History of the Wada Test ⓐ

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Abstract and Keywords

This chapter discusses the origins and development of the Wada test. Wada testing, named after Juhn A. Wada, M.D., is the technique of arterial administration of amobarbital (or other short acting barbiturate) to transiently inactivate brain function in the distribution of the injected artery during which cognitive testing is performed. The procedure was developed to establish cerebral language dominance in the late 1940s, and it became a routine component of the preoperative evaluation for epilepsy surgery in the mid-1950s. However, the use of Wada testing as the primary technique to identify cortical language regions and predict risk of post-operative memory decline has been increasingly displaced by electroencephalogram (EEG) video monitoring, magnetic resonance imaging (MRI) of hippocampus, positron emission tomography (PET), single photon emission computed tomography (SPECT), functional MRI (fMRI), and even multi-modality imaging.

Keywords: Wada testing, Juhn A. Wada, cognitive testing, cerebral language, epilepsy, preoperative evaluation

Wada testing is the technique of arterial administration of amobarbital (or other short acting barbiturate) to transiently inactivate brain function in the distribution of the injected artery during which cognitive testing is performed; it is an eponymous procedure named after Juhn A. Wada, M.D. The procedure was developed to establish cerebral language dominance in the late 1940s and became a routine component of the preoperative evaluation for epilepsy surgery in the mid-1950s. Memory testing was added in the 1960s to evaluate risk of significant memory decline following anterior temporal lobectomy. Although functional MRI has decreased the need for routine Wada testing in epilepsy surgery evaluation, Wada testing remains an important assessment tool for many surgical candidates whose language or memory function cannot be reliably established using other methods.

In addition to its clinical contribution to the pre-operative epilepsy surgery evaluation, the reversible neurologic impairment associated produced with Wada testing has facilitated the systematic study of many brain–behavior relationships, since it permits a direct contrast of relatively normal brain function with the transient brain impairment associat-

ed with the pharmacologic lesion (Gilmore, Heilman, Schmidt, Fennell, & Quisling, 1992; Heilman, Meador, & Loring, 2000; Lee, Loring, Meador, Flanigin, & Brooks, 1988; Meador et al., 1988; Ross, Edmondson, Seibert, & Homan, 1988). Barbiturate injections into other arterial systems are also often referred to as a Wada test, although these approaches are typically qualified (e.g., posterior cerebral artery Wada, spinal Wada) to readily differentiate these techniques from intracarotid injection.

Prior to functional brain imaging, and in particular before functional MRI was demonstrated as a reliable technique to determine language dominance, Wada testing was the only reliable approach to establish cerebral language representation pre-operatively. Results of Wada language testing were then used to inform neurosurgical approaches, since a more extensive resection could be performed in a non-language hemisphere. Group data derived from Wada testing have facilitated our understanding of how cerebral language representation can shift in the setting of early left hemisphere seizure onset and have provided important insight on the relationship between language dominance and handedness.

Pre-Wada Cortical Anesthesia for Language

Wada published his initial findings describing the cognitive and behavioral effects of intracarotid amobarbital administration in 1949 (Wada, 1949). The first use of anesthesia to evaluate cerebral language areas as part of pre-operative epilepsy surgery planning, however, was reported in 1941 by W. James Gardner, a neurosurgeon from the Cleveland Clinic (Gardner, 1941; Harris & Snyder, 1997). Because of the temporal proximity of Gardner's and Wada's techniques to identify language pre-operatively by using anesthesia of suspected language regions, it has been suggested that this reflects the "inevitability of scientific discovery" in which independent discoveries occur at roughly the same time because of a field's scientific maturity as well as its zeitgeist (Harris & Snyder, 1997; Ihde, 1948). Prior to Gardner's and Wada's reports, the only technique to reliably establish cerebral language outside the context of acquired neurologic injury was electric stimulation of exposed cortex during surgery.

The relationship between handedness and cerebral language representation was beginning to be linked during the 1930s and 1940s (Harris & Snyder, 1997), allowing handedness to be used as a proxy for language dominance when planning surgical resection.

