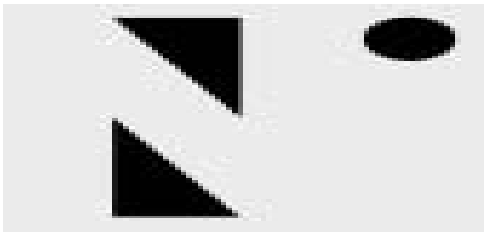

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October 6, 2002

Jeffrey Shuren, MD, JD Division Director, Division of Items and Devices CMS (formerly HCFA)
7500 Security Blvd. Baltimore, MD 21244

Re: CMS Decision Memorandum: Electrodiagnostic Sensory Nerve Conduction Threshold (CAG-#00106N)

Dear Dr. Shuren,

We respectfully request that CMS reconsider the above Decision Memorandum in light of the new information we are providing with this submission and the information previously provided to CMS but never reviewed.

This request is accompanied by three documents. The first is titled Rebuttal to Decision Memorandum and it documents and corrects the abundant, substantial and fatal flaws in the Memorandum. The second is titled Supplemental Information and it contains new and updated information about the sNCT/CPT sensory nerve evaluation procedure. The third document is titled Utilization Guidelines and it presents detailed guidelines for the clinical application of the sNCT/CPT procedure. Reprints of three recent significant studies are also included.

As you are aware, clerical errors at CMS kept much of our application and the supporting documents we and others had provided to CMS over a nine month period from being reviewed by the author(s) of the Memorandum. Also, personnel changes at CMS caused the Medical Officer we had worked with to be removed from our application at the last minute - along with his name and findings. Therefore, we respectfully request that CMS include the materials we and others had submitted previously to CMS along with the new submissions and thoroughly review them all with due diligence.

Also, the author(s) of the Decision Memorandum had so little understanding about the diagnostic procedure they were tasked with evaluating, that one of the two criticisms leveled against the sNCT/CPT sensory nerve test procedure was that it does not evaluate motor nerves! As a neurologist, we're certain you understand that motor nerves and sensory nerves perform different functions, suffer from different diseases and injuries and that they are evaluated using different methods - each with its own

sets of CPT procedure codes. Therefore, in addition to making ourselves available to answer any questions about our application, we are also available to help educate the reviewer(s) in the fundamentals of nerve testing so that an informed review can be conducted.

CMS Administrator Tom Scully's office assured us that our application would be fairly and competently reviewed by CMS personnel with the best interests of the United States Government and the Medicare population in mind. Additionally, Dr. Sean Tunis had assured us that the review process would be completely transparent and that we would be given the opportunity to respond to any criticisms before a decision was rendered. You, also, have provided us with the opportunity to supply you with a list of experts in neuropathies who are familiar enough with the sNCT/CPT procedure to be able to render opinions based upon experience and fact, not conjecture, ignorance or greed. We are greatly appreciative of these commitments and we are confident that they will help assure a fair and competent review of our application.

The materials we have provided CMS clearly demonstrate that the sNCT/CPT evaluation measures sensory nerve function with very high specificity and sensitivity and that it evaluates both large and small sensory fibers. There are a number of other modalities used to measure sensory nerve function and numerous peer reviewed studies have shown the sNCT examination to be at least equivalent to those other modalities and to be superior to some. We are not asking CMS to approve a new type of diagnostic function since sensory nerve evaluation is already a covered medical procedure. Instead, we're asking CMS to recognize the sNCT/CPT procedure in the same way and for the same purposes as currently covered electrodiagnostic sensory nerve testing procedures. There are no new benefit categories that need to be created and there's no reason to expect that the greater sensitivity and specificity of the sNCT/CPT procedure will do anything but lower Medicare's costs.

We respectfully await your decision on our request for reconsideration.

Sincerely,

Ralph P. Cohen
President

Jefferson J. Katims Founder,
Medical Director

cc: Senator Barbara Mikulski Congressman Benjamin Cardin Director Thomas Sculley

Neurotron, Incorporated

Request for Reconsideration CMS Decision Memorandum CAG# 00106N Electrodiagnostic Sensory Nerve Conduction Threshold

Part 1. Rebuttal to Decision Memorandum

Submitted by:

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664-0831

Submission List

Part 1. Rebuttal
Part 2. Supplemental Information Part 3.
Utilization Guidelines

Rebuttal to CMS Decision Memorandum for Electrodiagnostic Sensory Nerve Conduction Threshold (#CAG00106N)

Table of Contents

Rebuttal to CMS Decision Memorandum for Electrodiagnostic Sensory Nerve Conduction Threshold (#CAG00106N)

Introduction

The sNCT/CPT evaluation represents an advancement in electrodiagnostic sensory nerve testing technology that has been repeatedly and consistently validated in more than 350 peer reviewed studies published since 1985. Specifically, the sNCT/CPT evaluation methodology, the reliability of the sNCT/CPT measure and basis for the scoring of those measures have all been validated. There are no peer reviewed scientific publications that are critical of the sNCT/CPT methodology, normative measures or the evaluation of those measures. Every peer reviewed study ever published that followed the standardized testing methodology for the sNCT/CPT evaluation reported positively on its ability to objectively and accurately assess the integrity of sensory nerve function. Together, we believe these studies provide an irrefutable basis for a conclusion that the sNCT/CPT evaluation is a clinically effective diagnostic procedure beneficial, reasonable and necessary for the Medicare subpopulation at risk for nerve injuries or disease.

Unfortunately, immediately following publication of the Decision Memorandum (DM), CMS discovered that it had misplaced large portions of Neurotron's Formal Request for an NCD along with much of the supplemental information that had been provided to CMS. Consequently, those materials were neither reviewed nor considered for the DM and the glaring errors, inconsistencies and omissions in the DM clearly reflect that fact. According to CMS, those missing documents have now been located are available to CMS to review for this request for reconsideration. Those **t**emporarily **l**ost **d**ocuments will heretofore be referred to with the acronym TLD.

Another equally-as-serious but even-more-difficult-to-understand problem with the DM is that the authors evaluated the sNCT/CPT sensory nerve testing procedure by comparing it to a motor nerve testing procedure - apparently unaware that they are two entirely different things. In fact, of the two primary faults the reviewers found with the sNCT/CPT procedure, one was the fact that this sensory nerve tester doesn't test motor nerves!

It is hoped that comments, criticisms and corrections that follow will help CMS recognize that this DM is fatally flawed and should be granted reconsideration. If CMS does come to that conclusion, then hopefully this document will assist the new reviewer(s) in avoiding the same mistakes.

Clinical Background Section

The Clinical Background section commingles discussion of sensory and motor nerve test procedures. Sensory nerves and motor nerves perform separate physiological functions, suffer impairments from different groups of diseases and injuries and are evaluated using different procedures. Sensory and motor nerve test procedures are not interchangeable, they are separately coded and reimbursed and it is neither medically nor ethically justified to routinely apply them in tandem. It is completely unclear, therefore, why the reviewers repeatedly refer to motor nerve testing since the stated focus of the **D**ecision **M**emorandum (DM) is the sNCT/CPT evaluation, a sensory nerve test procedure.

The intent of the DM was also clouded by the repeated reference to the acronym NCS (**n**erve **c**onduction **s**tudies) as if it represented a single procedure that assesses the integrity of both the sensory and motor nerves. As mentioned above, there is no such single test or procedure. The **s**ensory **n**erve **c**onduction **t**hreshold (sNCT/CPT) and **s**ensory **n**erve **c**onduction **v**elocity (sNCV) are two types of electrodiagnostic sensory nerve conduction studies while the **m**otor **n**erve **c**onduction **v**elocity (mNCV) and electromyogram (needle EMG) are two types of electrodiagnostic motor nerve conduction and muscle physiology studies.

The sNCT/CPT and sNCV sensory test procedures both use electrical stimuli applied to the peripheral nervous system (PNS) to evaluate the ability of a sensory nerve to conduct a stimulus. The sNCT/CPT test stimulates the PNS to evaluate a sensory nerve's ability to conduct a signal from the PNS through to the Central Nervous System (CNS). It assesses the integrity of more than 90% of the fibers comprising the sensory nerve. The sNCV test stimulates the PNS to evaluate a sensory nerve's ability to conduct a signal between a short segment of the nerve. It assesses the integrity of less than 10% of the fibers comprising the sensory nerve. For certain conditions, it may be appropriate to use either sensory test in conjunction with a motor NCS such as mNCV or the needle EMG.

