TLE surgery. To provide a definite answer to these questions, a prospective randomized trial will be required.

A formal study would require standardization of the Wada test procedure and the failure/pass criteria. Of at least equal importance, also, would be the need to account for the variation in the patients being offered surgery and in the surgical procedures carried out in temporal lobe epilepsy. In the past, a standard anterior 2/3 resection was usually carried out, but now the operation is tailored to different pathologies, different approaches are used (transsylvian, transcortical, subcortical), and varying degrees of mesial and temporolateral resections are performed. Outcomes in mesiotemporal, temporal and extratemporal-related cognitive functions can be expected to vary depending on baseline parameters and the surgical approach (Helmstaedter et al., 2007). In the past, the primary function of the Wada test was to prevent catastrophic outcomes. However, with today's surgical techniques, one must doubt, that the gross measures provided by the Wada test and alternative techniques are valid in preventing or predicting less severe adverse outcomes in the individual patient.

In the immediate future, the unrestricted use of the Wada test may be justified for legal and research purposes, and for validation of alternative methods. However, it also may not be wise to blindly use the Wada as the "golden reference" for validation of new methods, without first having posed—and answered—the correct clinical questions with the Wada test itself.

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Should we "stick" with the Wada?: Probing practicable preferences—Commentary on Baxendale et al.

The Wada survey results reported by Baxendale are very timely, and address changing utilization preferences for this important component of preoperative epilepsy surgery evaluation. Notwithstanding general survey data concerns (e.g., Did the survey responders (44%) differ in any meaningful way from the nonresponders? Is there any important difference between epilepsy centers publishing their results (the targeted survey population) vs. centers whose experience has not been formally presented in the research literature?), Dr. Baxendale clearly documents a trend away from the expectation that all candidates for anterior temporal lobectomy or hippocampectomy should undergo bilateral Wada testing as part of their preoperative surgical evaluation.

Even the centers at which there is an expectation that all surgical candidates will undergo Wada testing preoperatively will, if queried differently, admit that there are individual cases that are successfully treated surgically without Wada results. These are patients who are either too young, have very low-cognitive function, or have atypical vasculature that precludes a typical Wada assessment. It is easy to agree, in principle, that patients exist who may not need to undergo Wada testing. The trick, however, is knowing which patients these are without the assessment and appropriate follow-up. Although memory risk is often treated as a unitary construct, the ability to predict the development of an amnesic syndrome differs from the ability to identify patients who are at risk for developing significant material-specific memory decline that, though not amnesia, is of sufficient severity to limit vocational options or otherwise affect quality of life.

The preoperative evaluation for epilepsy surgery is necessarily multidisciplinary, and as Dr. Baxendale observes, noninvasive neuropsychological testing is an important component of that evaluation on which some epilepsy centers primarily rely to establish postoperative risk to language and memory. Not only is there potential cause for concern regarding antiepilepsy drugs (AED) effects on Wada results, but AEDs can also significantly alter the pattern and specificity of neuropsychological test results. Similarly, epileptiform activity may affect neuropsychological test sensitivity and specificity, and the

effects of incomplete task-engagement on the validity of neuropsychological findings are well established. Thus, there are many factors that might diminish the utility of specific neuropsychological findings on the individual patient basis. For these reasons, the availability of multiple functional measures of mesial temporal lobe function avoids the reliance on any single method when establishing overall pattern of lateralized dysfunction, thereby minimizing (hopefully) both Type I and Type II patient classification errors.

One survey participant whose response was presented in the survey lamented that, given the current emphasis on evidence-based medicine, Wada protocols without an empirical foundation should be treated as suspect. Obviously, Wada method variance, such as differences in amytal dose, stimulus type (pictures vs. real objects), timing of stimulus presentation, and scoring of memory results (e.g., treating correct recognition of a foil the same as correct recognition of a target)—affects Wada memory performances and their interpretation. Fortunately, Wada protocols, such as the one that was developed at the Medical College of Georgia, have been empirically validated on multiple levels, including relationship to hippocampal volume, seizure onset laterality, memory outcome, and even seizure outcome (Loring & Meador, 2008).

Evidence-based medicine concerns also exist for both neuropsychology and functional magnetic resonance imaging (fMRI). Many different neuropsychological tests are used to test language and memory, and despite superficial similarities across many tests, similar measures have differing sensitivities and specificities (Loring et al., 2008). Further, it is far from clear whether list-learning vs. paragraph memory vs. paired-associate learning are comparable verbal memory measures, and whether specific revisions of popular tests should treated as comparable in the absence of appropriate comparative studies (Lezak et al., 2004; Strauss et al., 2006).

Evidence-based medicine concerns, however, are greater for fMRI given the many site-specific fMRI language and memory protocols reported, although there is greater empirical support for fMRI language paradigms than for fMRI memory protocols. As with the Wada test, different fMRI protocols cannot be expected to be equivalent in their ability to assess language and memory function, and each will need appropriate validation. Some centers employing fMRI as part of the preoperative evaluation have established the validity of their technique using Wada, stimulation mapping, and cognitive outcome measures. fMRI mapping of memory functions continues to be an area of active research, although it is noteworthy that despite the enthusiasm that greeted the initial reports of medial temporal lobe fMRI activation in the late 1990s and early 2000s, there has been a striking absence of replication studies, both in the formal research literature and at major professional meetings.