> *In right handed persons the center for motor speech always is located in the posterior part of the third left frontal convolution, just in front of the motor center for the face. In congenitally left-handed persons the speech functions usually are located in the corresponding area in the right hemisphere. The more pronounced the left handedness, the more certain it is that the speech function is located on the right side. Persons who acquire left handedness as a result of the occurrence of right hemiplegia early in life also usually will acquire complete right cerebral dominance, which the speech function located on the right side.*

(Gardner, *1941, p. 1035*).

The belief that congenital left-handed persons have right cerebral language dominance reflected the thinking of the time, and it was summarized by Weisenberg and McBride 's (1935) assertion that the probability of cerebral language dominance varied "in accord with the use of the left hand in writing" (Weisenberg & McBride, 1935). Thus, regardless of whether a patient's left handedness was congenital or was the result of an early left hemisphere lesion, right cerebral language representation was considered likely, and left-handed patients undergoing right brain surgery were expected to be at increased risk for meaningful postoperative language difficulty. "The removal of a tumor at the cost of the patient's speech is scarcely an accomplishment on which to congratulate oneself" (Gardner, 1941, p. 1035).

Gardner's (1941) approach to identify potential right hemisphere language involved injecting procaine (Novocain) into the cortex to inactivate suspected language areas. Gardner's first patient was congenitally left-handed, had a family history of sinistrality, and presented with a progressive left hemiparesis of three months' duration associated with Jacksonian seizures beginning in the left great toe. Although initial exploratory surgery identified a right subcortical astrocytoma, Gardner did not resect the tumor after its discovery due to concern over possible post-surgical aphasia from expected right cerebral language dominance. During a second operation, Gardner injected 27 cc of .75% solution of procaine into the right facial motor area resulting in left facial paralysis but no change in language. After assuring himself that there was no right-sided language, Gardner performed a right hemispherectomy with "no sign of aphasia" noted post-operatively.

Gardner's second patient developed scarlet fever at 18 months of age with right hemiplegia and seizures. When she was 5 years old, a left hemisphere brain cyst was resected; however, nearly daily convulsive seizures with right-hand onsets persisted. Gardner used a two-staged technique following left craniotomy to investigate cerebral language representation: (1) the motor area was first identified by cortical stimulation, and (2) left hemisphere language was tested following injection of a smaller amount than previously used of 10 cc of 1% solution into the left facial motor. In contrast to the first patient, there was no facial weakness induced and there was also no associated language change, which was interpreted as reflecting the shift of left hemisphere speech centers to the right hemisphere from the early injury and that the left motor facial cortex no longer was functional. Based upon these findings, a left hemisphere resection that included Broca's area was performed without any post-operative language change.

Procaine injection produced no language change in either case, and language representation in the contralateral hemisphere was inferred in the second patient based upon the absence of induced language disruption. "To the best of my knowledge no one has produced aphasia by injection of procaine into Broca's area, but that it would follow such a procedure seems beyond doubt." Given Gardner's belief that congenitally left-handed patients with positive family histories of sinistrality would be likely to be right cerebral lan-

guage dominant, it is interesting that he did not comment on the absence of right cerebral language representation in the second patient (Harris & Snyder, 1997).

Although no additional experience using procaine injection to identify cerebral language areas was reported, Gardner (1937) injected procaine into the sensory root of the trigeminal nerve to determine whether sensory root resection would be an effective technique for trigeminal neuralgia (Gardner, 1937). Procaine injections were also used as nerve blocks to determine the effectiveness of surgery for pain in various other areas (Gardner, 1952). These reports provide indirect evidence that injection into Broca's area would produce aphasia if language representation were present. Nevertheless, it remains unclear why Gardner's approach to identify language identification was not adopted by others or why Gardner failed to continue this approach, although we can speculate that it may be due to concern for long-term effects of injecting procaine into viable tissue that would not be resected.

