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Diagnostic Criteria: Tuberous Sclerosis Complex

Editorial Note: This issue of the Journal of Child Neurology carries the consensus report of the the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association. Reliable diagnostic criteria for tuberous sclerosis complex are important for a number of reasons. If we are to identify specific gene markers for tuberous sclerosis, it is essential that we accurately identify those patients with definite tuberous sclerosis and not include in our research individuals whose diagnosis is open to question. Debates about the validity of a gene marker should not fall on the issue of the accuracy of the diagnosis of tuberous sclerosis in those patients in whom a marker is first identified. Likewise, clinically useful laboratory tests for tuberous sclerosis complex based on these markers can not be developed without a carefully screened homogeneous population of patients with tuberous sclerosis. Eventually these same concerns will arise in conjunction with therapeutic issues. Thus, it is only through the use of a well-defined patient population that we can hope to develop the tools for the diagnosis, evaluation, and therapy related to tuberous sclerosis.

The National Tuberous Sclerosis Association now sponsors and supports tuberous sclerosis clinics in 11 medical centers around the country. Tuberous sclerosis clinics are ideal sites at which to collect patients with tuberous sclerosis and investigate the combinations and constellations of stigmata of tuberous sclerosis. The clinics provide an ideal opportunity to test many of the assumptions in the tuberous sclerosis diagnostic criteria, then to improve the criteria. The availability of large numbers of tuber-

ous sclerosis patients and a uniform system of diagnosis and classification should in turn promote research and eventually therapy. Thus, the development of uniform diagnostic criteria for tuberous sclerosis promotes better use of the tuberous sclerosis clinics for research.

Any attempt to arrive at a consensus stimulates debate about the validity and veracity of cherished assumptions which have not before been submitted to critical scrutiny. Debate often draws attention to the emperor's new clothes and recognition of his true form. Over the last 12 months, committee members realized that we do not have a consensus on what tuberous sclerosis really looks like. The disease is extremely variable from patient to patient, and there are few data on the general incidence of many of the stigmata of tuberous sclerosis. We are unsure how many of the phenomena are necessary or sufficient for the diagnosis of tuberous sclerosis. This debate forced the committee to make some assumptions about the specificity of lesions, assumptions which will need to be tested during the next decade. Are facial angiofibromas, subependymal giant cell astrocytomas, or ungual fibromas pathognomonic of tuberous sclerosis? Hypomelanotic macules, cysts, and seizures seem to be less reliable witnesses of tuberous sclerosis than the former group. The committee intends these criteria to be adaptable, susceptible to modification as data are collected by empiricism. It is our fervent wish that the criteria for the diagnosis of tuberous sclerosis will metamorphose into a stable support for molecular diagnosis and treatment of tuberous sclerosis complex.—Robert M. Shuman, MD

Report of the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association

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Tuberous sclerosis complex is a genetic disorder with protean clinical manifestations. Since there is presently no reliable molecular marker for tuberous sclerosis, we must rely on clinical diagnostic criteria, especially for patients with atypical features or subtle forms of the disorder. Accurate diagnosis underpins the clinical approach to individual tuberous sclerosis patients, influences the

estimated recurrence risk figures provided to families in the course of genetic counseling, and affects the validity of the results of clinical and basic research on tuberous sclerosis. The need for accurate diagnosis in research is critical; even if a definite diagnosis can not be established, it would be helpful to estimate the probability that an individual family member is affected. Unfortunately, there are few population-based studies of the various clinical features of tuberous sclerosis, and it is not always possible to establish a firm diagnosis on clinical grounds alone.

A definitive diagnosis of tuberous sclerosis is easy when many features of the disorder are present. However, since present day criteria are confined to clinical findings, it is impossible to absolutely

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