What is not presently known is how language and memory fMRI assessments provided by clinical vendors, and employed by clinicians without long-standing research expertise, will be used and interpreted. Thus, it is critical that we collect neuropsychological outcome data to determine if the reduction in number of preoperative Wada tests has negative effects on cognitive outcomes. Unfortunately, at least in the United States, fewer postoperative patients are being formally evaluated with neuropsychology given the absence of an explicit clinical indication for patients in whom clear and serious cognitive change does not develop.

Predicting low-base rate events is difficult, but predicating high-base rate events is quite simple. For example, the ability to statistically predict left-cerebral language laterality is quite high by identifying all patients as having left cerebral language dominance (probably 90% concordance). Similarly, the ability to correctly identify absence of amnesia risk is even higher (probably greater than 99%) by simply categorizing all patients as being risk-free. However, it is the low-base rate events for which diagnostic testing is critical in order to alter or shape the course of clinical care. Obviously, unless there is a perfect predictor, there will be a high rate of false positive as well as false negative errors. However, having two predictors of low-base rate events helps to mitigate this difficulty if both variables are interpreted within the context of clinical history and imaging findings.

In conclusion, Dr. Baxendale's survey documents an important shift toward less frequent/less routine Wada use in some epilepsy centers. Using Wada data, risk of memory decline can be determined with a high degree of numerical precision using regression estimation based upon large and representative sample sizes (e.g., Stroup et al., 2003), and comparable outcome data with fMRI do not yet exist. Because functional assessment will vary across epilepsy centers, it is premature to recommend that centers who rely on Wada testing as a routine component of preoperative evaluation should discontinue their practice. Although invasive testing should not be used without appropriate consideration of the alternatives, the appropriate evidence base must be developed so that postoperative cognitive risks using these predictors can be established, thereby maximizing the process of informed consent.

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The Wada vanishes—Commentary on Baxendale et al.

We congratulate Dr. Baxendale and colleagues on this long overdue survey. Technical and research advances necessitate reassessment of the Intracarotid Amobarbital Procedure (IAP) and call for a reevaluation of risks, benefits, and alternatives.

The IAP is variable. Lack of standardized protocols between centers and variations between procedures make comparisons of IAP results difficult. Interindividual response to anesthetic dose and medication, encephalopathy, stimulus presentation and passing criteria, differing vascular anatomy, variable cerebral representation of memory, and incomplete inactivation of the hippocampus during the procedure all limit the interpretation of test results (Loddenkemper et al., 2007). Additionally, ethical considerations complicate assessment of validity and reliability.

Risks are significant. Complications have been reported in up to 11.6% of patients. Such complications include strokes, transient ischemic attacks, carotid artery dissections, seizures, hemorrhages, allergic reactions, and infections. Lasting deficits from strokes were seen in up to 0.6% of patients (Loddenkemper et al., 2004).

Benefits and indications are limited. Based on this survey, prediction of memory decline after surgery is the most frequent IAP indication. Previous studies suggest poor positive predictive value of IAP for global amnesia due to high rate of memory failure (false positive test results) in the setting of overall low prevalence rates of global amnesic syndrome (Goldstein & Gilliam, 2006). Therefore, patients may be unnecessarily excluded from epilepsy surgery based on IAP results. Additionally, several cases of false negative test result, with no memory failure on IAP but subsequent global amnesia after surgery, have been described (Dodrill, 2006). These cases and other subtypes of verbal and visual memory loss after surgery may reliably be predicted by preoperative memory level, MRI findings, and side of surgery (Baxendale et al., 2006; Dodrill, 2006). In a review of 15 studies, the IAP was not an indicator for material-specific memory loss (Dodrill, 2006). IAP may at best minimally improve the prediction of postoperative memory decline.

Surprisingly many colleagues rely on IAP language lateralization in temporal lobectomies, although language areas are usually not removed. If noninvasive imaging techniques suggest language representation in the area targeted for resection, cortical stimulation should be used in order to tailor the resection and thus make the IAP redundant.

Reliance on IAP for seizure focus lateralization and seizure outcome prediction alone is rare and is usually an adjunct technique.

Alternatives for language testing (Abou-Khalil, 2007) and memory testing (Baxendale et al., 2006) are available. It has been argued that the IAP mimics effects of surgery better, because most alternatives include activation instead of inactivation paradigms. Advances in noninvasive inactivation procedures, such as transcranial magnetic stimulation, may silence this criticism in the future. Additionally, magnetencephalography and functional magnetic resonance imaging provide better localizing information.

The IAP vanishes. Epileptologists slowly move on to less invasive techniques. It may well take more awareness training and research to antiquate the test. This survey is a first step. Ethical concerns due to risks, benefits, and alternatives will further its demise. Few indications for IAP in selected cases may remain for now, mainly due to limited availability, experience and comfort levels with alternative techniques. Nevertheless, epilepsy surgery should not categorically be withheld based on memory IAP results alone, because knowledge of reliability and validity of the memory IAP remains limited.

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