Wada Testing

We (D.W.L., K.J.M.) first met Dr. Wada in 1986 when he visited the Medical College of Georgia to deliver an invited lecture. Later at the dinner reception, Wada gave an informal presentation about why he studied epilepsy. His lecture was filled with images of paintings, architecture, theater, and dance, noting that he was fascinated by the arts as they were expressions of the human brain. Similarly, Wada noted that he was fascinated with disorders of the brain such as epilepsy because they were pathological expressions of the brain.

Juhn Atsushi Wada was born in Tokyo in 1924, studied medicine at Hokkaido Imperial University, graduating in 1946, and obtained his medical license in 1947. He further specialized in nervous system diseases, earning a Doctorate in Medical Science with a specialty in clinical neurophysiology. Wada was appointed at the rank of lecturer in 1951 at Hokkaido University and was subsequently promoted to assistant professor in 1953 (Snyder & Harris, 1997; van Emde Boas, 1999).

Wada worked in the Department of Neurology and Psychiatry, which was responsible for evaluation and management of all neurologic patients. Although neurosurgery began to emerge as a medical specialty in the 1920s–1930s in many parts of the world, this was not the case in post-war Japan, and thus many of the patients seen by the Department of Neurology and Psychiatry had brain tumors. Because of the absence of effective brain tumor therapy, Wada explored the feasibility of establishing a surgical tumor resection program. Although the Department of Surgery was not interested in developing a tumor program, it did offer to provide technical support to develop neurosurgery by others in the institution, and Wada this opportunity to teach himself the neurosurgical skills needed for tumor resection. He obtained neurosurgery texts from his brother, Juro Wada, M.D., and from Dwight Harken at Harvard. (In 1968, Dr. Juro Wada performed the first heart transplantation in Japan and was subsequently charged with murder, even though the donor was brain dead; this charge occurred before brain death laws were introduced, and he

was subsequently exonerated.) Despite the medical success of tumor resection, Juhn Wada also observed the devastating effects of post-operative aphasia on recovery and overall quality of life. To provide some margin of safety for minimizing post-operative language deficits, Wada began using local anesthesia during surgery so that he could verbally engage patients during the operation in order to minimize extensive resection of language areas.

Although the Wada test is typically thought of in the context of pre-operative evaluation for epilepsy surgery, it was developed to better understand the cognitive side effects "electric shock" therapy, which was widely used to treat a variety of significant psychiatric diseases prior to the introduction of neuroleptics (Wada, 1997b, 2008). The two primary electrical stimulation techniques for psychiatric disorders were bi-frontal and bi-auricular; repeated bi-frontal stimulation produced convulsions with significant concomitant memory impairment and decreased speech output. In contrast, bi-auricular stimulation, which did not result in a convulsion, was associated with amnesia but only minimal effects on speech.

Wada questioned whether or not language impairment with frontal stimulation was a necessary component for treatment effectiveness, and he tried initially to answer this question with unilateral frontal electrical stimulation and unilateral carotid administration of pentylenetetrazol (pentylenetetrazol was a pharmacologic option to induce seizures similar to electric shock). Unfortunately, both approaches resulted in generalized convulsion. To prevent seizure generalization and allow a comparison of approaches, Wada hypothesized that hemispheric anesthesia would prevent seizure bilateralization and allow electrical stimulation without affecting the language-dominant hemisphere. Thus, unilateral "anesthetization through a carotid route to prevent seizure bilateralization" would be a formal test of whether unilateral frontal simulation without language effects would provide therapeutic benefit.

Prior to testing this hypothesis, Wada encountered a patient with multiple episodes of partial status epilepticus with occasional generalization resulting from a penetrating missile injury. The Japanese patient had been a cook at an American army base when he sustained a left parasagittal injury from a drunken American soldier who claimed he could shoot the cook's cap off. The patient's seizures were refractory to phenytoin and phenobarbital. Repeated treatment attempts using rectal chloral hydrate, the standard treatment at that time, as well as general sedation, were ineffective.

