personality, mood, and reality testing are common in the subcortical dementias. Like the intellectual disturbances, the neuropsychiatric alterations are products of the subcortical anatomic and biochemical changes, providing insight into the contributions of these regions to motivation, mood, and emotional function (Cummings, 1985a).

Personality alterations

Wilson (1912) called attention to the personality alterations associated with hepatolenticular degeneration when he observed that the patients appeared "docile" and "childish". Albert *et al* (1974) noted that patients with PSP were apathetic or irritable and had brief outbursts of rage. Similar changes have been observed in patients with idiopathic Parkinson's disease. Patients are less involved in family and social affairs, initiate fewer interpersonal interactions, and are more content with inactivity. Minnesota Multiphasic Personality Inventory (MMPI) profiles of Parkinson's disease patients have shown elevations on scales indicative of depression, hypochondriasis, and schizophrenia-like thought (Beardsley & Puletti, 1971; Hoehn *et al*, 1976).

The behaviour of Huntington's disease patients is characterised by apathy, inertia, hostility, and irritability (Rosenbaum, 1941; Goodman *et al*, 1966; McHugh & Folstein, 1975; Mayeux, 1983). Caine & Shoulson (1983) studied 30 patients with Huntington's disease and found that 22 were apathetic and 11 lacked insight into the nature and consequences of their disability. Chronic dysthymia, anxiety, and intermittent explosive disorder were also observed. They noted that apathy and loss of insight were more frequent among patients in the more advanced stages of the illness. Dewhurst *et al* (1969) investigated 102 patients with Huntington's disease and found that, among the 68 patients for whom behavioural information was available, 44 suffered from anxiety or personality alterations in the prodromal period, and the frequency of neuropsychiatric alterations increased as the disease progressed. Thus, apathy and inertia are common features of subcortical disorders and a variety of conduct and personality changes have also been reported. Few quantitative studies of this aspect of behaviour have been undertaken, and there has been little attempt to establish correlations between the presence and degree of intellectual impairment and the behavioural alterations.

Depression

Depression has received the most systematic study of all non-cognitive alterations in subcortical disorders and was recognised by Albert *et al* (1974) and McHugh & Folstein (1975) to be a cardinal feature of subcortical dementia.

Some degree of depression has been identified in 37–89% of patients with idiopathic Parkinson's disease (Mindham, 1970; Brown & Wilson, 1972; Celesia & Wanamaker, 1972; Robins, 1976; Horn, 1974; Mayeux *et al*, 1981). Moderate to severe depression occurs in 35–50% of Parkinson's disease patients, and depression is significantly more common than among patients with other types of neurological disorders or comparably disabling medical conditions. The depression correlates imperfectly with the degree of motor impairment, suggesting that it is not merely a reaction to physical disability but is biologically linked to the underlying neuropathological changes. Depression is reported to occur more frequently among patients with intellectual impairment than among those without evidence of dementia (Mayeux *et al*, 1981, 1983).

Depression is also common in patients with Huntington's disease. Dewhurst *et al* (1969) reported that of 102 patients 42 were depressed, and Caine & Shoulson (1983) found that six of 24 patients had major depressive episodes, with an additional six

suffering from dysthymic syndromes. Schoenfeld *et al* (1984) noted that suicide is approximately four times more common among patients with Huntington's disease than among the general population, and is eight times greater in the 50–69 year-old age group.

Depression has also been observed among patients with PSP, subcortical infarctions, Wilson's disease, and spinocerebellar degenerations but prevalence studies are not available (Davies, 1949; Albert *et al*, 1974; Trimble & Cummings, 1981; Jackson *et al*, 1983; Janati & Apple, 1984; Cummings 1985a,c). In contrast, severe depression is uncommon in cortical degenerative processes such as Alzheimer's disease (Cummings & Benson, 1986).

Mania

Mania is less common than other neuropsychiatric conditions associated with subcortical disorders but occurs too frequently to be considered a chance association. McHugh & Folstein (1975) reported that two of eight patients with Huntington's disease had manic episodes. Dewhurst *et al* (1969) found that of 102 patients with Huntington's disease, 14 were euphoric, two had hypomania, and five had grandiose delusions.

Mania has also been observed in Wilson's disease and post-encephalitic Parkinson's disease (Fairweather, 1947; Pandy *et al*, 1981), and Cummings & Mendez (1984) drew attention to the fact that a majority of focal lesions producing secondary mania are located subcortically in hypothalamic and perithalamic regions.

Psychosis

Psychosis manifested by the endorsement of delusional beliefs is closely correlated with subcortical dysfunction and has been observed with unusual frequency among patients with Huntington's disease, post-encephalitic Parkinson's disease, Wilson's disease, idiopathic basal ganglia calcification, and spinocerebellar degenerations, as well as subcortical vascular, traumatic, and neoplastic lesions (Cummings, 1985a,c). The psychosis may precede the dementia or may occur concomitantly with it. In the series of Huntington's disease patients reported by Dewhurst *et al* (1969), 50% had delusions at the time of admission to hospital. Six of 30 Huntington's disease patients reported by Caine & Shoulson (1983) had schizophrenia-like, paranoid, or atypical psychoses. Of 46 patients reviewed by Rosenbaum (1941), 38 were delusional for some period during the course of this illness. Thus, when the entire course of the disease is taken into account, it appears that a majority of patients with Huntington's disease will manifest psychotic ideation.

Psychosis is uncommon in idiopathic parkinsonism except when induced by anticholinergic or dopaminergic agents but was reported in 17–57% of patients with post-encephalitic Parkinson's disease (Fairweather, 1947; Mindham, 1970; Celesia & Wanamaker, 1972; Crow *et al*, 1976). Likewise, approximately 50% of all reported patients with idiopathic basal ganglia calcification have a schizophrenia-like psychosis (Cummings *et al*, 1983), and psychosis has also been reported among patients with Wilson's disease, spinocerebellar degenerations, and subcortical neoplasms and infarctions (Jackson & Immerman, 1919; Davies, 1949; Shepherd, 1955; Malamud, 1967; Keddie, 1969; Trimble & Cummings, 1981; Cummings 1985b,c). Cummings (1985b), in a comparative study of delusions in a variety of neurological disorders, found that patients with cortical dementing illnesses (Alzheimer's disease) had more severe dementias and manifested simple paranoid misbeliefs, whereas patients with subcortical dementias had less severe intellectual alterations and tended to have complex, highly structured delusions.

Pathology and pathophysiology

Correlations between the phenomenology of subcortical dementia and the anatomic structures and biochemical systems involved have not been fully established, but preliminary information derived from pathoanatomic investigations allow a tentative formulation of the structural and biochemical alterations involved in these conditions.

Histopathologic alterations

The pathological anatomy of the extrapyramidal syndromes is well established. In Huntington's disease, the greatest pathological alterations involve the caudate nuclei where Golgi type II interneurons are preferentially lost. The putamen and thalamus manifest less severe alterations (Corseillis, 1976; Dom *et al*, 1976; Cummings & Benson, 1983).

Lewy bodies and neuronal loss are the histopathologic alterations characteristic of idiopathic Parkinson's disease. The changes are most intense in the substantia nigra, ventral tegmental area, and locus coeruleus; less intense or variable alterations occur in the nucleus basalis, caudate, putamen, globus pallidus, and cerebral cortex (Greenfield &

Bosanquet, 1953; Den Hartog Jager & Bethlem, 1960; Oppenheimer, 1976; Javoy-Agid & Agid, 1980; Whitehouse *et al*, 1983).

