The term “Pick’s disease” (PiD) is used to designate clinically defined cases of progressive frontal and temporal degeneration, as was described by Arnold Pick, or a pathological entity defined histologically by the presence of argyrophilic globular inclusions (Pick bodies) and swollen achromatic neurons (Pick cells). Pick’s initial case of a progressive aphasic patient with a behavioral disturbance, and his subsequent cases of frontal lobe dementia and aphasia, included only anatomical examination. The histologic description came later.

It also became apparent that cases of clinical PiD with frontal and temporal lobe atrophy may not show the typical histological picture on autopsy. After reviewing a large series of their own, Constantinidis et al. classified PiD as: a) with Pick bodies; b) only with swollen neurons; and c) only gliosis and neuronal loss. They felt that, “in spite of the dissimilarities between these forms, considering the absence of sufficient knowledge about pathogenesis, it seems prudent at present to maintain the uniqueness of Pick’s entity.” Many subsequent publications of PiD were based on post-mortem findings, and variable clinical features were available retrospectively. This gave rise to the notion that PiD is difficult to diagnose in vivo.

Frontotemporal Dementia (FTD)

With the development of neuroimaging, frontal and temporal atrophy was demonstrated with increasing frequency in vivo. However, instead of shifting the diagnosis of PiD back to the clinic, more recent studies applied new labels such as dementia of the frontal lobe type, or frontal lobe dementia (FLD). The groups who described dementia of the frontal lobe type further changed the terminology to frontotemporal degeneration (FTD). Both of these groups recognized that the clinical syndrome was the same whether the cases had Pick bodies or only neuronal loss and gliosis.

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They estimated the incidence at 20% of degenerative dementias. The emphasis was on behavioral disturbances, and FTD is now used to refer to the syndrome of apathetic-disinhibition dementia and as a synonym for PiD.

**Primary Progressive Aphasia (PPA)**

A similar instance of relabelling PiD occurred with the description of PPA as a separate entity. However, many subsequent (and preceding) cases of PPA were described with Pick bodies. Other cases had histology characterized by gliosis, neuronal loss and layers II and III spongiosis in the cortex identical to that described in FLD, and subcortical involvement with neuronal achromasia similar to CBD. The nonfluent variety of PPA often leads to mutism undistinguishable from that seen in FLD. Other modalities are affected subsequently, particularly behavioral changes suggesting frontal deficit. At times, extrapyramidal complications and motor neuron disease (MND) appears. An interesting variety is characterized by preserved fluency and syntax, with loss of semantics, called “semantic dementia.”

**Corticobasal Degeneration Syndrome (CBDs)**

There have been many case descriptions of PiD in which patients had prominent extrapyramidal features. It was recognized that subcortical changes occur in PiD, even without extrapyramidal symptomatology. When Rebeiz et al described corticodentatonigral degeneration, they recognized the similarity of the pathology to PiD. Subsequently the extrapyramidal apraxic syndrome with variable gaze palsy and the “alien hand” was relabelled corticobasal degeneration (CBD) or corticobasal ganglionic degeneration (CBGD). Most patients with CBD develop a language disorder resembling PPA and FTD with considerable overlap of the syndromes. It is recognized that the pathological and clinical descriptions of CBD do not fully match. Therefore, it would be useful to...
distinguish the clinically appearing extra-pyramidal apraxic syndrome, corticobasal degeneration syndrome (CBDS), from CBD pathology (see below).

**Dementia with ALS**
(Motor Neuron Disease Type of Dementia)

Recently, a great deal of interest has been shown in the association of dementia with Motor Neuron Disease (MND). Initially, this was described with Creutzfeldt-Jakob disease, but it now appears many of these were not instances of prion protein disease but cases resembling FTD with spongiform changes in the superficial cortical layers. There is a burgeoning literature approaching this issue, from the point of view of FTD and PPA developing MND, as well as MND associated with dementia. Recently, it was suggested that cases of FTD with MND have specific neuronal inclusions, tau- and synuclein-negative, ubiquitin-positive (ITSNU). The specificity of this, however, has been challenged by several descriptions of this pathology without MND and several other cases of PiD or FTD with MND but without ubiquinated inclusions.