Since the patient's status could not be interrupted, Wada asked permission of the patient's family to try to treat the status using the amobarbital that he had obtained to study unilateral electrical stimulation effects. He injected it through the internal carotid artery, resulting in immediate arrest of the status, but the patient became transiently hemiplegic and mute. Wada described both the clinical history of the patient and the therapeutic use of amobarbital in several subsequent descriptions of the early history of intracarotid amobarbital administration (Wada, 1997b, 2008). Years later, Wada's original hypothesis on electrical stimulation and language was confirmed with the demonstration

that stimulation over the non-language-dominant right hemisphere resulted in a therapeutic benefit to patients but with a smaller magnitude of amnesia associated with the procedure (Sackeim et al., 1986; Snyder & Harris, 1997; Weiner, Rogers, Davidson, & Squire, 1986).

After one of Wada's surgical tumor patients became transiently aphasic following resection of a right frontal astrocytoma combined with the success/tolerability of amobarbital to treat status epilepticus, Wada started routinely assessing language dominance with intracarotid amobarbital injection. The first formal report of the language and behavioral effects of intracarotid amobarbital administration was published in Japanese in 1949 (Wada, 1949), and it was not until nearly 50 years later that this paper was translated into English (Wada, 1997a). Wada's intent in that study was to gain full knowledge of the effects of carotid amobarbital administration before combining it with unilateral electrical treatment. Fifteen right-handed patients with psychiatric disorders were administered 250 mg amobarbital sequentially, first in the right and then in the left carotid artery; this dose is much higher than what is typically used in contemporary Wada testing. Amobarbital injection caused contralateral flaccid hemiparesis of the arm and leg, contralateral facial paralysis, and slowed ipsilateral pupillary response. The pupillary slowing recovered approximately 2 minutes post-injection, although the facial paralysis did not return to baseline until 20 to 30 minutes after injection.

All 15 patients developed aphasia following left hemisphere injection, although one patient also developed a brief "speech impediment" following right hemisphere injection.

> *For all cases of injection on the left side, I observed a marked occurrence of aphasic symptoms, although the degree of the symptoms was not the same for all cases. Symptoms of motor aphasia were always observed, and moreover, in extreme cases, there was a suspicion of symptoms of sensory aphasia and apraxia. In addition, paraphasia, amnesic aphasia, and perseveration … were observed. These symptoms disappeared after about 30 min. (p. 12)*

Wada also described amobarbital's effect on consciousness. "A few cases complained of a mild drunken feeling, but actual loss of consciousness was never seen." He concluded by stating that the attentional "symptoms induced by left-sided injection produced more serious effects than that by right-sided injection," a finding that was experimentally confirmed nearly 50 years later (Glosser et al., 1999; Meador et al., 1997).

In the 1950s, Penfield and colleagues at the Montreal Neurological Institute (MNI) had been conducting epilepsy surgery for over a decade and were performing intraoperative stimulation to map cortical functions in some cases. They were interested in being able to determine language lateralization preoperatively. In 1954, Wada visited the MNI on sabbatical and introduced them to intracarotid amobarbital testing. Thus, additional patients were added to Wada's prior series and reported in the initial MNI report of this technique (Wada & Rasmussen, 1960). "Approximately 80 patients were tested … in Japan during the period 1948–1954, using doses of 50 to 300 mg of 10 percent Sodium Amytal, and no complications were encountered" (p. 266). The safety profile was further delineated in

this report based upon results from 8 macaque monkeys who underwent 11 experiments. In these studies, 7–350 mg amobarbital (corresponding to 1–35x the human reference of 200 mg) was studied using 10% and 20% concentrations (Wada & Rasmussen, 1960). The 10% concentration was safe for doses up to 210 mg (equivalent to 20x the maximal human dose), although large doses of 20% solution resulted in patchy microscopic infarction.

Similar to the prior studies by Wada, the initial MNI patients were administered amobarbital via a direct carotid stick using an 18 or 19 gauge need inserted into the common carotid artery, the approach used for carotid angiography at that time. The needle was positioned in the common carotid rather than the internal carotid to minimize puncture time. Amobarbital (10% solution) was injected over 1 to 2 seconds while the patient was counting, and clear behavioral differences were present based upon whether the left or right hemisphere was injected.