It is appropriate to compare the sNCT/CPT procedure to the sNCV and other sensory nerve tests and peer reviewed studies consistently demonstrate that sNCT/CPT can be successfully substituted for those other sensory tests and nerve biopsies for certain diseases and conditions. Studies also demonstrate the superior diagnostic utility if the sNCT/CPT test for certain pathological conditions. The Supplemental Information section of this submission provides additional detailed information that examines the relative diagnostic abilities of sensory nerve tests in greater detail.

We believe that the following sentence describing the sNCT/CPT procedure was not appropriate: (emphasis added)

"Measures are obtained using a portable, 6-V battery powered,

> microprocessor controlled, constant alternating current sinusoid waveform stimuli at intensities ranging from 0.001 mAmperes to 9.99 mAmperes and frequencies of 5 Hz, 250 Hz, and 2,000 Hz to, theoretically, assess the integrity of the three sensory nerve fiber types."

CMS was given extensive documentation derived from peer reviewed studies demonstrating the ability of the test to "assess the integrity of the three sensory nerve fiber types". Appendix E. Section 4 of Neurotron's original Formal Request included references and an overview of

sNCT/CPT research related to neuroselectivity. New publications continue to document the neuroselectivity of the sNCT/CPT test including and important study from the University of Texas[1]. A complete list of recent publications related to neuroselectivity are provided in the Supplemental Information portion of this communication to CMS.

We believe that the wording of another sentence later on in the description of the sNCT/CPT procedure was also not appropriate: (emphasis added)

> "The manufacturer asserts that abnormally high sNCT measures reportedly indicate a significant loss of nerve conduction, while abnormally low sNCT indicates a hyperesthetic state that corresponds with inflamed, irritated, or regenerating nerves"

Healthcare providers have long been aware that insensitivity to any stimulus that normally evokes a sensation, whether that stimulus is evoked by a safety-pin, tuning fork, Von Frey hair, hot test tube or electrical current, is indicative of a loss of sensory nerve function or a hypoesthetic state. It's not merely the manufacturer's assertion that a person requiring a higher than normal level of electrical stimulus (i.e. "high sNCT measure") before being able to perceive any sensation is indicative of a hypoesthetic state, it is a fundamental precept of the physiological understanding of the sensory nervous system. Healthcare providers are also aware that local anesthetic agents like lidocaine cause a loss of sensation or hypoesthesia and numerous peer reviewed publications have demonstrated the ability of the sNCT/CPT to accurately evaluate the effects of local anesthetics. (e.g. Appendix E ref 1,2 in Formal Application) Likewise, clinicians are aware that a person's sensitivity to a sensory stimulus source that does not normally evoke a sensation is indicative of a hyperesthetic state associated with inflamed or irritated nerves.

Also, contrary to the above statement from the DM, Neurotron is not aware of any relationship between nerve regeneration and hyperesthesia. In a meeting with Drs. Tunis, Shuren and Whyte at CMS, this point was specifically discussed in the context of a sixteen month nerve regeneration study at Johns Hopkins Medical

[1] Baron, G.C., Irving, G.A. Effects of Tourniquet Ischemia on Current Perception Thresholds in Healthy Volunteers. Pain Practice, Volume 2 (2):129-133, 2002 (Other studies replicating these findings available upon request.)

Institution by Dr. Lee Dellon[2]. The study used serial sNCT/CPT measures to monitor the return of sensory nerve function and demonstrated that sensory nerve conduction in regenerating nerves transitions from anesthetic to hypoesthetic to normal. The sNCT is insensitive to nerve regeneration.

Finally, the last statement in paragraph seven states: "Typically, the procedure takes less than 30 minutes." While technically accurate, it should be noted that the manufacturer demonstrated a typical sNCT/CPT procedure to Dr. Whyte at CMS and that procedure took less than 10 minutes to complete. Also, during that single 10 minute procedure, nine times as many sensory nerve fibers were evaluated as are capable of being evaluated in a sNCV procedure.

Note: Some of the shortcomings noted in this section of the DM may have resulted from the

TLD problem discussed in the Introduction.

[2] Dellon, A.L. Somatosensory testing and rehabilitation, published by the American Occupational Therapy Association, page 147, 1998.

General Principles for the Evaluation of Diagnostic Tests Section

The first part of this section of the DM discusses the importance of knowing the sensitivity and specificity of a procedure before being able to make an informed decision about coverage. During discussions with Dr. Shuren immediately following the posting of the DM, he indicated that one of the two major concerns he had about the sNCT/CPT procedure was that he wasn't aware of its accuracy having been defined in terms of sensitivity and specificity. CMS had, in fact, been provided with extensive documentation specifically addressing the high accuracy, sensitivity and specificity of the sNCT/CPT procedure in the Formal Request. We also responded to requests for additional information by providing extensive supplemental statistical analyses documenting the sensitivity of the procedure compared to other sensory nerve tests using published statistical data. Unfortunately, this information was never reviewed for the DM because it was part of the TLD problem discussed in the Introduction of this document. The Supplemental Information document included with this submission contains additional documentation of the high accuracy, sensitivity and specificity of the sNCT procedure.

The second concern voiced by Dr. Shuren was that our application had failed to specifically address the effects of the sNCT/CPT evaluation on patient management for specific patient conditions, i.e. utilization guidelines. His criticism came as a surprise since in a meeting on October 12, 2000 with Dr. Sean Tunis and his staff (and later confirmed by Dr. Whyte), we told that we were only burdened with demonstrating that our procedure was at least substantially equivalent to other covered procedures since the justification for coverage of sensory nerve testing procedures had already been established. Consequently, our Formal Response submission focused on documenting the substantial equivalence and even significant superiority of the sNCT procedure to other covered sensory nerve testing procedures. A new sNCT/CPT Utilization Guidelines document is included with this submission to address Dr. Shuren's concerns. It parallels utilization guidelines already recognized by CMS for covered sensory nerve tests.

Summary of Evidence Subsection

Several inclusion and exclusion criteria listed in this section are at odds with instructions we received during our initial meeting at CMS and during the 10 months of the review by Dr. Whyte. For instance, Dr. Tunis and his staff told us that CMS would accept unpublished studies, personal communications and abstracts in addition to peer reviewed published studies if they helped contribute to CMS' understanding of a procedure being reviewed. They explained that this was because CMS was often asked to determine coverage for new treatments or procedures for which only a very few studies had been published. We were also invited to submit any peer reviewed review articles about the sNCT/CPT evaluation to assist CMS with the review.

According to the DM, however, all these types of submissions were specifically excluded from consideration.

We also told the staff that since 1986 when the sNCT/CPT procedure first entered clinical use, nearly 300 peer reviewed studies had been published and we offered to supply

CMS with a copy and summary of each one. The staff quickly declined our offer, however, saying that it would take far too long to review that much information and they asked us to limit our submission to 5-10% of that number. We sent just 31 publications with our Formal Request.

At no time during the ten months of the review did anyone at CMS mention the inclusion and exclusion criteria listed in the DM. If they had, it would have been a simple matter for Neurotron to provide alternative publications to those excluded by the criteria since there are literally hundreds to choose from. For example, one of the DM's inclusion criteria states that "Studies must have at least 10 patients." While only two of the publications submitted with our Formal Request less than 10 subjects, there are peer reviewed studies with 48[3] subjects and 32[4] subjects that could have been used instead to make the same points.

Another paragraph in the Summary of Evidence section of the DM begins with the following statement:

> "Using various combinations of the following search terms: "sensory nerve conduction" "neurometer" "current perception threshold," a total of ten studies were obtained.

At the very least that statement would appear to indicate a severe flaw in the search process used by CMS. At the time we submitted our Formal Request, there were already nearly 300 peer reviewed publications concerning the sNCT/CPT test listed in its bibliography[5]. And, by the time the review was re-started 10 months later, there were nearly 350 peer reviewed publications available.

