Semantic dementia with ubiquitin-positive tau-negative inclusion bodies

M. N. Rossor, T. Revesz, P. L. Lantos and Elizabeth K. Warrington

Summary
Three cases are reported with dementia and ubiquitin-positive but tau-negative inclusion bodies. All patients had a semantic dementia and the clinical details of two of these have been published as the first description of a selective semantic memory impairment. The original diagnosis had been of Pick’s disease based on frontotemporal atrophy, but re-examination has revealed ubiquitin-positive but tau-negative inclusions as well as neurites in the frontotemporal cortices and ubiquitin-positive, intracytoplasmic inclusions in the granule cells of the dentate fascia. These inclusions are identical to those reported in association with amyotrophic lateral sclerosis (motor neuron disease), but none were seen in brainstem or spinal cord motor neurons.

Keywords: semantic dementia; frontotemporal dementia; Pick’s disease; frontotemporal degeneration; ubiquitin

Abbreviation: WAIS = Wechsler Adult Intelligence Scale

Introduction
A variety of selective cognitive deficits have been described in association with focal cortical degenerations (Caselli and Jack, 1992). Most are associated with degeneration of the frontal and temporal cerebral cortices, and include frontal dysexecutive syndromes, progressive orofacial dyspraxia, progressive prosopagnosia and progressive (non-fluent) aphasia. Warrington identified three patients in whom there was progressive selective impairment of semantic memory in both the visual and verbal domains with relative preservation of episodic memory (Warrington, 1975). The defining characteristics of this syndrome were 2-fold: firstly, a fluent dysphasia in which there was a loss of comprehension of the individual’s verbal vocabulary in the context of intact syntax and speech production; and second, the loss of visual object knowledge in the context of intact visual perceptual skills. Snowden and colleagues introduced the term semantic dementia to describe this syndrome in patients with progressive degenerative disease, and this was developed further by Hodges and colleagues (Snowden et al., 1989; Hodges et al., 1992). Radiological evidence is consistent in implicating focal atrophy of the temporal lobes, the left being affected more than the right (Hodges et al., 1992; Snowden et al., 1996).

A number of histopathological patterns underlie frontotemporal degeneration: frontal lobe degeneration of the non-Alzheimer type, Pick’s disease, corticobasal degeneration, Alzheimer’s disease and frontotemporal degeneration with motor neuron disease (Cooper et al., 1995; Snowden et al., 1996). Frontal lobe degeneration of the non-Alzheimer type may be unremarkable macroscopically but on histology there is mild loss of neurons in laminae II and III with slight gliosis and mild spongiosis in laminae I–III. This is most notable in the frontal cortex and to a lesser extent in the anterior temporal cortex. Pick’s disease is associated with circumscribed frontotemporal atrophy, usually asymmetric and more commonly left-sided. Histologically, there are ballooned neurons or Pick cells and intraneuronal Pick bodies in the affected areas; the latter are intraneuronal argyrophilic inclusion bodies which on immunohistochemistry are both tau and ubiquitin positive. Frontal lobe degeneration may also occur in the context of motor neuron disease with associated clinical features of anterior horn cell disease. Macroscopically, there may be circumscribed atrophy and, histologically, there are changes similar to frontal lobe degeneration with microvacuolation in layers II and III with mild gliosis. In addition, ubiquitin-positive, tau-negative, non-argyrophilic inclusions are found not only in the motor neurons of the brainstem and spinal cord, but also in affected areas of the frontotemporal cortex and the granule cells of the dentate fascia (Okamoto et al., 1991; Wightman et al., 1992).

Recently, Jackson and colleagues described nine patients
with a progressive frontotemporal dementia who had the neuropathological features normally associated with the motor neuron disease frontotemporal degeneration complex (Jackson et al., 1996). Thus there was microvacuolation in cortical layer II, variable gliosis and intraneuronal ubiquitin-positive but tau-negative inclusion bodies. There were, however, no clinical features of motor neuron disease, and they proposed the term motor neuron disease–inclusion dementia for their cases. Their brief description of the cognitive details indicates that in their series frontal lobe-type behavioural changes were a prominent feature. In addition, language disturbance was present in all nine cases. The authors comment that this was characterized by ‘a progressive decline in spontaneous speech output and development of reduced fluency, word finding and naming difficulties. Comprehension was relatively unimpaired’. Thus these patients would appear to have a progressive non-fluent dysphasia, in contrast to semantic dementia cases who present with a fluent dysphasia.