> *The patient would usually hesitate or stop counting near the end of the injection, but if the nondominant hemisphere had been injection, would resume on request within 5 to 20 sec. and then would name objects accurately while the contralateral hemiplegia was still complete. When it was the dominant hemisphere that had been injected, the patient was unable to continue counting while the contralateral hemiplegia was complete. On command, the patient would carry out voluntary movements with the ipsilateral extremities, as soon as the initial brief period of confusion had passed, demonstrating that the patient was co-operating and that the lack of speech was not caused by disturbances of consciousness or co-operation. As tone and power began to return in the contralateral arm and leg, the patient began to response with "yes and 'no,' and then was able to count. There was usually a period of 1–3 min. during which typical dysphasic responses such as perseveration and inability to name objects would occur, then normal speech returned*.

(Wada & Rasmussen, *1960*)

Of the 12 patients who self-identified as being left handed, Wada testing established right cerebral speech dominance in 6 patients and left cerebral speech dominance in 6 patients. In the 6 patients who were right handed, all were considered left cerebral speech dominant. Finally, in 2 patients with right-sided infantile hemiparesis, the clinically assumed speech dominance of the right hemisphere was established by carotid amobarbital injection. The authors also observed that "most patients believed that they had obeyed the various commands satisfactorily and were unaware of either the hemiplegia or inability to speak. We have no good explanation for this curious amnesia during this period of from 1 to 3–4 min. when the patients seemed to be quite clear and co-operative."

Throughout much of the early literature, the term "speech" is used rather than "language" when characterizing cerebral dominance. In Wada's original 1949 report, the language deficits are referred to via various terms including "speech loss," but also as aphasic symptoms, as well as specific motor aphasia, sensory aphasia, and paraphasia. In the

1960 report emphasizing speech lateralization, however, there are 2 descriptions of temporary "partial aphasia" developing post-operatively. Though speculative, the emphasis on speech likely reflects the preference of Penfield, who prior to Wada testing, relied exclusively on stimulation mapping in which disruption of counting or naming (i.e., speech) was used to establish cerebral dominance. However, as we will later discuss, the use of "speech" in the context of Wada testing has led some to characterize transient counting disruption following non-dominant hemisphere injection as evidence of language representation in the non-dominant hemisphere. Nevertheless, "speech" remains in common use in describing cerebral language dominance.

Language Laterality and Handedness

The first large patient series (n = 123) reporting language findings using amobarbital was published in 1964 (Branch, Milner, & Rasmussen, 1964). Four patients were excluded due to technically unsatisfactory studies, and unilateral rather than bilateral studies were conducted in in 22 patients. Patients were administered 200 mg amobarbital while counting, which represents a slightly lower dose than Wada reported in his initial 1949 patient series. Language testing included object naming, counting, and reciting the days of the week both forward and backward. This was an extremely influential paper addressing brain-behavior relationships beyond simply demonstrating the effectiveness of the procedure by empirically describing the relationship between handedness and cerebral language dominance, as well the effects of early lesions versus later lesions on altering cerebral language representation.

This patient series was extended several times, and the most widely cited report was published in 1977 (Rasmussen & Milner, 1977). Nevertheless, this was not a representative sample, since patients would undergo Wada testing only if atypical language was suspected based upon left- or ambidextrous handedness, although some right-handed patients were also referred for Wada testing if there were concerns about possible atypical language representation. Possible atypical language was suspected based upon left EEG abnormalities without post-ictal aphasia, right EEG abnormalities with post-ictal aphasia, left hemisphere injury that occurred before 2 years of age, or non-congruent neuropsychological findings including dichotic listening with clear left ear advantage. As seen in Table 1, most left-handed patients were left cerebral language dominant, which was the most robust data set to refute the Weisenberg and McBride (1935) hypothesis that the likelihood of right language dominance varied based on "the use of the left hand in writing."