The next sentence in the DM says:

> "In addition, several articles were submitted for consideration by the manufacturer."

As previously mentioned, reprints and summaries of more than 30 studies had been

[3] Yamashita, T., Kanaya, K., Sekine, M., Takebayashi, T., Kawaguchi, S., Katahira, G. A quantitative analysis of sensory function in lumbar radiculopathy using current perception threshold testing. Spine, Volume 27

[4] Falci, S.P., Best, L.G, Bayles, R., Cown, C. Dorsal Root Entry Zone (DREZ) microcoagulation for central pain of spinal cord injury: operative intramedullary electrophysiological guidance and clinical outcome. Journal of Neurosurgery (Spine 2), Volume 97:193-200, 2002.

[5] Appendix F of the Formal Request

included with the Formal Request. However, immediately following the posting of the DM we were informed that the bulk of the articles and the bibliography included with our Formal Request were part of the TLD problem and hadn't been reviewed.

The next part of the section summarizes the 10 references found by the reviewers. Not surprisingly, some of the summaries reveal a less than full understanding about what the articles are reporting. The extra supporting documents and statistical analyses we had

provided to CMS were part of the TLD problem and hadn't been reviewed for the DM. Our comments on seven of the summaries follow.

1. Rendell, M.S., Katims, J.J., Richter, R., Rowland, F. A comparison of nerve conduction velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. Journal of Neurology, Neurosurgery and Psychiatry, Volume 52:502-511, 1989.

The summary includes the criticism that "data on clinical utility was not provided". To the contrary, this study clearly demonstrates that the SNCT/CPT measure was found to be a more effective predictor of symptoms and physical impairments as determined by clinicians than sensory nerve conduction velocity testing. The correlation coefficients of the symptoms and physical findings were $p<0.001$ and $p<0.001$ for the sNCT studies $p<0.01$ and $p<0.05$ for sNCV studies, respectively. We believe this information represents "data on clinical utility" because there are occasions where a Medicare health care provider needs to objectively assess the severity of a patients metabolic neuropathy because the clinical examination and laboratory findings are equivocal and the efficacy of a therapeutic treatment regimen requires evaluation. The data presented in this study suggest that when clinically indicated, the sNCT evaluation had superior clinical utility for the evaluation of polyneuropathy than the sensory nerve conduction velocity evaluation.

2 Weseley, S.A., Sadler, B., Katims, J.J. Current Perception: Preferred Test for Evaluation of Peripheral Nerve Integrity. Transactions of the American Society of Artificial Internal Organs, Volume 34(3):188-193, 1988.

The summary states: "Grading the severity of the neuropathies was accomplished by using a concurrent test grade change, a convergent test grade change, a divergent test grade change, and a no test grade change. These measures were compared to those taken a year later." That statement is not correct. The grading criteria for CPT measures is presented in Table 3 in the paper and it is based on the number of standard deviations outside the normative mean a measure was located.

The summary also states, "The authors reported that CPT and NCS were highly correlated but that CPT was more sensitive." A chi-square SPSS statistical analysis was conducted to compare the detection of neuropathy by sNCT/CPT measure and SNCV measures in the median nerve and in the peroneal nerve. The tests were equally sensitive in their detection sensitivity for neuropathy ($p<0.119$, median nerve and $p<0.701$, peroneal nerve). These analyses were provided Dr. Whyte and in a

subsequent discussion he acknowledged their significance and said they answered his questions. All the analyses sent to CMS were performed using the original data included in this publication.

3. Menkes, D.L., Swenson, M.L., Sander, H.W. Current Perception Threshold: An Adjunctive Test for Detection of Acquired Demyelinating Polyneuropathies. Electromyography and Clinical Neurophysiology, Volume 40; Part 4:195-204, 2000.

The summary states: "The authors concluded that CPT should be considered an adjunctive test to NCS and EMG in the diagnosis of demyelinating polyneuropathies." Since the Decision Memorandum refers to the sNCV test as NCS, that statement is completely

false. The author of the study, Dr. Menkes, submitted correspondence to CMS stating specifically that this was **not** the conclusion of his paper. He said that the sNCT/CPT test should be used as an adjunctive test to other diagnostic tests but not to an electrodiagnostic sNCV test. Dr. Menkes August 19, 2001 correspondence to CMS also states:

> "Neurological disturbances of the sensory nervous system are no exception to this rule. While a sensory examination can provide some information, electrodiagnostic testing provides objective quantification of the location and degree of the sensory deficit. There are three important and complimentary tests that are important in this regard; sensory nerve conduction velocities (sNCV), somatosensory evoked potentials (SSEPs) and the Neurometer sensory nerve conduction threshold (sNCT).
>
> Sensory information is conveyed in three main types of sensory fibers designated A-beta, A-delta and C fibers. The A-beta fibers are large and thickly myelinated. A-beta fibers relay information regarding vibration and position. A-delta fibers are thinly myelinated and relay visceral afferent information. C fibers are unmyelinated and convey pain and temperature sensation. However, sNCV and SSEPs are only capable of analyzing the A-beta fibers. They provide no information whatsoever regarding A-delta of C fiber function. By contrast, the Neurometer sNCT is able to evaluate all three fiber types. This information should be contained in Dr. Katims's application.
>
> As an Assistant Professor of Neurology at the University of Tennessee who is the Director of the Clinical Neurophysiology Service, I am often asked to define the location and severity of a sensory deficit. This requires the ability to quantify sensory function in all three fiber subtypes. The anatomic distribution and the pattern of sensory dysfunction of the three main subtypes provides the best means of achieving an accurate diagnosis.
>
> I respectfully request that you approve the sNCT as being "reasonable and necessary" for the evaluation of sensory disturbances in the Medicare

> population. If you have any more questions, please do not hesitate to contact me."

Dr. Menkes comments clearly indicate the diagnostic superiority of the sNCT/CPT evaluation over other Medicare covered sensory electrodiagnostic tests.

4. Katims, J.J., Naviasky, E., Ng, L.K.Y., Bleecker, M.L., Rendell, M. New Screening Device for Assessment of Peripheral Neuropathy. Journal of Occupational Medicine, Volume 28(12):1219-1221, 1986.

Although this study describes the sensitivity and specificity data as it relates to the sNCT/CPT measures, this critical information was not included in summary in the DM and there's no indication that the reviewers were aware of. This is exactly the type of information the DM says is so critical for determining the accuracy of a test.

Additional detailed information about this study was provided to Dr. Whyte in the form of the FDA 510(k) application for the Neurometer CPT device which contained all of the

subject measures upon which the paper had been based. The Methods section of the study starts off by defining the sensitivity based on a specificity of 100%. However, the reviewers ask numerous questions in this summary that indicate that they did not understand that this article was a study of the sensitivity and specificity of sNCT/CPT measures and not a study of the sensitivity of sNCT/CPT measures compared to a physical exam. Also, the study included 54 control subjects not the 44 reported in the summary.

5. Masson, E.A., Veves, A., Fernando, D., Boulton, A.J.M. Current perception thresholds: a new, quick, and reproducible method for the assessment of peripheral neuropathy in diabetes mellitus. Diabetologia, Volume 32:724-728, 1989.

This concluding sentence of this summary makes a critical error when it states: "However, the authors point out that CPT may not directly stimulate nerve fibers." The Masson article actually states just the opposite.: "Neurometer stimulates nerve fibers directly...".

2 Ro, L.S., Chen, S.T., Tang, L.M., Hsu, W.C., Chang, H.S., Huang, C.C. Current Perception Threshold Testing in Fabry's Disease. Muscle & Nerve, Volume 22: 15311537, 1999.