Progressive supranuclear palsy has its greatest impact on the structures of the mesencephalic–diencephalic junction including the red nuclei, subthalamic nuclei, globus pallidus, thalamus, substantia nigra, and cerebellar nuclei (Steele *et al*, 1969). In Wilson's disease, the putamen is most involved, and the caudate, subthalamic nuclei, red nuclei, and thalamus show less intense alterations (Wilson, 1912; Smith, 1976). The pathologic geography of the spinocerebellar degenerations is variable but routinely includes the cerebellum and brainstem, and in many cases alterations are detectable in the basal ganglia, substantia nigra, and thalamus (Greenfield, 1954; Oppenheimer, 1976). Patients with idiopathic calcification of the basal ganglia have dense perivascular calcific deposits in the caudate, putamen, globus pallidus, and cerebellar nuclei (Oppenheimer, 1976; Cummings *et al*, 1983). Thalamic degeneration involves primarily the anterior and dorsal thalamic nuclei with variable involvement of putamen, cerebal white matter, cerebral cortex, and inferior olives (Stern, 1939; Schulman, 1957; Katz *et al*, 1984). A similar distribution of lesions was present in one case of post-herpetic thalamic dementia (Pilleri *et al*, 1981); whereas one patient with sarcoid-related subcortical dementia had prominent granuloma formation in the hypothalamus, fornix, and infundibulum (Hier *et al*, 1983). Multi-infarct syndromes with subcortical dementia have had lesions concentrated in the basal ganglia and thalamus (Cummings & Benson, 1983; Graff-Radford *et al*, 1984; Guberman & Stuss, 1983). In summary, the disorders reported to produce subcortical dementia routinely involve the striatal nuclei and/or thalamus with more variable involvement of subthalamic nuclei, substantia nigra, red nuclei, locus coeruleus, cerebellar nuclei, and cerebral cortex (Benson & Cummings, 1985).

The extent and nature of cortical involvement associated with dementia in Parkinson's disease is controversial. Hakim & Mathieson (1979) and Boller *et al* (1980) found an increased number of senile plaques and neurofibrillary tangles in the cerebral cortex of demented Parkinson's disease patients and suggested that the dementia was secondary to co-occurring Alzheimer's disease. Ball (1984), however, found no increase in Alzheimer-type pathology among Parkinson's disease patients with dementia, and epidemiological studies suggest that the two diseases co-occur no more frequently than predicted by chance in an elderly population (Heston *et al*, 1981). As outlined above, the nature of the neuropsychological alterations occurring in most patients with Parkinson's disease are unlike those noted in Alzheimer's disease. Progress towards the resolution of these discrepancies depends on thorough documentation of neuropsychological deficits in Parkinson's patients and correlation with quantitative analysis of cortical and subcortical pathologic and neurochemical changes.

Investigations of the anatomical foundations of dementia have emphasised the possible role of the nucleus basalis of Meynert (NBM). Whitehouse *et al* (1981) documented atrophy of the NBM in Alzheimer's disease and suggested that loss of these cholinergic neurons and their cortical projections could account for the cholinergic deficit and the dementia of Alzheimer's disease. Later, Whitehouse *et al*, (1983) demonstrated that NBM is also atrophic in Parkinson's disease patients with dementia and suggested that the two types of dementia might have a similar pathophysiology. More recent studies show that NBM cell loss occurs in a number of neurological illnesses including Parkinson's disease patients that lack neuropathological features of Alzheimer's disease, Wernicke-Korsakoff syndrome, and PSP (Arendt *et al*, 1983; Nakano & Hirano, 1984; Tagliavini *et al*, 1984). These observations suggest that atrophy of NBM is a feature common to several dementing disorders, occurs in diseases with and without Alzheimer-type neuropathological changes, and has been identified in disorders with a variety of types of neurobehavioural alterations. Atrophy of NBM cannot as yet be correlated with any specific neuropsychological or neuropsychiatric syndrome. No atrophic changes are found in NBM in Huntington's disease or in post-encephalitic parkinsonism (Clark *et al*, 1983; Whitehouse *et al*, 1983).

Biochemical alterations

Intellectual ability is no less a product of the activity of neurotransmitter systems than of neuroanatomical structures. In some cases the effects of structural alterations may be mediated through changes in transmitter function; in others, the biochemical alterations and resultant mental status deficits may occur in the absence of overt anatomical pathology. Consideration of the consequences of loss of neurotransmitter function is particularly important in subcortical disorders because several major transmitter systems (e.g., dopamine, norepinephrine, acetylcholine, serotonin) have their cells of origin in subcortical nuclei and project via subcortical tracts to diencephalic and telencephalic regions (Anden *et al*, 1966; Mesulam, 1983).

In Huntington's disease the principal abnormality is a 50–90% reduction in γ-aminobutyric acid (GABA) and related enzymes in the striatum (Perry *et al*, 1973; Bird & Iversen, 1974). Substantial reductions have also been found in angiotensin converting enzyme, substance P, methionine-enkephalin, and cholecystokinin-like immunoreactivity (McGeer & McGeer, 1976; Arregui *et al*, 1977; Emson *et al*, 1980a; Emson *et al*, 1980b). Choline acetyltransferase (CAT) is variably reduced and other enzymes associated with metabolism of acetylcholine and of catecholamines are normal (Perry *et al*, 1973; Bird & Iversen, 1974; McGeer & McGeer, 1976). The neurotransmitter and neuromodulator deficits are confined to subcortical structures; cortical enzyme activities are normal. Likewise, neurotransmitter receptor studies have shown decreased muscarinic cholinergic and GABA binding in neostriatum, increased pallidal GABA binding, and normal cortical receptor function (Enna *et al*, 1976; Wastek & Yamamura, 1978; Penny & Young, 1982; Whitehouse *et al*, 1985). Thus, in Huntington's disease there is a preferential loss of GABA and a number of neuromodulators and related enzymes from subcortical structures, whereas neurochemical analyses of cerebral cortex (including the frontal lobe) reveal no abnormalities.

In idiopathic Parkinson's disease, the type and distribution of neurotransmitter alterations have been extensively studied. The most prominent and consistent abnormalities involve the dopaminergic system including dopamine, homovanillic acid, tyrosine hydroxylase, and dopadecarboxylase (Hornykiewicz, 1973). The dopamine losses are not confined to the basal ganglia but involve the midbrain ventral tegmental area, hypothalamus, and limbic structures as well (Price *et al*, 1978; Javoy-Agid *et al*, 1981, 1984). Less pronounced losses of dopamine and related metabolites have also been identified in the cerebral cortex (Scatton, 1982). Noradrenalin, serotonin, methionine–enkephalin, neurotensin, bombesin, and cholecystokinin immunoreactivity are also reduced in subcortical structures (Studler *et al*, 1982; Taquet *et al*, 1982; Scatton *et al*, 1983; Bissette *et al*, 1985). GABA and related enzymes have been found to be reduced in most but not all studies of patients with Parkinson's disease. Efforts to relate neurobehavioural alterations to these chemical changes have revealed significant correlations between impaired intellectual performance and decrease norepinephrine metabolites in the CSF (Mann *et al*, 1983; Stern *et al*, 1984); neuropsychological abnormalities also correlate with increased CSF homovanillic acid and acetylcholinesterase levels (Direnfeld *et al*, 1984); and depression is associated with decreased CSF 5-hydroxyindoleacetic acid, the principal metabolite of serotonin (Mayeux *et al*, 1984). A correlation has also been found between severity of dementia and reduction of neurotensin in the putamen as measured at autopsy (Bissette *et al*, 1985). Studies of cholinergic system enzymes have raised several questions. Some investigators found no difference in cholinergic enzyme levels between parkinsonian and control subjects (McGeer & McGeer, 1971, 1976; Lloyd *et al*, 1975). Perry and colleagues (1983) however, found reduced levels of CAT in the cortex of demented Parkinson's disease patients. The latter cases also had widespread senile plaques and neurofibrillary tangles and may have been suffering from dementia of the Alzheimer type. Similarly, Ruberg *et al* (1982) and Epelbaum *et al* (1983) found that demented Parkinson's disease patients had decreased cortical acetylcholinesterase, but these patients also had Alzheimer-type histopathology and low somatostatin levels characteristic of Alzheimer's disease. Such observations along with the histologic studies described above, suggest that a number of patients with Parkinson's disease have dementia of the Alzheimer type with typical Alzheimer-type histopathology and chemopathology, other groups have cortical cholinergic deficits without Alzheimer-type histopathological changes, or more restricted subcortical, pathological and neurochemical alterations (Gaspar & Gray, 1984). The frequency with which dementia syndromes are noted in Parkinson's disease patients and the differences between the neuropsychological deficits of Parkinson's disease and Alzheimer's disease suggest that dementia is not confined to parkinsonians with cortical abnormalities, although Alzheimer's disease may account for a majority of *severe* dementias occurring among parkinsonian patients.