We report on two patients (E.M. and C.R.) in whom the defining features of a semantic dementia were originally described (Warrington, 1975). In a third case (T.O.B.), the semantic memory deficit was not only category specific but also modality specific. This pattern of impairment was interpreted as evidence for parallel visual and verbal meaning systems in the brain (McCarthy and Warrington, 1998, 1990). All three cases were found to have tau-negative, ubiquitin-positive inclusion bodies.

Neuropathology
At post-mortem examination, the brains of all three cases were immersed in 10% buffered formalin. After 3–4 weeks of fixation, the brains were cut in coronal slices and several representative blocks were taken and embedded in paraffin wax. Tissue sections were cut and stained with conventional techniques including haematoxylin and eosin, luxol fast blue cresyl violet and silver impregnation methods. As silver impregnations other than the modified Bielschowsky’s method were used originally in cases 2 and 3, additional paraffin sections were stained with this latter method at the time of the current study. Tissue sections were also used for immunohistochemistry with antibodies to GFAP (glial fibrillary acidic protein) (Dako), tau (Dako; in case 1 a second antibody SMI51, Sternberger Monoclonals Inc., Md., USA, was also used), αB-crystallin (Novocastra), βA4 protein (Dako), prion protein (in cases 2 and 3, 3F4, NYC Institute of Basic Research, New York, USA; and in case 1, SP40, provided by Professor B. H. Anderton, Institute of Psychiatry, London); α-synuclein antibody was also provided by Professor B. H. Anderton.

Case reports
Case 1 (E.M.)
This 58-year-old female right-handed ex-school teacher was admitted to the National Hospital in October 1972 for investigation of increasing difficulty with language. Approximately 3 years earlier, her husband was aware of a lack of precision in her speech, with occasional paraphrasias. For example, she referred to ‘pieces of wood in the garden’ for the garden fence. She was aware of difficulty in retrieving the names of objects, people and places. Shortly before admission, she was aware of spelling difficulties and increasing problems with comprehension. She stated ‘if I listen to the radio I do not understand what the people say, they are speaking too quickly’. She was aware of her difficulty with words for objects, e.g. ‘if I was to buy a cabbage I may not be able to remember its name’.

There was no significant past medical history and no other symptoms on general review. She was a non-smoker and drank only occasional social alcohol. There was no family history of cognitive impairment, with her parents dying at 84 and 87 years, and she was one of four siblings all of whom were alive and well. Abnormalities on examination were confined to higher cortical functions. Reflexes were brisk but symmetrical, and plantars were bilaterally flexor. There was no muscle wasting, no weakness and no fasciculation noted.

Investigations included normal full blood count, ESR (erythrocyte sedimentation rate), urea and electrolytes, liver function tests, vitamin B12, folic acid and negative treponemal serology. Thyroid function tests were normal. Examination of the CSF revealed normal pressure, one lymphocyte per microlitre and a protein concentration of 20 mg per cent. An EEG was within normal limits and a left carotid angiogram showed no abnormality. An air encephalogram was reported as showing some prominent frontal and parietal sulci, but ventricular size was considered to be normal. A diagnosis of dementia on the basis of cerebral atrophy was made.

E.M. was tested on the Wechsler Adult Intelligence Scale (WAIS) and obtained a low average verbal IQ of 89 and a high average performance IQ of 117. She scored at the 90th percentile on the standard progressive matrices. Her recognition memory was impaired for both words and faces (recognition memory test scores of 34/50 and 23/50, respectively). However, on an equally difficult recognition memory test for ‘paintings’, she obtained an average score (44/50). Clinically her autobiographical memory appeared to be intact. Not only were her non-verbal reasoning abilities at a good level, but her perceptual skills also were intact. On a test of shape discrimination, her performance was flawless (20/20). She obtained a satisfactory score on a ‘same and different’ face matching test. She passed Weigl’s sorting test and her word fluency was adequate (23 ‘s’ words in 60 s). She had a good digit span (eight forwards) and her calculation skills were still average (WAIS Arithmetic SS 11).

By contrast, her language skills were gravely impaired. She had great difficulty in naming common objects and in naming objects from their verbal description (5/15 and 3/15, respectively). This word retrieval difficulty was clearly underpinned by an inability to comprehend at the level of single words. For example, she failed to comprehend 14/40 spoken
names of objects. Of pictures of these same 40 objects, she failed to identify three. On the Peabody Picture Vocabulary Test, she obtained a defective score (69/100). In this context, it is of interest to note that on a short version of the Token Test of comprehension, which uses a simple high frequency vocabulary, her performance was entirely satisfactory. Her reading and spelling were both mildly compromised, having the characteristics of a surface dyslexia and a surface dysgraphia (Warrington, 1975).