This summary fails to mention the sensitivity and specificity data in the article and the reviewers also appear to have misunderstood and misinterpreted the clinical significance of the findings. Both the 2000 Hz sNCT/CPT measures and the sNCV had zero detection sensitivity for the smaller fiber neuropathy afflicting these patients. This was expected because the 2000 Hz CPT measure and the sensory nerve conduction velocity only evaluate the large diameter sensory nerve fibers. In contrast, 50% of the low frequency (250 Hz and 5 Hz) CPT measures detected sensory impairments based on a specificity of 100%. On November 8, 2001, Dr, Whyte was

sent a fax that summarized the following statistical findings from this publication derived from the original data presented in the article:

> "A chi-square SPSS statistical analysis was conducted to compare the detection sensitivity of neuropathy by sNCT/CPT and SNCV tests in this study. The CPT detected neuropathy in 50% of the patients. The SNCV detected neuropathy in 0% of the patients. There was a significant superiority of the detection sensitivity of the sNCT/CPT electrodiagnostic test over the SNCV test in this study ($p<0.001$, $df=1$). Please see the attached statistical SPSS analysis sheets." These analyses were conducted based on the original data that was included in this publication.

The diagnostic superiority of the sNCT/CPT evaluation compared directly to the sensory nerve conduction velocity relates to the clinical utility of the sNCT/CPT test in the management of Medicare patients suffering from smaller fiber neuropathies or diseases which effect the smaller fibers first. The sNCT/CPT evaluation tests over 90% of the sensory nerve fibers including both the large and small myelinated fibers and the small unmyelinated fibers from any cutaneous location. The sensory nerve conduction velocity evaluation, in contrast, tests less than 10% of the sensory nerve fibers and is limited to evaluating conduction in large myelinated fibers confined to a small segment of a large peripheral nerve in a distal extremity.

7. Rendell, M.S., Dovgan, D.J., Bergman, T.F., O'Donnell, G.P., Drobny, E.P., Katims, J.J. Mapping Diabetic Sensory Neuropathy by Current Perception Threshold Testing. Diabetes Care, Volume 12(9):636-640, 1989.

This review avoids a major point in this study which is mentioned in the title. The sNCT/CPT examination is able to map the distribution of a sensory impairment because it has the unique ability to test at any cutaneous site, a feature not found in any other electrodiagnostic sensory NCS.

This unique 'test anywhere' features offers a diagnostic advantage by permitting testing at the tips of the toes to detect the earliest stage of a distal axonal polyneuropathy. The sNCT/CPT evaluation also permits proximal testing to determine the extent of a dying back of the polyneuropathy. Testing proximally also permits earlier detection of nerve regeneration than possible with electrodiagnostic sensory NCS procedures.

Additional discussions about the clinical advantages of being able to test anywhere on the body can be found on pages 10 and 15 of Neurotron's Formal Request.

Technology Assessments Subsection

The only technology assessment referenced in the Decision Memorandum is a 1999 literature review by the AAEM. The **Summary of Evidence, Exclusion Criterion** section of the DM however lists the third exclusion criterion as: "3. Review Articles". (This may be why review articles included in Neurotron's Formal Request were ignored by the reviewers unless they were part of the TLD problem, too.) Further, AAEM's review plainly states, "This review was not written with the intent that it be used as a basis for reimbursement decisions." Therefore, use of the AAEM review in formulating the DM is clearly inappropriate by virtue of both CMS' Exclusion Criteria and AAEM's own disclaimer.

CMS was also made aware of the significant ethical and legal problems surrounding the AAEM article. AAEM fabricated twenty-one of the twenty-two authors listed on the article - none of whom had ever seen or approved the review. The organization also caused the literature review to be published without any peer review in a peer-reviewed journal over which they exercised editorial control. CMS was also shown AAEM documents that revealed that only a very small fraction of the studies listed in the article as providing the basis for its conclusions had ever actually been reviewed by the author. Much of this was discussed in the October 12, 2000 meeting with Dr. Tunis and his staff and in return they gave assurances that an article like AAEM fraudulent literature review would never be included in a CMS review. We didn't include any additional documentation about the AAEM article in the Formal Request other than a brief statement, because of the assurances we had received at that meeting. That documentation is still available, however, if CMS would like to see it.

Position Statements Subsection

The Decision Memorandum states, "We have not found any position statements by medical professional societies on sNCT". We strenuously disagree. The American Association of Clinical Endocrinology (AACE) provided CMS with a document that included utilization recommendations, careful scientific review, consultation with neurologists, evaluation by a committee and approved by their Board of Directors. This statement from the AACE was signed by the AACE President as well as its Coding Committee Chairman. One of the names appearing on the letterhead of the AACE submission, is that of Dr. Yank D. Cobel Jr. past president of AACE and president-elect of the AMA, who used the sNCT/CPT evaluation for many years and is extremely knowledgeable about and supportive of the procedure. Dr. Whyte also spoke directly with AACE to get additional comments and information. He told us that he considered the AACE submission to represent a valid position statement from a reputable organization. The DM cites supportive comments from the AACE position statement but then fails to offer any explanation why the position statement is afforded little or no credence or weight in the CMS review.

Professional Guidelines

The Decision Memorandum states, "we have not found any professional guidelines relating to the use of this technology". Once again, we strenuously disagree.. The State of Texas Workers Compensation Commission (TWCC) published "Guidelines" for the utilization of sNCT/CPT technology. They based their utilization recommendations upon a careful and scientific review of peer reviewed publications and consultation with physicians in a variety of fields including "neurosurgery, orthopedic surgery, physical medicine and rehabilitation, occupational medicine... and insurance." The TWCC's Director of the Medical Review Division wrote to CMS on September 12, 2001 confirming the basis for the guidelines. Dr. Whyte told us that he found the guidelines and the letter from TWCC to be extremely supportive for our request for Medicare coverage. Once again, although the DM cites supportive statements from the TWCC guidelines it offers no explanation the guidelines were given little or no credence or weight in the CMS review.

General utilization guidelines were also provided to CMS in Appendix B of our Formal Request and specific guidelines for twelve different medical/surgical specialities are presented in Appendix C of that document. Although. we discussed them at length with CMS, the author of the DM was completely unfamiliar with these parts of our Formal Request so it's likely they were also part of the TLD problem.

This submission includes a section titled "sNCT Evaluation Utilization Guidelines For the Management of Medicare Patient Sub-populations' that directly addresses the issue of professional guidelines.

Expert Opinions

When we met with Dr. Tunis and his staff in October 2000, we talked about how some local carriers shop for an "expert" unfamiliar with a procedure and then use their uninformed opinion to justify limiting or denying coverage. We also talked about the potential problem

caused by "experts" with a reason to fear financial harm if coverage is granted. We were assured, however, that CMS was aware of these type problems and we were invited to submit a list of experts familiar with the sNCT procedure to be contacted by CMS. We were also told we would be given the names of the experts who were ultimately consulted and the opportunity to respond to any of the comments received. This was all part of the "transparency" that Dr. Tunis and his staff promised is a hallmark of the CMS NCD review process.

On the topic of expert opinions the DM states:

> "We also contacted experts in the field of neuropathies. The experts were uniformly unaware of a use for sNCT that would alter patient management."

It's hard to imagine how any true expert in the field of peripheral neuropathy could fail

to see a use for a painless sensory nerve test with even greater accuracy (i.e. sensitivity and specificity) than the sNCV procedure that's currently covered by CMS. Experts in neuropathies generally derive a large portion of their patients from referrals for electrodiagnostic sensory nerve testing so presumably they know all about the value of such tests for patient management. An expert unfamiliar with the sNCT/CPT procedure or one threatened by a potential loss of income from coverage, however, might have cause to claim ignorance about the impact on patient management for a type of diagnostic service they regularly employ.

CMS was contacted by at least two neuropathy experts during the course of the review who expressed support for the sNCT/CPT procedure and offered to be interviewed by CMS but never were. We are also aware that Dr. Whyte spoke to experts and received uniformly positive feedback about the sNCT/CPT test. Appendix C of our Formal Request lists at least eleven different medical/surgical specialities that utilize the sNCT/CPT evaluation. During our initial meeting with Dr. Tunis and his staff, we were told that experts other than neurologists would also be consulted. To the best of our knowledge this did not take place.

Following the posting of the DM, however, Dr. Shuren did invite us to submit a list of experts familiar with the sNCT/CPT who would be willing to be interviewed by CMS for the reconsideration of the DM. We have provided that list with this submission in the Supplemental Information document.