Table 1. Speech lateralization as related to handedness in 262 patients without clinical evidence of early damage to the left cerebral hemisphere (Rasmussen & Milner, 1977)

Handedness	Sample	Left	Bilateral	Right
Right	N = 140	134 (96%)	0 (0%)	6 (4%)
Left/mixed	N = 122	86 (70%)	18 (15%)	18 (15%)

This report also described differences in how bilateral or atypical language can be expressed. In 9/18 bilateral patients, injection of one hemisphere produced naming errors without difficulty in series repetition tasks or in oral spelling, whereas injection of the other hemisphere projected errors and hesitation in serial ordering tasks without any naming impairment.

The 1977 data relating language, handedness, and age of seizure onset quickly became the most widely quoted numbers describing their interplay. Nevertheless, as more epilepsy centers were established in the 1980s and 1990s, and Wada began to be performed by many different centers, different approaches to assess language and to operationalize presence or absence of language representation were employed, and different figures regarding bilateral language representation emerged

Operational definitions of "dominance" versus "representation" were also a major source of confusion. In a survey of epilepsy surgery centers performing Wada testing in the late 1980s, the prevalence of mixed (i.e., bilateral) language representation varied from 0% to 60% of cases evaluated (Snyder, Novelly, & Harris, 1990). These methodological and definitional issues directly affect the detection of bilateral language representation since it is possible to have language dominance of one hemisphere with fewer, but clear, language errors present during injection of the "non-dominant" (bilateral but asymmetrical language, e.g., L > R). Different classification criteria were applied with language characterized both with respect to strict presence or absence of language representation, in which a bilateral language was considered independent of potential asymmetry (e.g., L > R) and also classified relative hemispheric dominance, in which a single side would be considered "dominant" despite bilateral language representation (e.g., L > R considered left dominant; Loring et al., 1990). In patients with bilateral language, an asymmetry was present 77% of the time (76% L > R, 24% R > L), and only ~2% of subjects having language restricted to only the right hemisphere (see Table 2).

Table 2. Incidence of language representation as a function of handedness without regard to early injury (Loring et al., 1990).

	Handedness	N	Left Language	Bilateral	Right Language
Exclusive Representation	Right	91	73 (80.2%)	17 (18.7%)	1 (1.1%)
	Left/mixed	12	6 (50%)	5 (41.7%)	1 (8.3%)
Relative Dominance	Right	91	83 (91.2%)	4 (4.4%)	4 (4.4%)
	Left/mixed	12	9 (75.0%)	1 (8.3%)	2 (16.7%)

Most patients who do not have exclusive left cerebral language dominance have some bilateral language representation. Exclusive right hemisphere language therefore seems to be relatively rare, a finding that has been supported by functional MRI studies (Binder et al., 1996). Language representation, therefore, may be best considered as a continuous rather than dichotomous variable (Loring et al., 1990). This suggested that he high rates of right hemisphere dominance reported by Rasmussen reflected either assessment method variance or an artifact of dichotomizing a continuous variable. fMRI was used to demonstrate that initial speech arrest alone following initial administration of amobarbital was not by itself a reliable index of language representation, with a more comprehensive language assessment during the Wada correlating with fMRI language activations (Benbadis et al., 1998).

Wada Memory Testing

As surgery was being developed as a viable treatment for epilepsy in the early 1950s, the specialized role of the hippocampus in recent memory formation was not yet understood. Two cases of significant memory impairment following left temporal resection in 1951–1952 were described (Penfield & Milner, 1958), and the cause of their significant memory decline was hypothesized to be due to the presence of pre-existing right temporal lobe damage. Thus, the combination of left sided surgical resection with pre-exiting right hemisphere damage produced bilateral temporal lobe impairment since there was insufficient temporal lobe function in the contralateral right temporal lobe to sustain memory. The hypothesis of significant contralateral mesial temporal disease was confirmed later in one of the patients whose brain was examined at autopsy (Penfield & Mathieson, 1974).

H.M.'s bitemporal resection for epilepsy was performed in 1953 by William B. Scoville, and Penfield became aware of H.M.'s amnesia in 1956 along with amnesia in patients undergoing bitemporal resections for psychiatric disorders.