The serendipidous discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a synthetic analogue of meperidine, produces the rapid onset of an irreversible form of parkinsonism has provided new insights into the biochemical basis of subcortical dementia (Ballard *et al*, 1985): MPTP produces a nearly pure hypodopaminergic state by selective destruction of dopaminergic neurons in the substantia nigra (Davis *et al*, 1979; Burns *et al*, 1983). Neuropsychological assessment of patients with MPTP-induced Parkinson's disease patients reveals abnormalities of attention and cognition consistent with subcortical dementia (Stern & Langston, 1985). These observations indicate that a pure dopamine deficiency is sufficient to produce subcortical dementia.

TABLE II
Characteristics of instrumental and fundamental functions

Characteristics	*Instrumental functions*	*Fundamental functions*
Neuropsychological activities	Language, memory, perceptual recognition, praxis, calculation	Timing, arousal, attention, motor programming, motivation, mood
Neuropsychological deficits	Aphasia, amnesia, agnosia, apraxia, acalculia	Slowing, forgetfulness, dilapidation of cognition, depression, apathy
Associated type of dementia	Cortical	Subcortical
Principal grey matter structures	Multi-layered cortex (neopallial association cortex and hippocampus)	Deep nuclei (basal ganglia, thalamus, rostral brainstem)
White matter connections	Discrete well myelinated intra- and interhemispheric tracts	More diffuse, shorter, less well myelinated projections
Organisational composition	Parallel connection of functional units; lateral dominance well developed	Serial connection of structures with overlapping functions; poorly lateralised
Phylogeny	Recent evolutionary acquisition, most well developed in humans	More primitive, present in triune structure of reptile brain
Ontogeny	Incompletely developed at birth, myelination and dendritic growth continue through childhood	Functional at birth or soon after
Major neurotransmitters	Acetylcholine	Dopamine, norepinephrine, serotonin, GABA, acetylcholine

Recently, the biochemical disturbances associated with PSP have been identified. There is a marked nigrostriatal dopamine deficiency with preserved mesocortical and mesolimbic dopamine levels (Kish *et al*, 1985; Ruberg *et al*, 1985). Ruberg and colleagues (1985) found 50% reductions of CAT in subcortical structures and a 20% reduction in the frontal cortex, whereas Kish *et al* (1985) found no CAT deficiencies even in two patients with severe dementia. Noradrenalin, serotonin, GABA, and aspartic acid levels were normal (Kish *et al*, 1985). Thus, PSP and its concomitant dementia correlate best with reduced dopamine levels and show little relation to cortical cholinergic system deficits.

Other subcortical disorders have not been adequately characterised neurochemically, but sufficient information is available to suggest that hypokinetic-rigid syndromes predictably reflect striatal dopamine deficiency (Hornykiewicz, 1973), and the dementias accompanying these disorders can be attributed to the dopamine loss (Bachman & Albert, 1984).

Metabolic investigations

Recent investigations using positron emission tomography (PET) and cerebral blood flow (CBF) techniques have added a new dimension to understanding the pathophysiology of subcortical dementia. Studies of Huntington's disease patients using PET reveal a distinctive pattern of metabolism characterised by decreased activity of caudate and putamen and normal cerebral metabolism (Kuhl *et al*, 1982). This pattern correlates well with the pathological and neurochemical findings in identifying impaired subcortical function and preserved cortical function. It contrasts with the cortical hypometabolism and relatively intact metabolic function of subcortical regions observed in Alzheimer's disease (Benson *et al*, 1983; Foster *et al*, 1984).

Studies of hemiparkinsonism with PET reveal decreased metabolism in the putamen and globus pallidus contralateral to the parkinsonian manifestations (Garnett *et al*, 1984; Martin *et al*, 1984). Studying bilateral parkinsonism, Kuhl *et al* (1984) found a generalised decrease in brain metabolism involving cortical and subcortical structures. Five of these patients were restudied 3–4 years later: one with severe dementia exhibited a PET pattern characteristic of Alzheimer's disease, three of the remaining patients had more modest dementias and showed an 18–40% decrease in cortical metabolic activity in a pattern unlike that of Alzheimer's disease. Cerebral cortical blood flow is also decreased

in Parkinson's disease, but the magnitude of CBF reduction shows no correlation with the presence or severity of intellectual deterioration (Lavy *et al*, 1979; Bes *et al*, 1983; Globus *et al*, 1985). This lack of association suggests that the two functions are separately mediated, with subcortical dysfunction (not reflected in CBF studies) accounting for much of the dementia. Positron emission tomography studies in PSP have demonstrated diminished metabolism in the frontal lobes (D'Antona *et al*, 1985). Metabolic studies of other subcortical disorders with dementia are not yet available; when completed and correlated with the type and extent of neuropsychological abnormality, such investigations should broaden understanding of the physiology of subcortical dysfunction and its intellectual consequences.

Mechanisms of subcortical dementia

Investigations of the neuropsychology, anatomy, and biochemistry of subcortical disorders have provided sufficient information on which to base á tentative explanation of how subcortical dysfunction results in a dementia syndrome. Subcortical structures are not merely relay nuclei linking the cerebral cortex with brainstem and spinal cord; rather they have important analytic and synthetic functions that modify, focus, and direct incoming and outgoing impulses. The thalamus mediates sensory, cognitive, and limbic activities through specific thalamocortical circuits and establishes cortical arousal through non-specific reticuothalamocortical projections (Walker, 1937; Jasper, 1949; Krieg, 1966). Arousal, activation, and attention are dependent on the integrity of these connections. The striatal nuclei receive afferents from all cerebral cortical areas, and there are particularly dense connections between the frontal lobe cortex and the caudate nucleus (Kemp & Powell, 1970; Graybiel & Ragsdale, 1979). These projections provide an anatomic basis for the similarities between subcortical dementias and of frontal lobe syndromes such as perseveration, impersistence, distractability, difficulty shifting sets, abnormal verbal fluency, poor abstraction, impaired categorisation, and difficulty with strategy generation and problem solving (Johnson *et al*, 1968). Terms such as 'frontal systems disorder', 'frontal-subcortical systems disorder', or 'frontal-subcortical dementia' are acceptable alternatives to 'subcortical dementia' and might more accurately reflect the realm of anatomic, metabolic, and neurochemical dysfunction found in this group of conditions.