CMS Analysis Section

The third paragraph in the CMS Analysis section states:

> "We have fully examined the medical and scientific evidence submitted with the request for a national coverage decision."

Because of the TLD problem discussed in the Introduction, we now know that the statement above is incorrect. Critical sections of Neurotron's Formal Request for an NCD were misplaced and never reviewed by the author(s) of the DM prior to publication. Included were reference papers, statistical analyses, letters to CMS from outside experts, supplementary information and analyses, utilization guidelines and other critical pieces of information.

The fifth paragraph of the "CMS Analysis" section cites only two "principal limitations" of the sNCT evaluation:

> "(1) it can only be performed on patients with normal attention and other cognitive abilities, as well as intact central nervous system sensory processing, because test results are based on the patient's ability to detect and report his or her perception of the administered stimuli;"

The first limitation is partially correct, i.e. a conscious responsive patient is required for the sNCT/CPT evaluation, just like for a hearing test. That's because the sNCT/CPT evaluation is a functional test of the sensory nerve and not a limited test of a short segment of a nerve like the sNCV test. The sNCT/CPT evaluation has been documented to be very effective in mapping neuropathies at any cutaneous site so it is good at localizing lesions in the PNS as well. We respectfully disagree, however, that the test requires the patient have "normal attention and other cognitive abilities". During a meeting at CMS we discussed this point and provided publications demonstrating that CPT measures may be successfully determined from individuals under the influence of narcotics such as opiates or inebriated by ethanol or who show evidence of encephalopathy[6] . (The lack of effect of analgesic doses of opiates on Current Perception Threshold (CPT) measures is also discussed in a publication submitted with our Formal Request and other studies[7].) We also discussed studies that demonstrate the successful use of the painless sNCT/CPT test with young diabetic children. (See Appendix E reference 8 in the Formal Request.)

> "(2) unlike NCS, sNCT does not assess the function of motor nerves."

[6] Katims, J.J., Taylor, D.N., Weseley, S.A. Sensory Perception in Uremic Patients. Transactions of the American Society of Artificial Internal Organs, Volume 37(3):M370-M372, 1991.

[7] Liu, S.S., Gerancher, J.C., Bainton, B.G., Kopacz, D.J., Carpenter, R.L: Effects of Electrical Stimulation at Different Frequencies on Perception and Pain in Human Volunteers: Epidural Versus Intravenous Administration of Fentanyl. Anesthesia & Analgesia, Volume 82:98-102, 1996.

As mentioned earlier, the is no single test called "NCS" that evaluates the functioning

of both the sensory and motor nerves in a single procedure. There are sensory nerve conduction studies (NCS) like the sNCT/CPT and sNCV tests, and there are motor nerve conduction and muscle studies like the mNCV and needle EMG tests. Sensory, muscle and motor nerve tests are not interchangeable, they are used to evaluate different types of diseases and conditions, they are separately coded and reimbursed and it is neither medically nor ethically justified to routinely apply them in tandem. It makes no more sense to criticize a sensory nerve test for not evaluating motor nerves than it would be to fault an MRI for not taking sonograms.

CMS told us that the sNCT/CPT test would be compared to other sensory tests that are already covered by Medicare, but a number of significant areas of comparison with the sNCV test were never mentioned in the DM. For instance, sNCV measures are single blind and based upon the subjective opinion of the tester[8] but sNCT/CPT measures are automated, double-blind and objectively determined by a microprocessor. sNCV studies can't be reliably compared between healthcare providers but sNCT/CPT measures have been proven to be comparable between health care providers and institutions around the world. sNCV studies require an environment with special shielding and temperature control for accuracy but sNCT/CPT studies produce accurate measures almost anywhere under a wide range of environmental conditions. sNCV evaluations almost always require a patient to be sent to a specialist's office for testing but automated sNCT/CPT evaluations can be reliably performed in a physician's office without delay or added inconvenience and expense for Medicare or the patient. (See the Supplemental Information section of this submission for additional related information cost savings for Medicare).

Point #2 also states that the "sNCT measures responses to three different stimulus intensities". That is an inaccurate statement. The sNCT/CPT test measures responses to three different neuroselective electrical stimuli, not stimulus intensities. The sNCT/CPT measures the minimum amount of current intensity needed to reliably evoke a sensation (± 20μAmps, $p<0.006$) using three different neuroselective constant AC current sinewave stimuli at 5 Hz, 250 Hz and 2000Hz with preset time duration. Each frequency of stimulus independently assesses the functioning of a specific subpopulation of sensory nerve fibers. Together, they evaluate the functioning of more than 90% of the fibers in a typical sensory nerve bundle compared to the less than 10% evaluated by the sNCV test.

Point #2 also referred to the following as being "problematic":

[8] Chaudry, V. et al. inter- and Intraexaminer reliability of nerve conduction measurements in patients with diabetic neuropathy. Neurology. Volume 44;1459-1462, 1994. and Chaudry, V. et al. inter- and Intraexaminer reliability of nerve conduction measurements in normal subjects. Annals of Neurology, Volume 30(6):841-831, 1991. This is discussed on page 16 of the Formal Request.

> "The greater number of measurements obtained with sNCT than with NCS may increase the likelihood of reporting an abnormal value. This is particularly problematic when the study population is determined to have a neuropathy using another testing modality, such as a physical examination."

Far from being "problematic", the ability of sNCT to assess the integrity of 90% of the sensory

nerve fibers instead of the less than10% assessed by sNCV is an obvious and clear advantage - especially since it retains both high sensitivity and specificity. Patients can suffer from either a small and or a large fiber neuropathy. The ability of the sNCT evaluation to detect impairments in the functioning of both types of fibers (which comprise over 90% of the sensory nerve fibers) enhances its sensitivity (while maintaining high specificity) for detecting sensory nerve dysfunction. By comparison, the sNCV evaluation evaluates only the large diameter fibers which comprise less than 10% of the nerve fibers. The Formal Request to CMS includes at least fifteen studies with some type of clinical measure, and none of these studies indicated that the sNCT/CPT measures were "problematic" so it's difficult to understand where the reviewers got their information.

The final statement under point #2 speculates that the ability of the sNCT/CPT test to evaluate 90% of the sensory nerve fiber "may lead to the reporting of a higher sensitivity, but a lower specificity due to a higher number of false positives." It was completely unnecessary for CMS to make that speculation since Neurotron had provided CMS with extensive statistical information documenting the high sensitivity and specificity of the sNCT/CPT measures. That data clearly shows that sNCT/CPT measures are very reliable and accurate and at least sensitive as sNCV measures for some conditions and superior for others. (e.g. radiculopathy, myelopathy and small fiber neuropathy)

The sixth paragraph of the CMS Analysis section states that only four studies compared sNCT/CPT to nerve conduction velocity. That statement is incorrect and reflective of the TLD problem. Neurotron's Formal Request included eight different studies that compared sNCT/CPT studies to sensory nerve conduction velocity (sNCV) studies. Neurotron had also provided extensive supplemental information to CMS including eighty-five comparisons of the sNCT/CPT evaluation to MRI, blood pressure, chemistry studies, biopsies and clinical studies as well as sNCV studies. Additional information can be found in the Supplemental Information section of this new submission.

The third sentence in the sixth paragraph states: "Each study had serious methodological flaws and specificity often was not or could not be determined." Extensive data documenting the sensitivity and specificity of sNCT/CPT studies had been provided to CMS.

The fourth sentence in the sixth paragraph states, "In general, the studies

evaluated a small number of subjects and none masked the individuals performing the electrodiagnostic studies." First, as previously mentioned, Neurotron was never informed that the number of patients in any study was a problem. Throughout the review process, CMS repeatedly assured us that it recognized the statistical foundation for scientific studies which take into consideration the number of subjects in each study.

The second part of the statement that says "none of the studies masked the individuals performing the electrodiagnostic studies." is also incorrect. All subjects receiving sNCT/CPT evaluation have always been blinded. It's a fundamental part of the forced-choice procedure used by the evaluation that couldn't possibly work without being blinded. The double-blinded fully automated objective sNCT/CPT evaluation was demonstrated at CMS during a meeting on July, 12, 2001. The sNCV evaluation is a non-blinded subjective procedure.