Overall, her cognitive profile conformed to that of a semantic dementia in which her verbal knowledge base was more impaired than her visual knowledge base. Her propositional language skills were well preserved, as were aspects of her episodic memory.

Over the ensuing 5 years, there was a steady deterioration and she was readmitted for investigation in 1977. During this time, her speech had deteriorated further but in addition there was marked loss of social skills. When out in the street, she would push people out of the way and she would go up to dogs and cats and pick them up and embrace them. She wore excessive amounts of clothing complaining that she was cold. There was a change in her eating behaviour; she would avoid vegetables and fruit which previously had been her favourite foods and would eat large amounts of sweet food, resulting in weight gain.

Examination again revealed abnormalities confined to those of higher cortical functions. Repeat routine blood tests including thyroid function were all normal. A CT scan on this occasion showed evidence of atrophy more prominent on the left than on the right. Formal neuropsychological assessment was no longer possible.

There was a steady decline following discharge, and reports from her husband 3 years later in 1980 stated that she had become very impulsive and lacked affection. She had difficulty with household chores but it was notable that up until then she had been able to find her way home from shopping expeditions. By that time, her speech had declined to one or two stereotype phrases such as ‘do the tea’ and ‘it’s very bad’. Following relentless decline, she died in May 1984 from bronchopneumonia.

Pathological findings
The post-mortem findings included multiple pulmonary emboli in both lungs, bronchopneumonia in both lower lobes, pulmonary oedema and thromboembolus in the right femoral vein. Brain weight was 1010 g and the brain showed severe shrinkage of gyri and widening of sulci, particularly in the frontal and anterior temporal areas where the gyri had ‘knife-edge’ appearances. On coronal slices, the lateral ventricles were symmetrically grossly dilated, while the third ventricle was only moderately enlarged. The cortical ribbon was thin in the affected areas, especially in the temporal lobes and insulae. The cerebral white matter was reduced in bulk, and the deep grey nuclei appeared small. The brainstem, including the substantia nigra and the cerebellum, was macroscopically normal.

Histological findings
The frontal, temporal and insular cortices were markedly thinned and showed severe depletion of cortical neurons and extensive gliosis, which was more prominent in the superficial cortical laminae and also extended throughout the entire cortex and underlying white matter (Fig. 1A and B). There was superficial microvacuolation throughout the affected cerebral cortices (Fig. 1A). Ballooned, achromasic neurons were not seen. In all the affected temporal and frontal cortices, there were ubiquitin-positive dystrophic neurites and neuronal inclusions, which were seen in both the superficial and deeper cortical laminae (Fig. 1C). In addition, the granule cells of the dentate fascia contained several ubiquitin-positive intracytoplasmic inclusions. Neither the cortical and dentate gyrus neuronal inclusions nor the dystrophic neurites were reactive for tau nor were they argyrophilic on the Bielschowsky’s silver impregnation. The caudate nucleus and putamen showed mild gliosis, but the globus pallidus and thalamus were normal. No significant pathology was seen in the midbrain, pons or medulla, and the hypoglossal, dorsal vagal and ambiguous nuclei were normal. The cerebellum, apart from mild focal loss of Purkinje cells, showed no significant abnormality.

The spinal cord was examined by conventional stains and ubiquitin immunohistochemistry at multiple levels including C7,T2, T12, L3, L5 and S1. Qualitative assessment showed no apparent depletion of motor neurons or long tract degeneration, nor the presence of ubiquitin inclusions, at any of the spinal cord levels. Prion protein and βA4 immunohistochemistry was negative.

Comment
The major neuropathological findings were those of severe frontotemporal atrophy accompanied by neuronal loss, gliosis and superficial vacuolation. In addition, cortical ubiquitin-positive, tau- and silver-negative intraneuronal inclusions and dystrophic neurites as well as ubiquitin-positive dentate fascia inclusions were present. These findings are consistent with those reported by Jackson and colleagues and termed motor neuron disease–inclusion dementia (Jackson et al., 1996).

