Narcolepsy is a usually sporadic disorder with a prevalence of 1:2,000—its importance is not just medical, for it has a major psychosocial impact. Narcolepsy, as described by Gélineau in 1880, presents with excessive daytime sleepiness (EDS) and cataplexy.1 These features and typical findings on multiple sleep latency tests (mean sleep latency < 5 to 8 minutes or ≥2 sleep onset REM periods in 70 to 80% of patients) are supported by positivity for HLA DQB1*0602 (85 to 95% of patients). The latter is useful for recognizing narcolepsy without cataplexy.1 Narcolepsy can also be considered as instability among the states of wakefulness, non-REM (NREM) and REM sleep. Such a “state boundary dyscontrol” arises from a cholinergic-aminergic imbalance and a deficiency in transmission of hypothalamic peptides, hypocretins.

Hypocretins (Hcrt or orexins), discovered in 1998 in the posterolateral hypothalamus, are excitatory upon their targets, the monoaminergic and cholinergic cells in the basal forebrain and brainstem, some of which project back and modulate Hcrt signaling. Hcrt regulates arousal, feeding behavior, locomotion and muscle tone, and may play a key role in orchestrating ergotropic behaviors with emotional/motivational content.2 In 1999, a link between Hcrt and narcolepsy was discovered in dogs and rodents. A mutation of the Hcrtr-2 receptor gene was found in familial canine narcolepsy, while cataplexy-like episodes were observed in hypocretin knockout mice.3,4 Involvement of the Hcrt system was later established in human narcolepsy: seven of nine patients had low or absent CSF Hcrt levels;5 and a 85 to 95% loss of neuronal staining for Hcrt was demonstrated at autopsy in six patients, five of whom had narcolepsy with cataplexy.6-7 CSF Hcrt deficiency is an accurate biologic marker of human narcolepsy, with a sensitivity and specificity around 90%.8 However, it remained unclear whether the loss of Hcrt was due to a loss of synthesis of Hcrt or from neuronal death. Two articles in this issue of Neurology address the issue.

In the first study, Blouin et al.9 examined the colocalization of neuronal activity-regulated pentraxin (Narp) and Hcrt in two normal humans brains, and investigated the colocalization of Narp and Hcrt in three normal and four narcoleptic brains. Colocalization of Narp and Hcrt occurred in the lateral, dorsomedial, and dorsal hypothalamic areas; further, the number of Narp-positive neurons was only 11% of controls in these areas of the narcoleptic brains, but not in the paraventricular and supraoptic nuclei of the hypothalamus. In the second study, Crocker et al.10 similarly assessed Hcrt and Narp expression in five normal and two narcoleptic human brains. They also examined the distribution of the endogenous opiate dynorphin, a neuropeptide that is also produced by Hcrt neurons. Colocalization of dynorphin and Narp occurred in most Hcrt neurons in the posterior, lateral, anterior, dorsomedial, and ventromedial hypothalamic nuclei. Compared to controls, the number of Hcrt neurons was markedly reduced in narcoleptic brains and was paralleled by a similar decrease for dynorphin and Narp. The conclusions of the two studies are similar despite the use of different techniques and markers. First, sporadic human narcolepsy is characterized by a selective and profound loss of hypothalamic Hcrt neurons. Second, disrupted Hcrt signaling is accompanied by a selective and parallel decrease in Narp and dynorphin transmission. Unfortunately, neither study gives information about the presence (or absence) of gliosis in the vicinity of Hcrt neuronal loss, a finding noted in one of the original autopsy reports.7 Despite methodologic limitations of both studies, including the small number of narcoleptic brains examined, the long interval between symptom onset and autopsy examinations and the possible influence of comor-
bidity and drugs, and limited clinical information (Blouin et al.), these results offer new insights into the neuropathology of narcolepsy.

This anatomic analysis prompts questions concerning the pathophysiology of narcolepsy. What is the mechanism of selective Hcrt neuronal loss? The strong association with HLA, the bimodal distribution of age at onset, the presence of gliosis in the hypothalamus, the recent detection of functional auto-antibodies in the serum, and the potential benefit of immunoglobulin treatment at the time of symptom onset suggest an autoimmune mechanism. On the other hand, the absence of clinical progression argues against a primary neurodegenerative disorder.

Is the Hcrt neuronal loss a rapid or a slow process? Head trauma, viral illness, acute psychological stress and other acute triggering factors can precede the onset of narcolepsy by days or weeks. Clinical observations suggest that CSF Hcrt levels are already low or undetectable at symptom onset. In addition, cataplexy can follow the onset of EDS by decades.

It is therefore plausible to hypothesize that Hcrt neuronal loss is a rapid event but that clinical manifestations are also influenced by other factors. Hypocretin deficiency in patients with narcolepsy, as assessed by CSF measurements, predicts the presence of clearcut (definite) cataplexy and severe EDS. However, normal CSF Hcrt levels are found in about 10% of narcoleptics, even those with cataplexy. Furthermore, CSF Hcrt can be low or undetectable in other neurologic disorders, including traumatic brain injury, even in the absence of narcolepsy-like symptoms. For these reasons it is possible that, in addition to Hcrt, other signaling systems may influence narcolepsy symptoms. Histopathologic studies in more narcolepsy brains, including patients with normal hypocretin-1 levels or without cataplexy are needed.

Do changes in Narp and dynorphin have any clinical relevance? Considering the large number of neurons expressing both peptides outside the hypothalamus it is difficult to postulate any clinical implications, although pain and depression—both common in narcoleptics—could be related to a deficiency in dynorphin.

While the present studies inform our understanding of narcolepsy, by showing that low levels of CSF Hcrt reflect a major reduction of Hcrt neurons in the posterolateral hypothalamus, critical issues remain to be explored. A better understanding of the underlying pathologic process and consequent signaling deficiencies is necessary for the development of new treatments for this still-mysterious disorder.

References