Important links have also been discovered between the basal ganglia and the limbic system. Limbic structures have largely unreciprocated projections to nearly all parts of the striatum creating a limbic-striatal system that utilises dopamine as an important neurotransmitter (Nauta & Domesick, 1978, 1981; Nauta, 1982; Iversen, 1984). These connections subserve motivation, mood, and aspects of reality testing, and disturbances of such functions contribute to the apathy, mood abnormalities, and psychoses observed in subcortical disorders.

Conceptually, cortical and subcortical abilities can be categorised as instrumental functions and fundamental functions, respectively (Table II) (Albert, 1978). Instrumental functions include language, praxis, perceptual recognition, memory, and calculation. These faculties depend on the integrity of focal cortical regions and are subject to interruption by localised cortical lesions or by disconnection of relevant cortical-to-cortical white matter tracts. Abnormalities of instrumental functions produce aphasia, apraxia, agnosia, amnesia, and acalculia — deficits associated with the cortical dementias. Available neuropsychological instruments are most sensitive to detection of these cortical disturbances. Instrumental abilities are the most highly evolved of human activities and depend on phylogenetically recent and ontogenetically late developing structures (Yakovlev, 1948). Organisationally, instrumental abilities involve discrete cortical areas with specialised functions connected by well myelinated intra- and interhemispheric white matter tracts. Acetylcholine plays an essential role in cortical neurotransmission.

Fundamental functions, on the other hand, include arousal, activation, attention, sequencing, motivation, and mood. These functions are much less discreetly organised and involve subcortical nuclei (basal ganglia and thalamus) that interconnect widely with the cerebral cortex. The major projections are reciprocal connections with the frontal lobe and afferent connections from the limbic system. Organisationally, subcortical nuclei are connected by shorter white matter projections, which are not so well myelinated (Yakovlev, 1948). A variety of neurotransmitters are utilised including dopamine, serotonin, noradrenalin, GABA, acetylcholine, and others. Fundamental functions are crucial to survival and emerge early in phylogenetic and ontogenetic development. Dysfunction of these fundamental abilities produces the cardinal features of subcortical dementia including slowed information processing, dilapidation of memory and cognition, and disturbances of mood and motivation. Direct neuropsychological assessment of fundamental functions is difficult, and subcortical dysfunction must often be inferred from the

behaviour of the patient and the pattern of effects on the more accessible instrumental abilities. The movement abnormalities that frequently accompany the subcortical dementias (rigidity, chorea, athetosis, dystonia, bradykinesia) are not coincidental but reflect the dependence of the extrapyramidal motor system on anatomic structures, neurotransmitters, and neurophysiological activities that also mediate fundamental functions.

Further investigation is needed to refine, modify, and extend the concept of subcortical dementia. Sufficient information is available, however, to demonstrate that subcortical dementia is characterised by a clinical syndrome that is identifiable and can be distinguished from the syndrome of cortical dementia. The clinical features of subcortical dementia correlate with dysfunction of striatum and thalamus and of specific neurotransmitter systems. The characteristics of subcortical dementia reflect disruption of fundamental functions associated with a phylogenetically and ontogenetically less advanced level of neurological organisation. Fundamental functions are essential components of human mental abilities, and their compromise has grievous consequences for human thought and emotion.

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References

ALBERT, M. L. (1978) Subcortical dementia. In *Alzheimer's Disease: Senile Dementia and Related Disorders* (eds R. Katzman, R. D. Terry, & K. L. Bick). New York: Raven Press.

——, FELDMAN, R. G. & WILLIS, A. L. (1974) The 'subcortical dementia' of progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, **37**, 121–130.

ALBERT, M. S., BUTTERS, N. & BRANDT, J. (1981) Patterns of remote memory in amnesic and demented patients. *Archives of Neurology*, **38**, 495–500.

ANDEN, N-E., DALSTROM, A., FUXE, K., LARSSON, K., OLSON, L. & UNGERSTEDT, U. (1966) Ascending monoamine neurons to the diencephalon. *Acta Physiologica Scandinavia*, **67**, 313–326.

ARENDT, T., BIGL, V., ARENDT, A. & TENNSTEDT, A. (1983) Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis, agitans, and Korsakoff's disease. *Acta Neuropathologica*, **61**, 101–108.

ARREGUI, A., BENNETT, J. P., JR., BIRD, E. D., YAMAMURA, H. I., IVERSEN, L. L. & SNYDER, S. H. (1977) Huntington's chorea: selective depletion of activity of angiotensin converting enzyme in the corpus striatum. *Annals of Neurology*, **2**, 294–298.

BACHMAN, D. L. & ALBERT, M. L. (1984) The dopaminergic syndromes of dementia. In *Brain Pathology* (eds G. Pilleri & F. Tagliavini). Bern, Switzerland: Brain Anatomy Institute.

BALL, M. J. (1984) The morphological basis of dementia in Parkinson's disease. *Canadian Journal of Neurological Science*, **11**, 180–184.

BALLARD, P. A., TETRAD, J. W., & LANGSTON, W. (1985) Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): seven cases. *Neurology*, **35**, 949–956.

BALES, K. A. & TOMOEDA, C. K. (1983) Confrontation naming impairment in dementia. *Brain and Language*, **19**, 98–114.

BEARDSLEY, J. V. & PULETTI, F. (1971) Personality (MMPI) and cognitive (WAIS) changes after levodopa treatment. *Archives of Neurology*, **25**, 145–150.

BENSON, D. F. & CUMMINGS, J. L. (1985) Subcortical dementia. In *Brain Pathology*, (eds G. Pilleri & F. Tagliavini). Bern, Switzerland: Brain Anatomy Institute.

——, KUHL, D. E., HAWKINS, R. A., PHELPS, M. E., CUMMINGS, J. L. & TSAI, S. Y. (1983) The fluoro-deoxyglucose ^{18}F scan in Alzheimer's disease and multi-infarct dementia. *Archives of Neurology*, **40**, 711–714.

BES, A., GUELL, A., FABRE, N., DUPUI, Ph, VICTOR, G. & GERAND, G. (1983) Cerebral blood flow studied by xenon-133 inhalation technique in parkinsonism: loss of hyperfrontal pattern. *Journal of Cerebral Blood Flow and Metabolism*, **3**, 33–37.

BIRD, E. D. & IVERSEN, L. L. (1974) Huntington's chorea: post-mortum measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in basal ganglia. *Brain*, **97**, 457–472.

BISSETTE, G., NEMEROFF, C. B., DECKER, M. W., KIZER, J. S., AGID, Y. & JAVOY-AGID, F. (1985) Alterations in regional brain concentrations of neurotensin and bombesin in Parkinson's disease. *Annals of Neurology*, **17**, 324–328.

BOLL, T. J., HEATON, R. & REITAN, R. M., (1974) Neuropsychological and emotional correlates of Huntington's chorea. *Journal of Nervous and Mental Disease*, **158**, 61–69.

BOLLER, F., MIZUTANI, T., ROESSMANN, U. & GAMBETTI, P. (1980) Parkinson disease, dementia, and Alzheimer disease: clinicopathological correlations. *Annals of Neurology*, **7**, 329–335.

——, PASSAFIUME, D., KEEFE, N. C., ROGERS, K., MORROW, L. & KIM, Y. (1984) Visuospatial impairment in Parkinson's disease. *Archives of Neurology*, **41**, 485–490.

BOWEN, F. P., KAMIENNY, R. S., BURNS, M. M. & YAHR, M. D. (1975) Parkinsonism: effects of levodopa treatment on concept formation. *Neurology*, **25**, 701–704.

BROUWERS, P., COX, C., MARTIN, A., CHASE, T. & FEDIO, P. (1984) Differential perceptual-spatial impairment in Huntington's and Alzheimer's dementias. *Archives of Neurology*, **41**, 1073–1076.