Case 2 (C.R.)
This 63-year-old right-handed retired industrial chemist was admitted in December 1972 for investigation of cognitive impairment. At the age of 59 years, he had developed a period of depression with disturbed sleep, and following that began to interrupt conversations and became repetitive in his speech. He became increasingly suicidal and claimed that he was forgetting how to do his job. In his words he ‘had forgotten his chemistry’, and he retired in July 1972. During
Fig. 1 Photomicrographs showing superficial vacuolation and neuron loss (A) as well as severe gliosis (B) in the temporal neocortex. A temporal cortical neuron containing a ubiquitin-positive intracytoplasmic inclusion and ubiquitin-positive neurites are also shown (C). Ubiquitin-positive inclusions in the dentate fascia neurons are numerous in all three cases (D). A ballooned, achronastic neuron in the temporal neocortex is strongly immunoreactive for αB-crystallin (E). Neuritic plaques (F) with deposition of Aβ4 peptide (G) are present in large numbers in case 3. (A) Haematoxylin and eosin, bar = 40 µm; (B) glial fibrillary acidic protein immunohistochemistry, bar = 80 µm; (C) ubiquitin immunohistochemistry, bar = 12 µm; (D) ubiquitin immunohistochemistry, bar = 12 µm; (E) αB-crystallin immunohistochemistry, bar = 8 µm; (F) Bielschowsky’s silver impregnation for axons, bar = 80 µm; (G) βA4 immunohistochemistry, bar = 40 µm.
that year, his social skills deteriorated and he became impulsive. He was involved in a road traffic accident and would often jump through traffic lights and be unaware of his behaviour. Towards the end of 1972, shortly before his admission, he was unable to recognize family members.

In his previous medical history, he had developed osteomyelitis of the left arm as a teenager. There was no significant family history of dementia. His mother died at the age of 93 years from a cerebrovascular episode. He was one of five siblings, all of whom were alive and well. His father, however, had died of an unknown cause at around the age of 50 years. The patient smoked three or four cigarettes a day and only occasionally drank alcohol. Examination on this admission revealed some weakness of elbow flexion with reduced reflexes which was attributed to the earlier osteomyelitis. There was neither muscle wasting nor fasciculation. Plantar responses were reported to be flexor. Routine blood tests, thyroid function and vitamin B12 were all normal, and treponemal serology was negative. Air encephalography had suggested cerebral atrophy. An EEG was normal. During this period, he developed chest pain and an ECG suggested a recent inferior infarct with developing left bundle branch block. Further investigations were therefore delayed. Following recovery, he was discharged but readmitted in March 1973.

By the time of this admission, he had begun to develop some repetitive behaviours at home, e.g., repeatedly cleaning the windows. His social skills continued to deteriorate. It was noted that he was unable to recognize objects when shown them, for example he did not recognize a battery but when he was able to read the label could deduce what it was. Examination on this admission was as previously, although the plantar response was thought to be equivocal or possibly extensor. A left carotid angiogram showed some minor narrowing at the bifurcation but the patient then removed the needle. Tc99m isotope scan was normal.

At this time (March 1973), C.R. was tested on the WAIS and obtained a verbal and performance IQ in the low average range (80 and 89, respectively). However, he was able to score at the 50th percentile on the standard progressive matrices. His memory on tests was globally impaired; he totally failed two subtests from the Wechsler Memory Scale (story recall and recall of designs) and he failed to identify any famous faces (0/15).

C.R.’s perceptual and spatial skills were fairly satisfactory. He scored within the normal range on tests of shape discrimination and shape detection (16/20 and 36/40, respectively). On same and different face and object matching tests, his scores were at the lower limits of normal (21/28 and 17/20, respectively). He passed Weigl’s sorting test. Apart from the language andagnosic difficulties described below, there were no other cognitive deficits of note.

Two major deficits were documented. He had grave verbal comprehension impairments at the single word level and a profound visual associative agnosia. For example, he was required to identify a picture of a common object (either by name or by gesture) or define the name of the same object presented auditorially, all items easily known to the average person. He scored 13/40 and 21/40, respectively. On the Peabody Picture Vocabulary test, he obtained a defective score (70/150). His reading and spelling were both impaired and had all the hallmarks of a surface dyslexia and a surface dysgraphia, (Schonell reading 70/100 and Schonell spelling 65/100). For further details of his cognitive skills, see Warrington (Warrington, 1975).

In summary, C.R.’s cognitive deficits had the cardinal features of a global semantic dementia. His word comprehension and object recognition skills were profoundly impaired.

The patient deteriorated during the year, with increasing nominal dysphasia and visual agnosia. He was also reported to stuff his mouth with food whenever it was available, leading to weight gain. A CT scan was performed in November 1973 which showed bilateral cerebral atrophy but, in addition, a low density area was noted extending laterally in relation to the lateral extremity of the quadrigeminal cistern and having the position of the choroidal fissure and proximal portion of the temporal horn. This was interpreted as representing dilatation of these structures.