The next to the last sentence in this sixth paragraph states that, "Only the Rendell study reported detailed inclusion and exclusion criteria." That statement is incorrect. We would welcome the opportunity to address this concern with CMS and point out the inclusion and exclusion criteria contained within the publications submitted with our Formal Request.

General Critique of Publications

A general critique of the publications reviewed in the CMS Analysis section was that the sNCT/CPT scores and the classification of the severity of nerve dysfunction cited in the submitted publications had not been "independently validated." That statement, which suggests a lack of "Evidence-Based Medicine" with respect to the sNCT/CPT evaluation, is not correct. Neurotron provided CMS with information about studies from around the world that included thousands of healthy subject measures. A table presenting these normative data from three thousand one hundred fourteen sNCT/CPT studies was faxed to CMS on December 14, 2001. Neurotron also provided CMS with the normative data from the 180 sNCT/CPT studies from sixty healthy subjects included with its FDA 510(k) application. A primary purpose for providing this data to CMS was specifically to demonstrate that normative CPT values exist that have been independently validated in scores of studies from around the world over the past seventeen years. Neurotron's submissions also included documentation of the coefficient of variation of repeated sNCT/CPT measures which serve to independently validate the reliability of the measures.

When the Rendell (1989) publication states that it used a CPT value 5 Standard Deviations above the normative mean as an abnormal value, no additional independent validation is required beyond that statistical criteria. When the publication states that unobtainable sensory nerve conduction velocity or CPT measures indicated that a very abnormal neuropathic condition exists, no independent validation of that point is

required either. When a physical evaluation finding of complete insensitivity to light touch, pin prick, vibratory and thermal sensation at six sites symmetrically confined to only the distal portion of both lower extremities is classified as a "severe" impairment, no independent validation is required. Scientific studies often contain critical information that may not be obvious to a person unfamiliar with the jargon and statistical concepts. Neurotron did have discussions and correspond with CMS about some of the unobvious statistical data in some of the studies and CMS responded positively.

Rendell (1989) study critique: The DM's comments about this study's statistics are directly addressed in the twenty-one page fax sent to the CMS on November 8, 2001. Also, contrary to another stated concern, the neurological physical valuation was independently evaluated by Dr. Peter Dyck, Mayo Clinic - a fact which is noted by the reviewers earlier in the Summary of Evidence section of the DM.

The last sentence of the critique of the Rendell (1989) study states:

> "Moreover, the diagnosis of neuropathy was based on history and physical examination, raising into question whether sNCT is more accurate in diagnosing diabetic polyneuropathy than a history and physical examination."

The above statement completely ignores and directly contradicts the conclusion the authors of the study reached:

> "CPTs proved the more effective (than sensory nerve conduction velocity) as predictors of both symptomatic and physical impairment. NCVs appear to lack the resolving power necessary to evaluate subtle differences in clinical state of diabetic sensory neuropathy. The supplementary use of current perception threshold testing may improve the quantitative assessment of this condition."

The study says that the sNCT/CPT evaluation can provide a reliable objective quantitative measure of sensory nerve dysfunction that correlates better with the patients clinical condition than the sNCV study which is currently covered by Medicare.

Weseley (1988) study critique: This critique states that the classification of the severity of the neuropathy in this publication was not independently validated. That statement is not correct. The information at the beginning of the General Critique of Publications section above explains the independent verification of sNCT/CPT scores and the classification of severity. The critique of this study also ignores the statistical comparison between sNCT and sNCV measures based on published data that Neurotron provided to CMS on November 8, 2001. Another criticism leveled was that the specificity for the study was not reported. That is also not correct. This study

states that subjects were classified as normal if "All measures fell within healthy limits". That translates into a detection specificity of 100% (i.e. no false positives). The healthy range limits are presented in Table 2 of this publication.

The critique of this study also expressed concerns about the effects of dialysis therapy on CPT measures. However, there was no significant difference between the detection sensitivity of the sNCT/CPT measures and the sensory nerve conduction velocity measures over the two year period in this study. A study[9] that's discussed in Appendices D and E of the Formal Request publication evaluates the coefficients of variation (CV) of repeated sNCT measure obtained from dialysis patients while they received their dialysis therapy. These CV measures were identical to or better than other studies of sNCT/CPT CV's from healthy individuals discussed in Appendix D of the Formal Request.

Katims (1989) study critique: The critique of this study states that "The grading system and CTS questionnaire used in the study were not independently validated." That statement is not correct as is explained at the beginning of the General Critique of Publications section above and by the additional independent studies validating the grading system and CTS questionnaire provided to CMS with the Formal Request.

The reviewer(s) appear to have been unaware of the statistical analyses of peer reviewed published data Neurotron provided to CMS on November 9, 2001 comparing the sNCV findings to the sNCT/CPT findings as well as the sensitivity and specificity data for uremic neuropathy detected by the sNCT/CPT evaluation from this study that are provided in Appendix D of the Formal Request. The reviewer(s) also appear not to have appreciated the fact that uremic neuropathy can obfuscate or mimic Carpal Tunnel Syndrome (CTS)

symptoms and that it's sometimes necessary to conduct electrodiagnostic studies to prevent permanent disability of the afflicted hand - a point both reviewed and referenced in this study.

Another statement in the critique of this study is also without any basis:

> "This is consistent with the above observation that multiple measurements would result in a higher sensitivity but a lower specificity than NCS."

As we previously noted, that "observation" is purely speculative and incorrect. Neurotron gave CMS extensive statistical information documenting the high sensitivity and specificity of the sNCT/CPT measures. That data clearly shows that sNCT measures are very reliable and accurate and at least equivalent or superior to

[9] Katims, J.J., Rouvelas, P., Sadler, B.T., Weseley, S.A. Current Perception Threshold: Reproducibility and Comparison with Nerve Conduction in Evaluation of Carpal Tunnel Syndrome. Transactions of the American Society of Artificial Internal Organs, Volume 35(3):280-284, 1989.

sNCV measures. The reviewer(s) also appears not to have been aware of the fact that sNCV evaluations depend upon multiple measurements subjectively interpreted by the operator.

Ro (1999) study critique: This critique starts off questioning the clinical utility of the sNCT/CPT evaluation for the Medicare population, because although this study found the test to be accurate and effective in assessing small fiber neuropathy, the reviewer(s) said that Fabry's patients on whom the study was conducted do represent a significant portion of the Medicare population. The function of a diagnostic test, however, doesn't change because of the type of condition being evaluated. A thermometer is used to measure the temperature of a patient with tonsillitis, but it is also used to measure the temperature of a patient whose condition has not yet been diagnosed. Knowing a patient's body temperature can be a critical piece of the puzzle when forming a diagnosis. The Ro study demonstrates that the sNCT/CPT evaluation is capable of accurately measuring small fiber neuropathy, a condition that afflicts a very large portion of the Medicare population including diabetics. Knowing the condition of a patient's small sensory nerve fibers - which comprise about 80% of the sensory nerve - can be a critical for puzzle for diagnosing patients with a wide range of disorders. The only electrodiagnostic sensory nerve tests currently covered by Medicare, the sNCV and ER tests, are completely insensitive to small fiber neuropathies. Small fiber dysfunction can result in cardiac arrest, a major cause of mortality in the Medicare population. (See Appendix E, Ref. 9, Formal Request)

This critique goes on to state:

> "The study also suggests that sNCT may distinguish between sensory fiber types and may be more sensitive than NCS in detecting sensory neuropathies that affect only small myelinated and unmyelinated fibers. However, the patient population tested in this study was small (only 16 patients) and the symptoms scores were not independently validated."

The Ro study demonstrates categorically that the three different sNCT/CPT stimuli do

distinguish between fiber types and that they are more sensitive than sNCV studies. The study also states that each of the sixteen patients was compared against fifty matched control subjects. Further, the symptom scores in this study were validated by previous studies, and comparison with biochemical and genetic studies. Additional comments concerning this publication appear on page E-7 of the Appendix to the Formal Request. It should also be noted that all sixteen patients afflicted with this small fiber neuropathy disease had normal sNCV tests.