BROWN, G. L. & WILSON, W. P. (1972) Parkinsonism and depression. *Southern Medical Journal*, **65**, 540–545.

BURNS, R. S., CHIUEH, C. C., MARKEY, S. P., EBERT, M. H., JACOBOWITZ, D. M. & KOPIN, I. J. (1983) A primate model of parkinsonism: selective destruction of dopaminergic neurons in pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proceedings of the National Academy of Science*, **80**, 4546–4550.

BUTTERS, N., TARLOW, S., CERMAK, L. S. & SAX, D. (1976) A comparison of the information processing deficits of patients with Huntington's chorea and Korsakoff's syndrome. *Cortex*, **12**, 134–144.

——, SAX, D., MONTGOMERY, K. & TARLOW, S. (1978) Comparison of the neuropsychological deficits associated with early and advanced Huntington's disease. *Archives of Neurology*, **35**, 585–589.

CAINE, E. D., EBERT, M. H. & WEINGARTNER, H. (1977). An outline for the analysis of dementia. *Neurology*, **27**, 1087–1092.

——, & SHOULSON, I. (1983) Psychiatric syndromes in Huntington's disease. *American Journal of Psychiatry*, **140**, 728–733.

CARTER, H. R. & SUKAVAJANA, C. (1956) Familial cerebello-olivary degeneration with late development of rigidity and dementia. *Neurology*, **6**, 876–884.

CELESIA, G. G. & WANAMAKER, W. M. (1972) Psychiatric disturbances in Parkinson's disease. *Diseases of the Nervous System*, **33**, 577–583.

CHANDLER, J. H. & BEBIN, J. (1956) Hereditary cerebellar ataxia. *Neurology*, **6**, 187–195.

CLARK, A. W., PARHEAD, I. M., FOLSTEIN, S. E., WHITEHOUSE, P. J., HEDREEN, J. C., PRICE, D. L. & CHASE, G. A. (1983) The nucleus basalis in Huntington's disease. *Neurology*, **33**, 1262–1267.

CORSELLIS, J. A. N. (1976) Ageing and the dementias. In *Greenfield's Neuropathology* (eds. W. Blackwood & J. A. N. Corsellis). Chicago: Yearbook Medical Publishers.

CROW, T. J., JOHNSTONE, E. C. & MCCLELLAND, H. A. (1976) The coincidence of schizophrenia and parkinsonism: some neurochemical implications. *Psychological Medicine*, **6**, 227–233.

CUMMINGS, J. L. (1985a) Psychosomatic aspects of movement disorders. In *Interface Between Neurology and Psychiatry* (ed. M. R. Trimble). Karger: New York.

—— (1985b) Organic delusions: phenomenology, anatomical correlations, and review. *British Journal of Psychiatry*, **146**, 184–197.

—— (1985c) *Clinical Neuropsychiatry*, New York: Grune & Stratton.

—— & BENSON, D. F. (1983) *Dementia: A Clinical Approach*. Boston: Butterworths.

—— & —— (1984) Subcortical dementia: review of an emerging concept. *Archives of Neurology*, **41**, 874–879.

—— & —— (1986). Dementia of the Alzheimer type: an inventory of diagnostic clinical features. *Journal of the American Geriatrics Society*, **34**, 12–19.

——, GOSENFELD, L., HOULIHAN, J. & MCCAFFREY, T. (1983) Neuropsychiatric manifestations of idiopathic calcification of the basal ganglia: case report and review. *Biological Psychiatry*, **18**, 591–601.

—— & MENDEZ, M. F. (1984) Secondary mania with focal cerebrovascular lesions. *American Journal of Psychiatry*, **141**, 1084–1087.

——, Benson, D. F., Hill, M. A. & Read, S. (1985) Aphasia in dementia of the Alzheimer type. *Neurology*, **35**, 394–397.

DANIA, G. & HILTON, R. C. (1975) Judgement of the visual vertical and horizontal in patients with parkinsonism. *Neurology*, **25**, 43–47.

D'ANTONA, R., BARON, J. C., SAMSON, Y., SERDARI, M., VIADER, F., AGID, Y. & CAMBIER, J. (1985) Frontal cortex hypometabolism detected by positron tomography in patients with progressive supranuclear palsy. *Brain*, **108**, 785–799.

DAVIES, D. L. (1949) Psychiatric changes associated with Friedreich's ataxia. *Journal of Neurology, Neurosurgery, and Psychiatry*, **12**, 246–250.

DAVIES, G. C., WILLIAMS, A. C., MARKEY, S. P., EBERT, M. H., CAINE, E. D., REICHERT, C. M. & KOPIN, I. J. (1979) Chronic parkinsonism secondary to intravenous injection of mepiridine analogues. *Psychiatry Research*, **1**, 249–254.

DAVIES, P. H., BERGERON, C. & MCLACHLAN, D. R. (1985) Atypical presentation of progressive supranuclear palsy. *Annals of Neurology*, **17**, 337–343.

DEN HARTOG JAGER, W. A. & BETHLELM, J. (1960) The distribution of Lewy bodies in the central and autonomic nervous systems in idiopathic paralysis agitans. *Journal of Neurology, Neurosurgery, and Psychiatry*, **23**, 283–290.

DEWHURST, K., OLIVER, J., TRICK, K. L. K. & MCKNIGHT, A. L. (1969) Neuropsychiatric aspects of Huntington's disease. *Confinia Neurologica*, **31**, 258–268.

DIRENFELD, L. K., ALBERT, M. L., VOLICER, L., LANGLAIS, P. J., MARQUIS, J. & KAPLAN, E. (1984) Parkinson's disease: the possible relationship of laterality to dementia and neurochemical findings. *Archives of Neurology*, **41**, 935–941.

DOM, R., MALFROID, M. & BARO, F. (1976) Neuropathology of Huntington's chorea. Studies of the ventrobasal complex of the thalamus. *Neurology*, **26**, 64–68.

EMSON, P. C., ARREGUI, A., CLEMENT-JONES, V., SANDBERG, B. E. B. & ROSSOR, M. (1980a) Regional distribution of methionine-enkephalin and substance P-like immunoreactivity in normal human brain and in Huntington's disease. *Brain Research*, **199**, 147–160.

——, REHFELD, J. F., LANGEVIN, H. & ROSSOR, M. (1980b) Reduction in cholecystokinin-like immunoreactivity in the basal ganglia in Huntington's disease. *Brain Research*, **198**, 497–500.

ENNA, S. J., BIRD, E. D., BENNETT, J. P., JR., BYLUND, D. B., YAMAMURA, H. I., IVERSEN, L. L. & SNYDER, S. H. (1976) Huntington's chorea: changes in neurotransmitter receptors in brain. *New England Journal of Medicine*, **294**, 1305–1309.

EPELBAUM, J., RUBERG, M., MOYSE, E., JAVOY-AGID, F., DUBOIS, B. & AGID, Y. (1983) Somatostatin and dementia in Parkinson's disease. *Brain Research*, **278**, 376–379.

EVARTS, E. V., TERAVAINEN, H. & CALNE, D. B. (1981) Reaction time in Parkinson's disease. *Brain*, **104**, 167–186.

FAIRWEATHER, D. S. (1947) Psychiatric aspects of the post-encephalitic syndrome. *Journal of Mental Science*, **93**, 201–254.

FISK, J. D., GOODALE, M. A., BURKHART, G. & BARNETT, H. J. M. (1982) Progressive supranuclear palsy: the relationship between ocular motor dysfunction and psychological test performance. *Neurology*, **32**, 698–705.

FOSTER, N. L., CHASE, T. N., MANSI, L., BROOKS, R., FEDIO, P., PATRONAS, N. T. & DI CHIRO, G. (1984) Cortical abnormalities in Alzheimer's disease. *Annals of Neurology*, **16**, 649–654.