Following continued deterioration, the patient died of bronchopneumonia in December 1977.

Pathological findings
The cause of death was bronchopneumonia. The brain weight was 1150 g and the macroscopic changes of the formalin-fixed brain included severe frontotemporal atrophy with markedly dilated sulci and narrowed gyri, several of which were of the ‘knife-edged’ type. The temporal atrophy was especially severe in the polar and medial temporal regions. In addition, mild atrophy was visible in posterior hemispheric areas. There was dilatation of the lateral and third ventricles. The amygdala was severely atrophic, but the striatum, globus pallidus, thalamus and subthalamus were macroscopically normal. The substantia nigra was well pigmented and no macroscopic changes were seen in the remaining areas of the brainstem, cerebellum and spinal cord. This had previously been reported as case 4 of Cummings and Duchen (Cummings and Duchen, 1981).

Histological findings
Microscopic examination showed thinning of cerebral cortex with severe neuronal loss, astrogliosis and spongy vacuolation of the superficial laminae in the affected temporal and frontal areas including the orbitofrontal cortex. αB-crystallin immunohistochemistry showed that ballooned, achromatic neurons were relatively frequent in the affected cortices (Fig. 1E). Another cytoskeletal abnormality was the presence of ubiquitin-positive and tau- as well as silver-negative intracytoplasmic inclusions in many of the granule cells of the dentate fascia. In addition, in both the temporal
and frontal cortices, there were ubiquitin-positive and tau-negative dystrophic neurites, which were more numerous in the superficial than in the deeper cortical laminae. In a similar localization, rounded or comma-shaped neuronal intracytoplasmic inclusions were also noted. In the affected areas, there was marked reactive astrocytosis in the white matter, which often showed myelin pallor. Occasional neurofibrillary tangles were found in the pre-alpha neurons of the entorhinal cortex, the CA1 subregion of the hippocampus and the temporal neocortex, but the presence of senile plaques was not a feature. The amygdala showed severe reduction in size with neuron loss and gliosis. There was mild neuronal loss and gliosis in the caudate, but not in the putamen, globus pallidus, thalamus or subthalamus. Apart from occasional neurofibrillary tangles in the locus coeruleus, no abnormality was noted in the brainstem and, in particular, no inclusions or dystrophic neurites were found in the hypoglossal and dorsal vagal nuclei or the nucleus ambiguous.

Using conventional stains as well as immunohistochemistry with an antibody to ubiquitin, no microscopic changes and, in particular, no loss of motor neurons, long tract degeneration or ubiquitin inclusions were noted in the spinal cord at the levels examined, which included C7, T6, T12, L2–3, L5 and S1. Immunohistochemistry for βA4 peptide and prion protein was negative.

Comment
In this case, the neuropathological findings include severe frontotemporal atrophy with neuronal loss, gliosis, superficial spongiosis, ballooned neurons and ubiquitin-positive, tau- and silver-negative neuronal intracytoplasmic inclusions as well as dystrophic neurites. These, in combination with ubiquitin-positive dentate fascia granule cell inclusions, are consistent with those reported by Jackson and colleagues for motor neuron disease–inclusion dementia (Jackson et al., 1996).

Case 3 (T.O.B.)
This 63-year-old right-handed civil servant was referred to The National Hospital with a 4-year history of ‘memory’ impairment. He attributed his difficulty to a minor road accident 3 years earlier. Although this had not required hospitalization, he was diagnosed as suffering from a post-traumatic stress syndrome and treated with antidepressants. The history suggested an increasing difficulty with language comprehension. Thus, for example, when asked if his students would have to submit dissertations, he interrupted ‘Dissertations, now what do you mean by that?’ He continued to work until the time of admission and was able to lecture, although he tended to speak freely, fluently and even volubly using a repetitive and limited vocabulary with frequent circumlocutions. He tended to use expansive gestures whilst talking and lecturing. He claimed that he was still congratulated on the clarity of his lectures but acknowledged that he was unable to teach a new course.

He had no significant past medical history except for asthma, but his mother had apparently been demented for some years before her death at the age of 93 years; however, a histological diagnosis was not available. There was no other significant family history of dementia.

Examination on admission was normal, apart from abnormalities of higher cortical function.