CMS Analysis Section

1. The first sentence in this section states:

> "In summary, the available scientific evidence is not adequate to demonstrate the accuracy of sNCT or the accuracy of sNCT as compared to NCS."

As has been repeatedly pointed out in the preceding pages, there is no valid basis for that conclusion because so many critical parts of Neurotron's application, including reference papers, statistical analyses, letters to CMS from outside experts, supplementary information and analyses, utilization guidelines, etc. were never seen or reviewed by the author of the DM due to the TLD problem.

2. The second sentence states:

> "Unlike NCS, sNCT does not assess the integrity of motor nerves..."

As previously mentioned, this particular criticism is a non sequitur. The sNCT/CPT evaluation test is a sensory nerve test - not a motor nerve test. The sNCV evaluation is also a sensory nerve test - not a motor nerve test. Neither test assesses the integrity of motor nerves - which is not a shortcoming for a sensory nerve test. Faulting a sensory nerve test for not assessing motor nerves is like faulting an MRI for not performing sonograms.

3. The third sentence states:

> " In addition, it is not evident that sNCT offers any diagnostic advantages over a history and physical examination in detecting the presence of a neuropathy."

Neurotron provided CMS with extensive documentation that directly contradicts that statement, including publications specifically makes the case that there a need for an objective electrodiagnostic sensory nerve evaluation of Medicare patients to more accurately determine the distribution of a sensory impairment than the clinical evaluation. The author also ignores the fact that CMS already covers the sNCV another sensory nerve test that is less sensitive and accurate than the sNCT/CPT procedure.

4. The fourth sentence states:

> "There are also no clinical studies that we identified that demonstrate that the use of sNCT leads to changes in patient management in a particular Medicare subpopulation."

Neurotron had been told it was unnecessary to provide that type of information since

Medicare already recognized the value of sensory nerve testing and reimbursed for the procedure. We were instructed that the goal of our application for an NCD should be to provide sufficient information and documents to CMS to allow a determination that the sNCT/CPT electrodiagnostic evaluation was at least as safe and accurate as other sensory nerve evaluations already covered by Medicare. Toward that end, we provided CMS with extensive documentation proving not only equivalency, but in many cases superiority over covered sensory nerve tests. We also included information about the cost savings to Medicare (eliminating costly referrals, using a single test to replace three, etc.) and the added comfort and convenience and cost savings for the Medicare patient. Unfortunately, much of this information appears to have been part of the TLD problem and never reviewed for the DM.

Our understanding of what was required for our application was further reinforced by The HCFA Federal Register statements of May 16, 2000[10] and "Medicare Coverage Policy ~ MCAC, Executive Committee, Recommendations for Evaluating Effectiveness, by the Executive Committee Working Group (Revised February 23, 2001)" to which we were referred which states:

> "In the absence of direct evidence of the effects of a test on health outcomes, it will sometimes be possible to conclude with great confidence that improved accuracy will lead to better outcomes."

During a meeting at CMS on July 12, 2001, in response to a direct question the CMS Medical Officer reiterated that establishing that the sNCT/CPT test is effective for the objective and accurate measurement of sensory nerve function was **the** fundamental point that had to be proven in order to get coverage. Medicare already provides coverage for electrodiagnostic sensory nerve conduction velocity testing and biopsies for the evaluation of sensory nerves which indicates that the clinical value of sensory nerve testing is already recognized by CMS.

5. The sixth sentence states:

> "In our discussions with experts, we were also unable to identify a subpopulation in whom the results of sNCT would alter medical care."

We disagree with that statement for several reasons. First, it's difficult to understand how any true expert in the field of peripheral neuropathy could fail to see a use for a painless sensory nerve test that has greater accuracy (i.e. sensitivity and specificity) than the sNCV procedure that's currently covered by CMS. These experts generally

Federal Register/ Vol. 65, No. 95 / Tuesday May 16, 2000. Department of Health and Human Services, Health Care Finance Administration, 42 CFR Part 405 [HCFA-3432-NOI] RIN 0938-AJ31. Medicare Program: Criteria for Making Coverage Decisions. Also, "HCFA Outlines Standards Medicare Will Use in Making Coverage Decisions". BNA's Health Law Reporter, Volume 9(20), 748-749, May 18, 2000. by The Bureau of National Affairs, Inc. Wash., D.C. HLR ISSN 10642137.

derive a significant portion their patient from referrals for electrodiagnostic sensory nerve testing so presumably they should be able to identify subpopulations in whom the results of sNCT or sNCV would alter medical care - assuming, of course, they actually knew the facts about the sNCT and not the misconceptions - many of which appeared in the DM.

Also, as previously mentioned, none of the neuropathy experts who contacted CMS and volunteered to be interviewed about the sNCT/CPT were ever contacted by CMS. Page E-1 in the appendix accompanying our formal application states: "Several authors of publications cited in this Appendix, have expressed a willingness to discuss their research experience with the sNCT/CPT procedure with HCFA. " Unfortunately, none of these experts in electrodiagnostic medicine were ever consulted by CMS either.

6. The seventh sentence states:

> "Although the Association of Clinical Endocrinologists believe that sNCT is useful to detect sensory neuropathies in some diabetic patients, we were unable to establish the specific changes in patient management that would occur with its use."

On November 16, 2001 at CMS's request, Dr. Katims sent a thirty-nine page fax which provided numerous examples "demonstrating where the increased sensitivity of sNCT in diagnosing sensory neuropathies can affect patient management". Three of these examples directly related to diabetes. CMS never indicated that these vignettes were in any way inadequate and in fact, just the opposite was the case. Presumably this fax fell victim to the TLD problem and so was never seen by the author of the DM.

7. The eighth sentence states:

> "Moreover, the potentially lower specificity of sNCT as compared to NCS may lead to the administration of unnecessary and possibly harmful treatments."

This baseless speculation appears elsewhere in the DM and as previously stated, it is incorrect. All of the information Neurotron provided to CMS says exactly the opposite i.e. the sensitivity and specificity of the sNCT is substantially the same or superior to sNCV tests. Nowhere did the DM were there citations any study which supported the authors' speculation that the sNCT is any less accurate than the sNCV.

Decision

The DM's Decision states:

> "CMS concludes that the scientific and medical literature do not demonstrate that the use of sNCT to diagnose sensory neuropathies in Medicare beneficiaries is reasonable and necessary. Therefore, we intend to issue a national noncoverage decision.

The information provided in the preceding pages clearly demonstrates that CMS did not perform an adequate review of the scientific and medical literature with which it had been provided or that was available from other sources. It also demonstrates that the author(s) of the Memorandum had a such a critically limited understanding of the diagnostic procedure they were evaluating that one of the two major faults they found with this sensory nerve diagnostic procedure was that it didn't perform the function of a motor nerve or muscle physiology diagnostic procedure - the author(s) apparently completely unaware of the profound differences. Neurotron, Incorporated respectfully calls on CMS to immediately rescind this fatally flawed Decision Memorandum.

Request for Reconsideration CMS Decision Memorandum CAG# 00106N Electrodiagnostic Sensory Nerve Conduction Threshold

Part 2. Supplemental Information

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Submission List

Part 1. Rebuttal
Part 2. Supplemental Information
Part 3. Utilization Guidelines

Supplemental Information: Request for Reconsideration of CMS Decision Memorandum for Electrodiagnostic Sensory Nerve Conduction Threshold

(#CAG00106N)

Table of Contents

Supplemental Information - Introduction

The information provided in this document is provided in support of Neurotron Incorporated's Request for Reconsideration of CMS Decision Memorandum for Electrodiagnostic Sensory Nerve Conduction Threshold (CAG#-00106N. It consists of both new and updated information from Neurotron's Formal Request for an NCD.

Important Notes

Immediately following publication of the Decision Memorandum (*DM*), CMS discovered that it had misplaced large portions of Neurotron's Formal Request for an NCD along with much of the supplemental information that had been provided to CMS. Consequently, those materials were neither reviewed nor considered for the *D*M and the glaring errors, inconsistencies and omissions in the *DM* clearly reflect that fact. According to CMS, those missing documents have now been located are available to CMS to review for this request for reconsideration. Those **t**emporarily **l**ost **d**ocuments will heretofore be referred to with the acronym *TLD*.