FREEDMAN, M., RIVORIA, P., BUTTERS, N., SAX, D. S. & FELDMAN, R. G. (1984) Retrograde amnesia in Parkinson's disease. *Canadian Journal of Neurological Science*, **11**, 297–301.

GAINOTTI, G., CALTAGIRONE, C., MASULLO, C. & MICELI, G. (1980) Patterns of neuropsychologic impairment in various diagnostic groups of dementia. In *Aging of the Brain and Dementia* (eds. L. Amaducci, A. N. Davison, & P. Antuono). New York: Raven Press.

GASPAR, P. & GRAY, F. (1984) Dementia in idiopathic Parkinson's disease. *Acta Neuropathologica*, **64**, 43–52.

GARNETT, E. S., NAHMIAS, C. & FIRNAU, G. (1984) Central dopaminergic pathways in hemiparkinsonism examined by positron emission tomography. *Canadian Journal of Neurological Science*, **11**, 174–179.

GLOBUS, M., MILDWORF, B. & MELAMED, E. (1985) Cerebral blood flow and cognitive impairment in Parkinson's disease. *Neurology*, **35**, 1135–1139.

GOLDSTEIN, N. P., EWART, J. C., RANDALL, R. V. & GROSS, J. B. (1968) Psychiatric aspects of Wilson's disease (hepatolenticular degeneration): results of psychometric tests during long-term therapy. *American Journal of Psychiatry*, **124**, 1555–1561.

GOODMAN, R. M., HALL, C. L., JR., TERANGO, L., PERINE, G. A., JR. & ROBERTS, P. L. (1966) Huntington's chorea. A multidisciplinary study of affected parents and first generation offspring. *Archives of Neurology*, **15**, 345–355.

GRAFF-RADFORD, N. R., ESLINGER, P. J., DAMASIO, A. R. & YAMADA, T. (1984) Nonhemorrhagic infarction of the thalamus: behavioral, anatomic, and physiologic correlates. *Neurology*, **34**, 14–23.

GRAYBIEL, A. M. & RAGSDALE, C. W. JR. (1979) Fiber connections of the basal ganglia. *Progress in Brain Research*, **51**, 239–283.

GREENFIELD, J. G. (1954) *The Spinocerebellar Degenerations*, Oxford: Blackwell Scientific Publications.

—— & BOSANQUET, F. D. (1953) The brainstem lesions in parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, **16**, 223–226.

GUBERMAN, A. & STUSS, D. (1983) The syndrome of bilateral paramedian thalamic infarction. *Neurology*, **33**, 540–546.

HAKIM, A. M. & MATHIESON, G. (1979) Dementia in Parkinson disease: a neuropathologic study. *Neurology*, **29**, 1209–1214.

HALGIN, R., RIKLAN, M. & MISIAK, H. (1977) Levodopa, parkinsonism, and recent memory. *Journal of Nervous and Mental Disease*, **164**, 268–272.

HART, R. P., KWENTUS, J. A., LESHNER, R. T. & FRAZIER, R. (1985) Information processing speed in Friedreich's ataxia. *Annals of Neurology*, **17**, 612–614.

HESTON, L. L. (1981) Genetic studies of dementia: with emphasis on Parkinson disease and Alzheimer's neuropathology. In *The Epidemiology of Dementia* (eds J. A. Mortimer & L. M. Schuman). New York: Oxford University Press.

HIER, D. B., THOMAS, C. & SHINDLER, A. G. (1983) A case of subcortical dementia due to sarcoidosis of the hypothalamus and fornices. *Brain and Cognition*, **2**, 189–198.

HOEHN, M. M., CROWLEY, T. J. & RUTLEDGE, C. O. (1976) Dopamine correlates of neurological and psychological status in untreated parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, **39**, 941–951.

HORN, S. (1974) Some psychological factors in parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, **37**, 27–31.

HORNE, D. J. DEL. (1971) Performance on delayed response tasks by patients with parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, **34**, 192–194.

HORNYKIEWICZ, O. (1973) Parkinson's disease: from brain homogenate to treatment. *Federation Proceedings*, **32**, 183–190.

IVERSEN, S. D. (1984) Recent advances in the anatomy and chemistry of the limbic system. In *Psychopharmacology of the Limbic System* (eds M. R. Trimble & E. Zarifian). New York: Oxford University Press.

JACKSON, J. A. & IMMERMAN, S. L. (1919) A case of pseudo-sclerosis associated with a psychosis. *Journal of Nervous and Mental Disease*, **49**, 5–13.

——, Jankovic, J. & Ford, J. (1983) Progressive supranuclear palsy: clinical features and response to treatment in 16 patients. *Annals of Neurology*, **13**, 273–278.

JANATI, A. & APPEL, A. R. (1984) Psychiatric aspects of progressive supranuclear palsy. *Journal of Nervous and Mental Disease*, **172**, 85–89.

JASPER, H. (1949) Diffuse projection systems: the integrative action of the thalamic reticular system. *Electroencephalography and Clinical Neurophysiology*, **1**, 403–420.

JAVOY-AGID, F. & AGID, Y. (1980) Is the mesocortical dopaminergic system involved in Parkinson disease? *Neurology*, **30**, 1326–1330.

——, TAQUET, H., PLOSKA, A., CHERIF-ZAHAR, C., RUBERG, M. & AGID, Y. (1981) Distribution of catecholamines in the ventral mesencephalon of human brain with special reference to Parkinson's disease. *Journal of Neurochemistry*, **36**, 2101–2105.

——, RUBERG, M., PIQUE, L., BERTAGNA, X., TAQUET, H., STUDLER, J. M., CESSELIN, F., EPELBAUM, J. & AGID, Y. (1984) Biochemistry of the hypothalamus in Parkinson's disease. *Neurology*, **34**, 672–675.

JOHNSON, T. N., ROSVOLD, H. E. & MISHKIN, M. (1968) Projections from behaviorally-defined sections of the prefrontal cortex to the basal ganglia, septum, and diencephalon of the monkey. *Experimental Neurology*, **21**, 20–34.

JOSIASSEN, R. C., CURRY, L., ROEMER, R. A., DEBEASE, C. & MANCALL, E. L. (1982) Patterns of intellectual deficit in Huntington's disease. *Journal of Clinical Neuropsychology*, **4**, 173–183.

KATZ, A., NASEEM, A., HOROUPIAN, D. S., ROTHNER, A. D. & DAVIES, P. (1984) Familial multisystem atrophy with possible thalamic dementia. *Neurology*, **34**, 1213–1217.

KEDDIE, K. M. G. (1969) Hereditary ataxia presumed to be of the Menzel type, complicated by paranoid psychosis, in a mother and two sons. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 82–87.

KEMP, J. M. & POWELL, T. P. S. (1970) The cortico-striate projection of the monkey. *Brain*, **93**, 525–546.

KIMURA, D., BARNETT, H. J. M. & BURKHART, G. (1981) The psychological test pattern in progressive supranuclear palsy. *Neuropsychologia*, **2**, 301–306.

KISH, S. J., CHANG, L. J., MIRCHANDANI, L., SHANNAK, K. & HORNYKIEWICZ, O. (1985) Progressive supranuclear palsy: relationship between extrapyramidal disturbances, dementia, and brain neurotransmitter markers. *Annals of Neurology*, **18**, 530–536.

KNEHR, C. A. & BEARN, A. G. (1956) Psychological impairment in Wilson's disease. *Journal of Nervous and Mental Disease*, **124**, 251–255.