T.O.B. was first assessed on the WAIS in November 1987 and obtained a verbal IQ of 95 and a performance IQ of 116. On Raven’s Advanced Progressive Matrices (set A), he obtained a superior score (12/12). His recognition memory for non-verbal material was very satisfactory, scoring at an above average level on both the Camden pictorial recognition memory test (30/30) and the Camden topographical recognition memory test (26/30). His recognition memory for words was quite creditable considering his aphasic difficulties (37/50). His autobiographical memory was both accurate and fairly detailed.

At this stage of the disease, he spoke fluently and with normal articulation and syntax, albeit using a limited vocabulary with many circumlocutions and stereotyped phrases. However, his word retrieval and comprehension skills were gravely compromised. He failed to name any items on the Graded Naming Test and he was only able to name six items on the much easier Oldfield naming test. His word retrieval skills appeared to be equally impaired for all categories of objects. This was in contrast to his word comprehension abilities which appeared to be category specific. A detailed assessment demonstrated that his comprehension of spoken names of animals was severely impaired (e.g. cow ‘don’t know’; 33% correct) whereas his comprehension of spoken names of inanimate objects appeared to be relatively preserved (e.g. saw ‘tool for cutting wood’; 89% correct). There was no evidence of a corresponding impairment of his knowledge of animals in the visual domain; pictures of animals were identified (though not named) with considerable detailed information (e.g. polar bear ‘animal right up in the north, in the snow, female digs hole in the snow with youngster for 3 to 4 months’; 94% correct). Thus, at this time, his category-specific semantic memory impairment appeared to be confined to the verbal domain. In addition, his reading and spelling skills were compromised: on graded difficulty tests requiring him to read and write irregular words, he made numerous regularization errors characteristic of a surface dyslexia and a surface dysgraphia.

His semantic memory impairment progressively worsened, and 1 year later encompassed both the verbal and the visual domain. There was no longer evidence of a category-specific impairment in one modality, but rather an island of category-specific sparing. Inanimate objects were still known but only in the visual domain (McCarthy and Warrington, 1988, 1990).

Routine investigations were normal but MRI revealed left
Pathological findings
Post-mortem examination was limited to the removal of the brain. The brain weight was 1368 g. The leptomeninges were considerably thickened particularly over the convexity. The large cerebral arteries showed many confluent atherosclerotic plaques with up to 50% narrowing of lumina. The cranial nerves and other structures at the base of the brain were normal.

There was evidence of frontotemporal atrophy, which was more severe on the left than on the right. The anterior and medial aspects of the temporal lobes were particularly severely affected. The superior parietal lobule showed mild atrophy. Coronal slices revealed narrowed gyri and widened sulci in the frontotemporal regions and enlarged lateral ventricles with rounding of the angles. The white matter of the temporal lobes appeared greyish; otherwise there was no obvious macroscopical pathology.

Histological findings
The frontal and temporal lobes, particularly the anterior and medial aspect of the latter, showed severe neuronal loss with disappearance of the normal layering of the cortex, superficial vacuolation (status spongiosus) and astrocytosis. Many neuritic plaques and a few neurofibrillary tangles were seen in the neocortex: while plaques occurred throughout the cortex, tangles were found mainly in the frontal and temporal cortices (Fig. 1F). However, tangles were noted in the deep grey matter including the nucleus basalis Meynert and locus coeruleus. Quantitative assessment showed that plaques were most numerous in the occipital cortex, followed by the temporal, frontal and parietal cortices. In addition, the frontal and temporal cortices showed ubiquitin-positive abnormal neurites: these were often found in association with the superficial vacuolation. A few swollen, achromatic cells were also noted. The hippocampus was relatively well preserved, although there were granulovacuoles, plaques and tangles. The neurons of the dentate gyrus contained many ubiquitin-positive, but tau-negative inclusions (Fig. 1D). The caudate nucleus showed neuronal loss, astrocytosis and a couple of swollen cells. There was some extraneuronal pigment in the substantia nigra. The lentiform nucleus, the thalamus, the medulla oblongata and the cerebellum were unremarkable. There was βA4 protein in the cerebral parenchyma (in the form of plaques and diffuse deposits) and in the vascular walls. Immunostaining for glial fibrillary acidic protein confirmed severe astrocytosis in the affected areas. Immunostaining for prion protein was negative, as was α-synuclein immunostaining, with the exception of two inclusions in the locus coeruleus.