> *During the preparation of our reports, William Scoville, MD, described to me the psychotic patients on whom he had operated, removing both hippocampal zones in one procedure, with the untoward results similar to my own. Our talk took place during a meeting of neurosurgeons (the proper place for discussion of unhappy results!). He had used an anterior approach to each temporal fossa and employed deep suction to remove the cerebral tissue.*
>
> (Penfield & Mathieson, *1974, p. 145*)

H.M.'s amnesia provided the strongest clinical evidence for the role of the temporal lobe in recent memory. However, the 1950s were also a time for psychosurgery, since there were few treatment options for patients with significant psychiatric disease (Dittrich, 2016; Loring & Hermann, 2017). Although H.M.'s memory impairment is now well known, many patients had bitemporal resection as part of psychosurgical management for diagnoses such as manic-depressive disorder or schizophrenia (Scoville & Milner, 1957). The 1957 report also contains formal testing on additional temporal lobectomies performed

on "seriously ill schizophrenic patients who had failed to respond to other forms of treatment" (p. 11); two of the testable patients also developed significant amnesia following bitemporal resection. Orbital undercutting was extended to include the medial temporal lobes in the "hope that still greater psychiatric benefit might be obtained" (p. 11). The significant psychiatric disease of these patients decreased clinical awareness of memory change, since "the psychotic patients were for the most part too disturbed before operation for finer testing of higher mental functions to be carried out" (p. 12). Thus, the extent of the memory impairment was not recognized due to the significant overlaying psychiatric disease in the non-epilepsy patients.

Also during this time, there were many other reports of memory change following temporal lobectomy for the treatment of epilepsy (Loring, Meador, Lee, & King, 1992). In a series of 65 temporal lobectomies performed at the National Institutes of Health, 4 patients experienced significant post-operative memory decline (Baldwin, 1956). Four patients with marked memory declines from Johns Hopkins were also presented (Baldwin, 1956). Thus, findings from multiple centers identified risks associated with unilateral temporal lobe resection, and it became clear that methods to identify at-risk patients preoperatively would be needed to offer surgery as a safe treatment option. Penfield considered seizure freedom but with significant memory impairment as a treatment failure (Loring, 2010; Penfield & Jasper, 1954). Because of his concern for treatment-emergent cognitive change, he recruited Brenda Milner to study the effects of epilepsy surgery on cognition.

Memory declines were attributed to significant bilateral disease that went unrecognized during the pre-surgical evaluation. Dr. Milner modified the Wada test to assess the risk of postoperative amnesia following unilateral temporal lobectomy. By introducing items to be remembered during the period of hemispheric anesthesia, Milner reasoned that the effects of surgical resection on memory could be modeled and risk for significant postsurgical decline estimated (Milner, Branch, & Rasmussen, 1962). The use of Wada memory testing to assess risk of post-surgical decline is based upon 3 assumptions (Loring et al., 1992): (1) Unilateral temporal lobe inactivation from amobarbital is not sufficient to create global amnesia; (2) Appropriate regions of the mesial temporal lobe and hippocampus are rendered functionally inactive from intracarotid amobarbital injections; and (3) If significant mesial temporal lobe dysfunction exists contralateral to the injection, then a state of bitemporal dysfunction was created leading to significant memory impairment. Thus, Wada memory testing was introduced as a way of determining whether there was sufficient hippocampal function to sustain memory postoperatively in the temporal lobe contralateral to the side of the proposed temporal lobe resection.

The initial series reporting Wada memory findings included a consecutive series of 50 patients (Milner et al., 1962). Memory impairment was observed in 5 dominant hemisphere injections and 7 non-dominant injections. More importantly, memory impairment was present in 11 patients following injection contralateral to the seizure focus, and in only 1 patient ipsilateral to seizure focus. In a larger series from the MNI (Milner, 1972), memory impairment was present only 27 times following 226 injections; memory failure was

present in 25/110 following injection contralateral to seizure onset, but in only 2/116 ipsilateral injections.