KRIEG, W. J. S. (1966) Thalamic afferents to the frontal lobe: of the macaque. *Journal of Neurology*, **5**, 317–329.

KUHL, D. E., PHELPS, M. E., MARKHAM, C. H., METTER, E. J., RIEGE, W. H. & WINTER, J. (1982) Cerebral metabolism and atrophy in Huntington's disease determined by ^{18}FDG and computed tomographic scan. *Annals of Neurology*, **12**, 425–434.

——, METTER, E. J. & RIEGE, W. H. (1984) Patterns of local cerebral glucose utilization determined in Parkinson's disease by the ^{18}F fluorodeoxyglucose method. *Annals of Neurology*, **15**, 411–424.

LAVY, S., MALAMED, E., COOPER, G. BENTIN, S. & RINOT, Y. (1979) Regional cerebral blood flow in patients with Parkinson's disease. *Archives of Neurology*, **36**, 344–348.

LEES, A. J. & SMITH, E. (1983) Cognitive deficits in the early stages of Parkinson's disease. *Brain*, 106, 257–270.

LLOYD, K. G. & HORNYKIEWICZ, O. (1973) L-glutamic acid decarboxylase in Parkinson's disease: effect of L-dopa therapy. *Nature*, **243**, 521–523.

——, MOHLER, H., HEITZ, PH. & BARTHOLINI, G. (1975) Distribution of choline acetyltransferase and glutamate decarboxylase within the substantia nigra and in other brain regions from control and parkinsonian patients. *Journal of Neurochemistry*, **25**, 789–795.

MAHER, E. R., SMITH, E. M. & LEES, A. J. (1985) Cognitive deficits in the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Journal of Neurology, Neurosurgery, and Psychiatry*, **48**, 1234–1239.

MALAMUD, N. (1967) Psychiatric disorders with intracranial tumors of the limbic system. *Archives of Neurology*, **17**, 113–123.

MANN, J. J., STANLEY, M., KAPLAN, R. D., SWEENEY, J. & NEOPHYTIDIES, A. (1983) Central catecholamine metabolism *in vivo* and the cognitive and motor deficits in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **34**, 209–218.

MARSH, G. G., MARKHAM, C. M. & ANSEL, R. (1971) Levodopa's awakening effect on patients with parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, **34**, 209–218.

MARTIN, W. R. W., BECKMAN, J. H., CALNE, D. B., ADAM, M. J., HARROP, R., ROGERS, J. G., RUTH, T. J., SAYRE, C. I. & PATE, B. D. (1984) Cerebral glucose metabolism in Parkinson's disease. *Canadian Journal of Neurological Science*, **11**, 169–173.

MARTONE, M., BUTTERS, N., PAYNE, M., BECKER, J. T. & SAX, D. S. (1984) Dissociations between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology*, **41**, 965–970.

MATISON, R., MAYEUX, R., ROSEN, J. & FAHN, S. (1982) "Tip-of-the-tongue" phenomenon in Parkinson's disease. *Neurology*, **32**, 567–570.

MAYEUX, R. (1983) Emotional changes associated with basal ganglia disorders. In *Neuropsychology of Human Emotion* (eds K. M. Heilman & P. Satz). New York: The Guildford Press.

——, STERN, Y., ROSEN, J. & LEVENTHAL, J. (1981) Depression, intellectual impairment, and Parkinson's disease. *Neurology*, **31**, 645–650.

——, ——, —— & BENSON, D. F. (1983) Is 'subcortical dementia' a recognizeable clinical entity? *Annals of Neurology*, **14**, 278–283.

——, ——, COTE, L. & WILLIAMS, B. W. (1984) Altered serotonin metabolism in depressed patients with Parkinson's disease. *Neurology*, **34**, 642–646.

MCGEER, P. L. & MCGEER, E. G. (1971) Cholinergic enzyme systems in Parkinson's disease. *Archives of Neurology*, **25**, 265–268.

—— & —— (1976) Enzymes associated with the metabolism of catecholamines, acetylcholine and GABA in human controls and patients with Parkinson's disease and Huntington's chorea. *Journal of Neurochemistry*, **26**, 65–76.

—— & —— Wada, J. A. & Jung, E. (1971) Effects of globus pallidus lesions and Parkinson's disease on brain glutamic acid decarboxylase. *Brain Research*, **32**, 425–431.

McHugh, P. R. & Folstein, M. F. (1975) Psychiatric syndromes of Huntington's chorea: a clinical and phenomenologic study. In *Psychiatric Aspects of Neurologic Disease* (eds D. F. Benson & D. Blumer). New York: Grune & Stratton.

Mesulam, M-M., Mufson, E. J., Levey, A. I. & Wainer, B. H. (1983) Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *Journal of Comparative Neurology*, **214**, 170–197.

Mindham, R. H. S. (1970) Psychiatric symptoms in parkinsonism. *Journal of Neurology, Neurosurgery, and Psychiatry*, **33**, 188–191.

Monfort, J. C., Javoy-Agid, F., Hauw, J. J., Dubois, B. & Agid, Y. (1985) Brain glutamate decarboxylase in Parkinson's disease with particular reference to a premortem severity index. *Brain*, **108**, 301–313.

Mortimer, J. A., Pirozzolo, F. J., Hansch, E. C. & Webster, D. D. (1982) Relationship of motor symptoms to intellectual deficits in Parkinson's disease. *Neurology*, **32**, 133–137.

Nakano, H. & Hirano, A. (1984) Parkinson's disease: neuron loss in the nucleus basalis without concomitant Alzheimer's disease. *Annals of Neurology*, **15**, 415–418.

Nauta, W. J. H. (1982) Limbic innervation of the striatum. In *Gilles de la Tourette Syndrome* (eds A. J. Friedhoff & T. N. Chase). New York: Raven Press.

—— & Domesick, V. B. (1978) Crossroads of limbic and striatal circuitry: hypothalamo-nigral connections. In *Limbic Mechanisms* (eds K. E. Livingston & O. Hornykiewicz). New York: Plenum Press.

—— & —— (1981) Ramifications of the limbic system. In *Psychiatry and the Biology of the Human Brain* (ed. S. Matthysse). New York: Elsevier/North-Holland.

Oppenheimer, D. R. (1976) Diseases of the basal ganglia, cerebellum and motor neurons. In *Greenfield's Neuropathology* (eds W. Blackwood & J. A. N. Corsellis). Chicago: Yearbook Medical Publishers.

Pandey, R. S., Sreenivas, K. N., Patih, N. M. & Swamy, H. S. (1981) Dopamine-B-hydroxylase in a patient with Wilson's disease and mania. *American Journal of Psychiatry*, **138**, 1628–1629.

Penny, J. B., jr. & Young, A. B. (1982) Quantitative autoradiography of neurotransmitter receptors in Huntington's disease. *Neurology*, **32**, 1391–1395.

Perry, R. H., Tomlinson, B. E., Candy, J. M., Blessed, G., Foster, J. F., Bloxham, C. A. & Perry, E. R. (1983) Cortical cholinergic deficit in mentally impaired parkinsonian patients. *Lancet*, **2**, 789–790.

Perry, T. L., Hansen, S. & Kloster, M. (1973) Huntington's chorea: deficiency of γ-aminobutyric acid in brain. *New England Journal of Medicine*, **288**, 337–342.

Pilleri, G., Pietrini, V., Tagliavini, F., Trabattoni, F. & Lechi, A. (1981) "Thalamic" dementia in herpes encephalitis: clinicopathological report. *Acta Neuropathologica*, (Suppl) **7**, 156–159.

Pirozzolo, F. J., Hansch, E. C., Mortimer, J. A., Webster, D. D. & Kuskowski, M. A. (1982) Dementia in Parkinson disease: a neuropsychological analysis. *Brain and Cognition*, **1**, 71–83.