Comment
This brain shows two neuropathological processes. First, there is Alzheimer-type pathology as evidenced by neuritic plaques and neurofibrillary tangles. This is atypical in two aspects: plaques greatly outnumber neurofibrillary tangles and the greatest density of plaques is in the occipital lobe. In addition, there is an emphasis on frontotemporal pathology, both macroscopically in the form of atrophy and histologically with neuronal loss, status spongiosus and astrocytosis. Moreover, the presence of ubiquitin-positive, but tau-negative inclusions in the dentate gyrus and ubiquitin-positive inclusions in areas of vacuolation suggest a second neurodegenerative process, i.e. that reported as frontotemporal degeneration associated with motor neuron disease-type inclusions.

Discussion
The clinical features of these three cases would all fall within the broad definition of a frontotemporal dementia due to degeneration of the frontal and/or temporal lobes. The term frontotemporal dementia is a clinically descriptive one. A number of broad presentations have been identified which include frontotemporal dementia with prominent frontal behavioural disturbances, a progressive non-fluent aphasia or slowly progressive aphasia (Mesulam, 1982; Snowden et al., 1992; Tyrrell et al., 1990) and semantic dementia (Snowden et al., 1989, 1992, 1996; Hodges et al., 1992; Hodges and Patterson, 1996). A recent consensus statement has provided diagnostic features of these presentations of frontotemporal degeneration and draws attention to the behavioural features that may accompany semantic dementia and which emerged during the course of illness in our cases (Neary et al., 1998).

The concept of semantic dementia was built on the original description of three patients, two of whom (E.M. and C.R.) are reported here, in whom a selective impairment of semantic, as opposed to episodic, memory was identified. Specifically, semantic memory impairment in the verbal domain affects word comprehension and word retrieval, the individual’s vocabulary being depleted of all but the most common words. At the same time, within the limitations of their reduced vocabulary, their propositional speech is fluent and syntactically correct. Speech production and repetition are entirely
normal. Reading and writing are fluent but marred by regularization errors for exception words characteristic of a surface dyslexia and surface dysgraphia. In the visual domain, object knowledge is lost, the individual’s visual vocabulary is depleted yet primary visual and perceptual processing is intact. Cases 1 and 2 can be considered as index cases of semantic dementia (Warrington, 1975; Snowden et al., 1989; Hodges et al., 1992), and case 3 developed typical features of a semantic dementia.

Cases of semantic dementia are associated with asymmetric atrophy of the temporal lobes, left more than right. This can be seen most readily with MRI, but when severe is also apparent on CT scans, as were our cases even with the earliest CT imaging systems. Case 3 underwent MRI scanning together with $^{15}$O-PET which also demonstrated maximum change in the left temporal cortex (Tyrrell et al., 1990).

Asymmetric focal atrophies are associated classically with Pick’s disease. Indeed, the original case of Pick was of macroscopic focal atrophy. The microscopic features were delineated by Alzheimer (Alzheimer, 1911) with the observation of inclusion bodies, subsequently referred to as Pick bodies, and swollen ballooned cells subsequently referred to as Pick cells. These observations were confirmed and extended by Altman (Altman, 1923). In modern classifications, Pick’s disease is one of the tauopathies as abnormal tau is the major component of the Pick bodies (Dickson, 1998), which ultrastructurally consist of loosely arranged straight filaments (Munoz-Garcia and Ludwin, 1984; Murayama et al., 1990; Itoh et al., 1997) and have a characteristic migration pattern on immunoblotting (Delacourte et al., 1996). These observations support the notion that distinct cellular mechanisms may lie behind the different tau patterns seen in different neurodegenerative conditions, including Pick’s disease (Spillantini et al., 1998).