The overall high rate of successful memory following injection contralateral to the seizure focus, however, presented a challenge to the basic assumptions associated with Wada memory performance; namely, impaired memory should be a common finding when tested following contralateral injection. Further, if performance following contralateral injection is considered to reflect the patency of the temporal lobe to be resection, then contralateral injection may be useful as an indicator of the risk of material-specific decline following surgery rather than as a measure of global post-surgical amnesia (Kneebone, Chelune, Dinner, Naugle, & Awad, 1995). This was demonstrated for patients undergoing language- dominant temporal resection whether contralateral performance was characterized as pass/fail or as a continuous variable; patients with higher contralateral scores had greater declines in verbal memory post-operatively. No relationship with performance contralateral to a non-dominant temporal lobectomy and decline in visual memory was observed. This relationship was formalized by Chelune (1995) by characterizing the *functional adequacy* of the to-be-resected hippocampus—as reflected by less hippocampal atrophy, higher hippocampal cell counts, or better preoperative memory performance—as a primary mediator of pre- to postoperative memory change, rather than the *functional reserve* of the contralateral temporal lobe as initially proposed (Milner, Branch, & Rasmussen, 1962).

The preoperative evaluation for epilepsy surgery includes not only the localization of the seizure onset zone, but also the localization of dysfunction and determination of functional regions. These functional evaluations not only to prediction of postoperative risks, but they can contribute to prediction of success in reducing seizures. For example, the Wada test has been shown to predict postoperative seizure outcomes (Loring et al., 1994).

Diagnostic Wada Testing of Epileptic Discharges

Although Wada testing is primarily used to characterize unilateral language and memory function, amobarbital injection has also been used in other contexts to provide additional diagnostic clarity. Because focal epileptogenic lesions may produce bilaterally synchronous EEG abnormalities resembling spike and wave patterns associated with generalized seizures, hemispheric anesthesia was proposed as a technique to differentiate patients with unilateral discharges that spread bilaterally from those that are generalized discharges arising from the hypothesized midline centencephalic system. Thus, if the EEG abnormality was focal in nature, injection ipsilateral to the lesion would be expected to fully abolish the spike and wave complexes, whereas if the EEG abnormality reflected a generalized onset, the spike and wave complexes on the contralateral side would be expected to persist (Rovit, Gloor, & Rasmussen, 1961). This approach was successful, with drug injection inhibited epileptiform EEG in patients with focal abnormalities with "secondary bilateral synchrony," but had no similar inhibitory effect on EEG abnormalities in patients with generalized epilepsy. Review of the literature, however, provides no clues regarding why this approach was not continued, although we can speculate that it may be

related to issues with crossflow, diaschisis, or simply a paucity of data about the amount of anesthesia needed.

Origin of the Erroneously Capitalized WADA

One of the enduring questions regarding Wada testing is why it is frequently in all capital letters when the term is eponymous. The earliest description of this approach to identify cerebral language dominance describes the procedure in a footnote: "The intracarotid arterial injection of amobarbital sodium was introduced by Dr. Juhn Wada in 1949 and is now being studied by him and Dr. Theodore Rasmussen" (Roberts, 1958). In the earliest published report describing the procedure as the Wada test establishing cerebral language dominance, there is no such capitalization (Ommaya & Baldwin, 1963). "A Wada test revealed a clear left cerebral hemisphere dominance for speech" (p. 13). Although perhaps apocryphal, it has been suggested that during the construction of the first Current Procedural Terminology (CPT) codebook in the 1960s, Wada was simply typed in all capital letters in one of the early manuscript versions, since it was an unfamiliar term and seemed to the typist that it must have been an acronym.

Conclusions

The use of Wada testing as the primary technique to identify cortical language regions and predict risk of post-operative memory decline has been increasingly displaced by EEG video monitoring, MRI of the hippocampus, PET, SPECT, fMRI, and even multi-modality imaging. Nevertheless, the technique of selective arterial barbituration of critical brain regions developed by Wada has played a critical role in the advancement of clinical neuroscience and made a meaningful impact on both the practice of epilepsy surgery and on our understanding of brain-behavior relationships.

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History of the Wada Test

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