Price, K. S., Farley, I. J. & Hornykiewicz, O. (1978) Neurochemistry of Parkinson's disease: relation between striatal and limbic dopamine. *Advances in Biochemical Psychopharmacology*, **19**, 293–300.

Proctor, F., Riklan, M., Cooper, I. S. & Teuber, H-L (1964) Judgement of visual and postural vertical by parkinsonian patients. *Neurology*, **14**, 287–293.

Rafal, R. D. & Grimm, R. J. (1981) Progressive supranuclear palsy: functional analysis of the response to methysergide and antiparkinsonian agents. *Neurology*, **31**, 1507–1518.

——, Posner, M. I., Walker, J. A. & Friedreich, F. J. (1984) Cognition and the basal ganglia. *Brain*, **107**, 1083–1094.

Reitan, R. M. & Boll, T. J. (1971) Intellectual and cognitive functions in Parkinson's disease. *Journal of Consulting and Clinical Psychology*, **37**, 364–369.

Robins, A. H. (1976) Depression in patients with parkinsonism. *British Journal of Psychiatry*, **128**, 141–145.

Rosenbaum, D. (1941) Psychosis with Huntington's chorea. *Psychiatric Quarterly*, **15**, 93–99.

Rosenberg, C., Nadleman, K. & Starr, A. (1985) Cognitive evoked potentials (P300) in early Huntington's disease. *Archives of Neurology*, **42**, 984–987.

Ruberg, M., Ploska, A.., Javoy-Agid, F. & Agid, Y. (1982) Muscarinic binding and choline acetyltransferase activity in parkinsonian subjects with reference to dementia. *Brain Research*, **232**, 129–139.

——, Javoy-Agid, F., Hirsch, E., Scatton, B., L'Heureux, R., Hauw, J. J., Duyckaerts, C., Gray, F., Morel-Maroger, A., Rascol, A., Serdaru, M. & Agid, Y. (1985) Dopaminergic and cholinergic lesions in progressive supranuclear palsy. *Annals of Neurology*, **18**, 523–529.

Sax, D. S., O'Donnell, B., Butters, N., Menzer, L., Montgomery, K. & Kayne, H. L. (1983) Computed tomographic, neurologic and neuropsychological correlates of Huntington's disease. *International Journal of Neuroscience*, **18**, 21–36.

Scatton, B., Rouquier, E., Javoy-Agid, J. & Agid, Y. (1982) Dopamine deficiency in the cerebral cortex in Parkinson disease. *Neurology*, **32**, 1039–1040.

——, Javoy-Agid, F., Rouquier, E., Dubois, B. & Agid, Y. (1983) Reduction of cortical dopamine, noradrenalin, serotonin, and their metabolites in Parkinson's disease. *Brain Research*, **275**, 321–328.

Schoenfeld, M., Myers, R. H., Cupples, L. A., Berkman, B., Sax, D. S. & Clark, E. (1984) Increased rate of suicide among patients with Huntington's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **47**, 1283–1287.

Schulman, S. (1957) Bilateral symmetrical degeneration of the thalamus. *Journal of Neuropathology and Experimental Neurology*, **16**, 446–470.

Shepherd, M. (1955) Report of a family suffering from Friedreich's disease, peroneal muscular atrophy, and schizophrenia. *Journal of Neurology*, Neurosurgery, and Psychiatry, **18**, 297–304.

Smith, W. T. (1976) Intoxications, poisons and related metabolic disorders. In *Greenfield's Neuropathology* (eds W. Blackwood & J. A. N. Corsellis). Chicago: Yearbook Medical Publishers.

Steele, J. C., Richardson, J. C. & Olszewski, J. (1964) Progressive supranuclear palsy. *Archives of Neurology*, **10**, 333–359.

Stern, K. (1939) Severe dementia associated with bilateral symmetrical degeneration of the thalamus. *Brain*, **62**, 157–171.

Stern, Y. & Langston, J. W. (1985) Intellectual changes in patients with MPTP-induced parkinsonism. *Neurology*, **35**, 1506–1509.

——, Mayeux, R. & Cote, L. (1984) Reaction time and vigilance in Parkinson's disease. *Archives of Neurology*, **41**, 1086–1089.

Studler, J. M., Javoy-Agid, F., Cesselin, F., Legrand, J. C. & Agid, Y. (1982) CCK-8-immunoreactivity in human brain: selective decrease in the substantia nigra from parkinsonian patients. *Brain Research*, **243**, 176–179.

Tagliavini, F., Pilleri, G., Bouras, C. & Constantinidis, J. (1984) The basal nucleus of Meynert in patients with progressive supranuclear palsy. *Neuroscience Letters*, **44**, 37–42.

TALLAND, G. A. & SCHWAB, R. S. (1964) Performance with multiple sets in Parkinson's disease. *Neuropsychologia*, **2**, 45–53.

TAQUET, H., JAVOY-AGID, F., CESSELIN, F., HAMON, M., LEGRAND, J. C. & AGID, Y. (1982) Microphotography of methionine-enkephalin, dopamine and noradrenalin in the ventral mesencephalon of human control and parkinsonian brains. *Brain Research*, **235**, 303–314.

TRAUNER, D. A. (1985) Olivopontocerebellar atrophy with dementia, blindness, and chorea. *Archives of Neurology*, **42**, 757–758.

TRIMBLE, M. R. & CUMMINGS, J. L. (1981) Neuropsychiatric disturbances following brainstem lesions. *British Journal of Psychiatry*, **138**, 56–59.

TWEEDY, J. R., LANGER, K. G. & MCDOWELL, F. H. (1982) The effect of semantic relations on the memory deficit associated with Parkinson's disease. *Journal of Clinical Neuropsychology*, **4**, 235–247.

VILLARDITA, C., SMIRNI, P. & ZAPPALA, G. (1983) Visual neglect in Parkinson's disease. *Archives of Neurology*, **40**, 737–739.

WALKER, A. E. (1937) The thalamus in relation to the cerebral cortex. *Journal of Nervous and Mental Disease*, **85**, 249–259.

WARBURTON, J. W. (1967) Memory disturbance and the Parkinson syndrome. *British Journal of Medical Psychology*, **40**, 169–171.

WASTEK, G. J. & YAMAMURA, H. I. (1978) Biochemical characterization of the muscarinic cholinergic receptor in human brain: alterations in Huntington's disease. *Molecular Pharmacology*, **14**, 768–780.

WHITEHOUSE, P. J., PRICE, D. L., CLARK, A. W., COYLE, J. T. & DELONG, M. R. (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of Neurology*, **10**, 122–126.

——, HEDREEN, J. C., WHITE, C. L. III & PRICE, P. L. (1983) Basal forebrain neurons in the dementia of Parkinson disease. *Annals of Neurology*, **13**, 243–248.

——, TRIFILETTI, R. R., JONES, B. E., FOLSTEIN, S., PRICE, D. L., SNYDER, S. H. & KUHAR, M. J. (1985) Neurotransmitter receptor alterations in Huntington's disease: autoradiographic and homogenate studies with special reference to benzodiazepine receptor complexes. *Annals of Neurology*, **18**, 202–210.

WILSON, R. S., KASZNIAK, A. W., KLAWANS, H. L. & GARRON, D. C. (1980) High speed memory scanning in parkinsonism. *Cortex*, **16**, 67–72.

WILSON, S. A. K. (1912) Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain*, **34**, 295–509.

YAKOVLEV, P. I. (1948) Motility, behavior, and the brain. *Journal of Nervous and Mental Disease*, **107**, 313–325.

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