Historically, however, the usage of the term Pick’s disease has been variable. Thus it has been applied clinically to patients with progressive focal neuropsychological deficits related to frontal dysexecutive syndromes or language impairment. It has been used, as was Pick’s original description, to refer macroscopically to lobar atrophy, with or without histological evidence of Pick bodies. The presence of Pick bodies was not compulsory in a classification based on histological criteria (Constantinidis et al., 1974). This variable use of the term has led to confusion in the literature. Indeed, Neary, Gustafson and colleagues (Lund and Manchester Groups) have suggested the term frontotemporal dementia as being the appropriate diagnostic label for patients with progressive language or frontal lobe syndromes with focal atrophy since further delineation is only possible on the basis of histology. Indeed, the initial diagnosis on macroscopy of our three cases was of Pick’s disease, and case 2 (C.R.) was reported in the series of Pick’s disease cases having Kluver–Bucy syndrome by Cummings and Duchen (Cummings and Duchen, 1981). More detailed subsequent immunohistochemical studies, however, have revealed intraneuronal inclusion bodies that were ubiquitin positive but tau negative, in all three cases, including C.R. In Lewy body dementia, ubiquitin-positive intracytoplasmic inclusions are present in both cerebral cortical and brainstem neurons. However, the cortical Lewy bodies are different from those seen in our cases in that they not only have a different anatomical distribution but they are also α-synuclein as well as ubiquitin positive (Baba et al., 1998; Mezey et al., 1998). In the cases presented here, the inclusions and neurites have been found to be negative on α-synuclein immunohistochemistry, which seems to be a feature of extramotor neuronal inclusions in motor neuron disease cases (T. Revesz, personal observation). Furthermore, the morphological appearances as well as the topographical distribution of the inclusions were indistinguishable from those seen in association with motor neuron disease. Frontotemporal degeneration can occur in a setting of motor neuron disease or amyotrophic lateral sclerosis, and, in such cases, ubiquitin-positive and tau-negative inclusions as well as neurites are present in the frontotemporal cortices, in addition to ubiquitin-positive inclusions in the granule cells of the dentate fascia and the typical ubiquitin-positive inclusions of the motor neurons (Okamoto et al., 1991; Wightman et al., 1992). Jackson and colleagues described nine cases with a frontotemporal dementia and focal atrophy (Jackson et al., 1996). Although none of the clinical features of motor neuron disease were observed in their cases, the main microscopic abnormality was the extramotor pathology that is associated characteristically with motor neuron disease. In none of their nine cases was there clinical evidence of either an upper or a lower motor neuron disorder, and ubiquitinated inclusion bodies were seen in the brainstem motor nuclei only in three cases. However, no spinal cord tissue was available for neuropathological examination in any of the cases presented by these authors. On the basis of the morphological findings, they referred to these cases as motor neuron disease–inclusion dementia. Our cases are similar to those described by Jackson and colleagues (Jackson et al., 1996) and we were also able to establish that the brainstem motor nuclei were not affected in our cases and that the anterior horn cells were not involved in the two cases where the spinal cord was examined. Our case 3 is unusual by virtue of abundant plaque formation, albeit in the absence of neurofibrillary tangles, although plaque-dominant Alzheimer’s disease is recognized (Terry et al., 1987; Hansen et al., 1993). In neurodegenerative diseases, the brain may be affected by more than one type of lesion, resulting in combined pathology. Thus, the simultaneous occurrence of Alzheimer-type pathology and motor neuron disease has been reported (Hedera et al., 1995), occasionally presenting as frontal lobe dementia (Muller et al., 1993).

From the controversy regarding the pathological diagnosis of Pick’s disease, cases similar to ours may well have been diagnosed as Pick’s disease if reliance was made primarily on focal atrophy and silver staining, in the absence of tau immunohistochemistry. Although silver impregnation methods including the Bodian and modified Bielschowsky
preparations stain Pick bodies as dark homogeneous masses (Munoz-Garcia and Ludwin, 1984; Perry et al., 1987) and are generally regarded as reliable pointers of the histological diagnosis, the interpretation of the results of the silver stains may sometimes be difficult. It is possible that this may be the explanation of earlier reports of Pick’s disease in association with amyotrophic lateral sclerosis (von Braunmuhl, 1932).

The striking focal nature of the clinical deficit early in the disease can be related to the intense focal cell loss from the left temporal lobe. However, although all three of our cases presented with a semantic memory impairment, the phenotypic expression of motor neuron disease–inclusion dementia is clearly wider, and indeed the cases described by Jackson and colleagues presented with frontal dysexecutive syndromes rather than semantic memory impairment (Jackson et al., 1996).

It is difficult to know how common such cases are, although it is notable that our neuropathological review of these three historic cases of semantic memory impairment were found not to have Pick’s disease, which was the original clinical diagnosis, but rather ubiquitin-positive inclusions similar to those seen in extramotor areas in association with motor neuron disease. The clinical presentation of the cases reported by Jackson and colleagues did not include detailed neuropsychology but suggested that they did not have prominent semantic memory impairment (Jackson et al., 1996). Thus it is likely that as with Pick’s disease diagnosed by tau immunohistochemistry, there may be a variable clinical expression. It is clearly important to establish how common ubiquitin-positive inclusion body disease is as a cause of frontotemporal degeneration. For clarity, we would suggest that this condition is referred to as dementia with ubiquitin inclusion bodies.

References
Altman, E. Uber die umschriebene Gehirnatrophie des spateren Alters. Z Gesamte Neurol Psychiat 1923; 83: 610–43.


Received April 27, 1999. Revised August 4, 1999. Accepted August 6, 1999