**Neuropathological Varieties**

Until recently, the presence or absence of Pick bodies and ballooned neurons, and their distribution, were used to establish subgroups. The differential staining with phosphorylated epitopes, tau, ubiquitin, αB crystallin and Gallyas have more or less distinguished the following varieties of pathology:

1) Pick body dementia defined by the presence of argyrophilic tau immunoreactive Pick bodies in the dentate gyrus of the hippocampus, as well as other neocortical and subcortical sites with ballooned neurons (Pick cells), gliosis and spongiform change in the II and III layers of cortex (PiD);
2) Gliosis and neuronal loss with or without spongiosis or the presence of ballooned neurons in the deep layers, also known as Dementia Lacking Distinctive Histology (DLDH);
3) CBD type of pathology characterized by ballooned neurons, Gallyas-positive and tau-immunoreactive astrocytic plaques, argyrophilic threads in the white matter, cortex and basal ganglia, and globose or ring-like neurofibrillary tangles in the substantia nigra (corticobasal inclusion bodies) (CBD);
4) Cytoplasmic inclusions, tau- and synuclein-negative, ubiquitin-positive in the dentate and other cortical and subcortical sites with or without MND, as described above.

**Figure 1. The unifying concept of Pick complex.**
Since these variations overlap in morphological features and their distribution, and are not specific to any of the clinical phenotypes, it is premature to regard them as distinct entities.

**Pick Complex**

We suggested the term “Pick complex” to avoid the confusion that continues to surround the terms PiD and FTD. Pick complex is a unifying concept of the overlapping clinical syndromes of FTD, PPA, CBDS, and the underlying neuropathological findings, emphasizing commonalities rather than differences between them. It designates both the pathological and the clinical overlap, avoids the restriction of pathology and clinical symptomatology to the frontotemporal cortex, and acknowledges the relationship to PiD (Figure 1). The terms “frontotemporal degeneration” and “frontotemporal dementia” do not include the frequent subcortical involvement, parietal pathology and extrapyramidal symptomatology and association with MND. Furthermore, use of the term FTD creates confusion because this term designates the behavioral presentation of the syndrome or the whole syndrome including the aphasis presentation (PPA). A similar confusion has been associated with the use of PiD, and has led to the under-diagnosis of both conditions.

**Treatment**

The treatment of PiD has not been established. Zinc metabolism was considered abnormal at one time, but chelation therapy was not successful. More recently, symptomatic treatment of restless, compulsive behaviors with selective serotonin reuptake inhibitors (SSRIs) or trazodone in FTD has been considered useful. Lithium also has been tried in a few patients, because it may have an effect on tau dephosphorylation, but the results have been poor.

**Genetics**

Recent evidence of genetic linkage to chromosome 17 q21-22 of several large families with a significant resemblance to Pick complex has emerged. The chromosome region common to all these contains the gene for the microtubule stabilizing protein tau. More than 20 tau mutations have been identified with various phenotypic manifestations. This genetic finding adds considerable support to the unity of this syndrome, and suggests a possible pathogenesis. Recent biochemical fractionation of tau protein may account for some of the variations in pathology and clinical manifestations, but it is too early to link the subtypes to clinical patterns. Gene mapping, biochemical and histochemical distinctions provide further understanding of the syndrome, but we must be careful not to lose sight of the clinical, pathological, and genetic cohesiveness, or of the exercise of caution in interpreting the differences.

**Summary**

The diagnosis of FTD, or Pick’s disease, is made when a patient, usually under the age of 70 years, has a history of disinhibition, “frontal” dementia or primary progressive aphasia and imaging shows frontotemporal atrophy. Tertiary referral is advisable.

References