letters to the editor

Evaluating cortical disinhibition signs

To the Editor: Conflicting data abound regarding the utility of the signs of cortical disinhibition in reliably predicting diffuse cerebral dysfunction at the bedside.¹⁻⁴ The results suffer from inadequate quantitation of cognitive function by standardized neuropsychometric testing, inter-study variability of clinical techniques, and uniformly small subject populations. The most recent report by Tweedy et al⁵ is to be applauded for including portions of standardized psychological tests in their cognitive assessment battery. Importantly, they confirm the association of at least two signs, the snout and grasp reflexes with cognitive impairment, confirming our observations.¹ While the grasp with or without distraction was significantly ($p < 0.01$) related to cognitive dysfunction in our series, false negative rates approaching 80% were felt to obviate its usefulness in routine testing. The authors also speculate that degenerative or destructive lesions in descending white matter tracts (corticobulbar, corticospinal) may contribute to the manifestation of these signs. This is of particular interest given the recent work elucidating the nature of subcortical dementia.⁶ On the other hand, cortical degeneration of motor gray matter would be expected to mimic such a process, but signs of disinhibition are not commonly encountered in motor neuron disease in our experience unless accompanied by metabolic encephalopathy or pronounced depression. It is unfortunate that the ocular signs of tracking (pursuit) and vertical gaze were not investigated in Tweedy's study, as we found them particularly sensitive in predicting subclinical or early diffuse cerebral dysfunction. Clearly, further work investigating the evolution of these economical and easily elicited signs in uncomplicated aging (senescence), senility, and diffuse cerebral dysfunction at any age is warranted.

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Reply from the Authors: Future studies of cortical

disinhibition signs would benefit from the use of standardized neuropsychological testing procedures, but they could also be improved by objective measurement of the signs themselves. Uniform stimulation and quantitative recording procedures would make comparisons between studies more fruitful, and would permit the study of subtle aspects of the signs. Even when clinical ratings are obtained, using more than one evaluator and determining the inter-rater reliability provides a measure of the confidence one may have in the data.

Larger studies would also be helpful, but they carry with them the prospect of producing reportable (ie, statistically reliable) associations that are of little practical or clinical significance. In addition to reporting p values, future studies should include measures of the proportion of variance accounted for (r^2 or ω^2) by the presence or absence of the sign. In our study,¹ patients exhibiting the snout reflex performed more poorly ($p < 0.05$) than those without it on 10 of 14 tests administered, yet the value of r^2 obtained indicated that less than 10% of the variability in cognitive test scores was related to the presence or absence of this sign. The large false negative rates obtained in every diagnostic category for both the snout and the grasp reflex sharply limited the clinical value of these signs as markers of dementia.

We view the emergence of the snout, root, suck, grasp, and palmomental reflexes as evidence of disinhibition of spinal and brainstem reflexes from cortical upper motor neuron control. Jenkyn and Reeves point out in their letter that the primitive reflexes are not prominent in patients with motor neuron disease, but this disorder usually involves a mixture of upper and lower motor neuron dysfunction. No patient in our series had evidence of lower motor neuron dysfunction. These findings do not argue against our hypothesis but they do suggest that intact lower motor neuron function may be required for the expression of these reflexes.

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Klüver-Bucy syndrome in Pick's disease

To the Editor: Cummings and Duchon¹ described five cases of Pick's disease, which they stated could be identified by the early appearance of the Klüver-Bucy syndrome (KBS) and the later development of amnesia and spatial disorientation. There are two difficulties with that presentation. First, there are important differences between the emotional changes in their patients and those originally observed in monkeys after bilateral temporal lobectomy.^{2,3} Second, most patients with Pick's disease who subsequently developed true KBS symptoms did so only after there was cognitive impairment in

memory, language, and spatial orientation.

The authors state that affect in KBS is blunted or depressed. While Klüver and Bucy noted nearly complete absence of fear and anger reactions in the monkeys, their desire to engage in playful activities with the experimenter and hypersexuality suggest that all affects were not absent. Furthermore, neither sadness nor other signs of the depressive syndrome were described in KBS.

It seems more likely that the affective changes described by Cummings and Duchon were due to frontal rather than temporal lobe damage. All five cases had a blunted or depressed affect, but four were also said to be irritable or agitated at times. Among 10 other cases of autopsy-proved Pick's disease with prominent emotional alterations,⁴⁻⁹ lability was observed in 7; and 3 of them had episodes of violent behavior. Oscillation of mood from apathy to irritability often follows bilateral damage to prefrontal cortex, a lesion present in most cases of Pick's disease. These changes in depth of affect should not be ascribed to the KBS.

The third case reported by Cummings and Duchon did not have any behavioral changes of KBS. Depression accompanied by agitation is not part of this syndrome; begging for pills is not hyperorality. These were the only features that could possibly have been related to KBS, and neither was typical.

Cummings and Duchon suggest that some cases of Pick's disease can be identified by the appearance of KBS symptoms before there is loss of memory or spatial functions, thus allowing differentiation from Alzheimer's disease. It is difficult to accept this view. Of the four patients with at least one genuine KBS symptom reported by Cummings and Duchon, two had documented impairment of memory before the emotional change. In the others, one had difficulty remembering names, people, places, and things before there were any KBS symptoms. The other patient missed appointments and showed memory impairment when first tested. In summary, of their four cases reported, not one clearly had KBS symptoms before any memory impairment. In 10 other cases of KBS symptoms in Pick's disease,⁴⁻⁹ 5 had memory loss before and 3 at the same time as the KBS symptoms. Therefore, among 14 cases of Pick's disease with at least one KBS symptom, only 2 clearly had a KBS symptom before loss of memory. Cummings and Duchon also suggest that spatial disorientation follows KBS symptoms in Pick's disease, an observation that is unsupported because only one of their patients was tested (minimally) for spatial functions. In conclusion, the pattern of early KBS symptoms followed by cognitive impairment is not typical of Pick's disease and would not allow confident differentiation from Alzheimer's disease.

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Reply from the Author: Dr. Devinsky and Dr. Bear raise some interesting factual and conceptual issues regarding the Klüver-Bucy syndrome (KBS) and the clinical identification of Pick's disease. They take issue with ascribing blunted or depressed affect to the KBS and suggest that hypersexuality would not coexist with impaired affect. Klüver and Bucy¹ clearly described both blunting of emotional responses and altered sexual activity in their operated monkeys, and the view that there is a necessary association between emotional and sexual behavior is not supported by clinical or laboratory observations of sexual activity. For example, Dr. Bear² has pointed out the dissociation between affect and sexual behavior in some temporal lobe epileptics who have intensified emotional reactions but profound hyposexuality. The fact that the expression of bilateral anterior temporal lobe damage in humans is not identical in KBS monkeys is not surprising, and the complete symptom complex accompanying bitemporal injury in humans has yet to be determined.

The suggestion that some of the behavior observed in our patients with Pick's disease might relate to frontal lobe changes cannot be contested. The pathological abnormalities in all cases were most severe in the temporal lobes, but the frontal lobes were also involved. Apathy and depression are not unusual with frontal disorders, and the frontal abnormalities may well have contributed to the observed behavioral disturbances. However, the frontal lobe changes cannot explain many of the abnormalities observed in our cases, and KBS has not been associated with frontal lesions. Whether the begging for pills that was prominent in our third case might be a behavioral manifestation of hyperorality is a matter of interpretation. It is the prerogative of Devinsky and Bear not to regard it as such, but it is consistent with the altered oral activity of KBS.

Their final point relates to the clinical differentiation of Pick's disease and Alzheimer's disease. Our study and an extensive review of the literature revealed that a common presentation of Pick's disease includes early

continued

appearance of language disturbances and KBS, whereas Alzheimer's disease causes early memory impairment and visuospatial disorientation. Patients, their families, and many clinicians misconstrue the aphasic abnormalities of Pick's disease as memory impairment. The patients do not use the correct words or names, and language abnormalities make formal testing difficult, but intact memory and visuospatial function are evident in other aspects of behavior.

Our major finding was that KBS often occurs early in Pick's disease and is not seen until the late stages, if at all, in Alzheimer's disease. As we pointed out, some cases of Pick's disease do not manifest KBS. Among the 10 cases selected from the literature and cited by Devinsky and Bear, KBS appeared either as the first symptomatic change or simultaneously with other cognitive alterations in 50%. Thus, this distinctive symptom complex can serve as an important marker of Pick's disease and may aid in the clinical identification of Pick's disease in more cases.

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Adrenoleukodystrophy an X-linked disorder

To the Editor: With reference to the article by O'Neill et al,¹ we were surprised to see a pedigree that had been changed from the one previously published by O'Neill et al,² without mention in the text of this change. We think this is a significant omission because in the 1981 article and pedigree, Case V-14 was designated as having endocrine disease, thus suggesting male-to-male transmission in a disease that had previously been thought to be X-linked. In the 1982 article and pedigree, Case V-14 is no longer identified as having endocrine disease and the designation mark has been so removed. Yet no mention of this is made in the paper. We feel that a published clarification of this omission is in order.

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Reply from the Authors: We appreciate the comments of Drs. McMillan and Hutchison. We agree that the patient indicated as V-14 in the second paper¹ should have been accompanied by a clarifying comment in the text. The biochemical data are consistent with the interpretation that the kindred follows an X-linked pattern. Male-to-male transmission is not supported by the laboratory findings or the subsequent clinical events.

In the original paper,² the statement ascribing endocrinologic abnormality on the basis of dark complexion and a slightly elevated ACTH value was premature. The statements based on clinical observations were meant to be tentative. The child remains free of evidence of Addison's disease or neurologic disease. Since other males in the kindred have been dark (V-2, 17),² without neurologic disease, and normal by chemical analysis, we assume that they represent one end of the range of normal skin pigmentation.

Abundant clinical and biochemical data support *adrenoleukodystrophy* (ALD) as an X-linked disorder. However, precise understanding of the range of phenotypic expression will await characterization of the enzymatic error.

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Corrections

In letter to the editor "False-negative CT in astrocytomas" May 1983, page 671. The address for Dr. Michael I. Weintraub should read: Department of Neurology, Phelps Memorial Hospital, N. Tarrytown, NY.

In "Pharmacokinetics of valproic acid in children: I. Multiple antiepileptic drug therapy" by Cloyd, et al, February 1983, page 190, line 13 of column 2 should read: This finding suggests that phenytoin may alter VPA serum protein binding. At least one in-vitro study supports this observation while several other studies have shown no effect of phenytoin on VPA serum protein binding.^{22,23,27} (27. Bruni J, Gallo JN, Wilder BJ. Effective Phenytoin Binding of Valproic Acid. *Can J Neurol Sci* 1979;6:453.)

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