During a conversation Dr. Shuren the day after the DM was published, he requested that Neurotron include the following information in its request for reconsideration of the *DM*.

1 A review of the errors, inconsistencies and omissions in the *DM* whether due to the *TLD* problem or otherwise. The Rebuttal to CMS Decision Memorandum for Electrodiagnostic Sensory Nerve Conduction Threshold (CAG#-00106N) section of this Request for Reconsideration.

2 A list of publications and synopses submitted with the Formal Request that were neither mentioned nor cited in the *DM* with regard their relevance to medical management issues for the sNCT/CPT evaluation. This information was sent to Dr. Shuren via email on February 14, 2002 in the form of a PDF file named Omitted_Pubs01.pdf . The title of the document is Omitted Publications. Neurotron can supply another copy of this document if the original has been misplaced.

3 An brief outline listing how the sNCT/CPT evaluation could be utilized to provide information necessary to direct Medicare patient management. This information was sent to Dr. Shuren via email on February 14, 2002 in the form of a PDF file named Patient_Mgmt_01.pdf. The title of the document is Sensory Nerve Evaluation and Patient Management. Neurotron can supply another copy of this document if the original has been misplaced.

Accuracy Analyses of sNCT/CPT Data and Statistics

The accuracy of a diagnostic procedure is usually defined in terms of its sensitivity, specificity and reliability, i.e. its ability to avoid false negatives, to avoid false positives and to produce repeatable results, respectively. The high reliability of the automated double-blind sNCT/CPT evaluation measures between different investigators as well as the test's high sensitivity and specificity have been repeatedly confirmed in studies conducted during past sixteen years.

[**Note**: The superscripted numbers in the following tables reference the studies from which the data was gathered listed in Accuracy Analysis References at the end of this section. They are not footnotes.]

1. **Healthy Mean CPT Values (SD)**

This analysis shows the healthy/control mean sNCT/CPT values for three different body sites using three different neuroselective stimuli that were gathered during studies conducted in different countries by different groups of researchers. The data includes both the Mean CPT value (1 CPT=10 μAmperes) and the Standard Deviation (SD) for each data

point as well as the n value for the study. The analysis illustrates that the standardized sNCT/CPT measures are extremely consistent comparable not only between different examiners, but also between different cultures, and institutions. There is no statistically significant difference between any of the comparisons shown in the table for like data points.

Healthy Mean CPT Values (SD) , (1 CPT = 10 microAmperes)

CPT Frequency	**Face** (Trigeminal Nerve)		**Finger**(Median Nerve)			**Toe** (Peroneal Nerve)	
	USA[28] (n=338)	Korea[26] (n=400)	USA (n=334)	Japan[23] (n=1632)	Taiwan[15] (n=50)	USA (n=310)	Taiwan[15] (n=50)
5 Hz	10 (10)	11 (8)	46 (27)	61 (30)	50 (25)	73 (34)	74 (30)
250 Hz	19 (14)	21 (12)	81 (42)	93 (44)	78 (30)	125 (52)	126 (50)
2000 Hz	118 (52)	99 (28)	226 (80)	236 (62)	230 (70)	322 (110)	325 (106)

By contrast, studies from repeatedly show that there is no good reliability between the sNCV measures obtained by different health care providers. The following two publications from the Department of Neurology at the Johns Hopkins Medical Institution discuss this problem with the sNCV evaluation:

(Chaudry, V. et al. inter- and Intraexaminer reliability of nerve conduction measurements in

patients with diabetic neuropathy. Neurology. Volume 44;1459-1462, 1994;
Chaudry, V. et al. inter- and Intraexaminer reliability of nerve conduction measurements in normal subjects. Annals of Neurology, Volume 30(6):841-831, 1991.)

2. **Coefficients of Variation Table**

This analysis examines the coefficients of variation for CPT measures gathered in four different countries by different groups of researchers. The numbers show that the standardized sNCT/CPT electrodiagnostic evaluation measures are extremely consistent and comparable - not only between different examiners, but also between different cultures, decades and body sites. There is no statistically significant difference between any of the comparisons shown in the table for like data points.

Coefficients of Variation Table

CPT Frequency	% Coefficients of Variation of sNCT/CPT Values			
	Japan (23)	**USA** (13)	**UK** (7)	**Hungary** (8)
5 Hz	15-27	28	16-20	18
250 Hz	11-12	14	-	12
2000 Hz	5-6	7	8-11	8

3. **sNCT/CPT Sensitivity and Specificity Table**

This table presents the sensitivity and specificity data from eight different subject populations and studies. Please note that despite the speculative concerns in the *D*M regarding a potential loss of specificity using the multi-neuroselective sNCT/CPT procedure, no such loss is evident.

Sensitivity and Specificity Table

Study #	Sensitivity	Specificity	Subject Populations
24	94%	100%	n = 33 diabetic patients and 54 controls
13	77%	100%	n= 29 dialysis patients and 137 controls
4	84%	88%	n = 70 radiculopathy patients *
8	23%	100%	n = 92 diabetic children and 80 controls
15	50%	95%	n = 16 Fabry's disease patients and 50 controls
11	54%	95%	n = 2360 diabetic patients *
25	60%	95%	n = 73 diabetic patients and 47 controls
3	93%	100%	n = 10 syringomyelia patients and 15 controls

Specificity determined using established normative CPT values as controls.

4. **Sensitivity Comparison Between sNCT/CPT and sNCV Evaluations**

This analysis compares sensitivity data for the sNCT/CPT and sNCV evaluations from studies in which both procedures were used to evaluate sensory neuropathy for specific conditions.

Sensitivity Comparison Between sNCT/CPT and sNCV Evaluations

Condition (study #)	n=	Electrodiagnostic Test Sensitivity		
		sNCV	sNCT/CPT	p value
Fabry Disease[15]	16	0%	50%	<0.001
Nerve Regeneration[21]	22*	0%	100%	<0.001
Uremic Polyneuropathy[13]	29	79%	92%	ns
Uremic Polyneuropathy[14]	23	72%	83%	ns

Vibration Neuropathy[20A] Stage 3 Vibration Neuropathy Stage 2 Vibration Neuropathy Stage 1 Vibration Neuropathy	33 13 13	100% 0% 0%	92.3% 77% 0%	ns <0.000 ns
		sNCV and sNCT/CPT Test Correlations		
Diabetic Neuropathy[5] (based upon Symptom and Physical Scores) (169 examinations) Discriminate "Normal" from "Abnormal" Discriminate "Relatively Abnormal" from "Very Abnormal"	71	ns ns	p<0.01 p<0.01	
Diabetic Neuropathy[7](peroneal measures) 2000 Hz CPT 5 Hz CPT	90	r = -0.66 ns		<0.005 ns

* Including historical reference: Muscle & Nerve 18:1257-1264, 1995

5. **Additional Sensitivity and Specificity Data Analysis**

The FDA 510(k) Premarket Notification (N412 270 688 8) delivered to CMS July 13, 2001. Appendix B of this 510(k) Premarket Notification binder included all the individual patient data typed in a spreadsheet format. A separate binder contained copies of each patients original data sheet. Specificity and sensitivity data from studies conducted under the Johns Hopkins University School of Medicine that were submitted to the FDA in 1985 is part of this 510(k) application. These documents include all the clinical and sNCT data from these studies of 60 healthy control subjects and 86 subjects in a neuropathic comparison group.

Accuracy Analysis References

(3) Zhu, P.Y., Fu, H., Starr, A: Neuroselective Current Perception Threshold (CPT) Evaluation in Syringomyelia. Presentation at the Annual Meeting of the North American Spine Society, Washington, D.C., 1995 and Zhu, P.Y., Cui, Y.L., Weber, R.J. American Academy of Physical Medicine and Rehabilitation, Annual Meeting, No. 63, 1998

(4) BenEliyahu, D.J., Tartaglia, S.V., Spinelle, R. Current Perception Threshold/ Quantitative Sensory Testing and MRI Findings In Patients with Signs and Symptoms of Cervical or Lumbar Disc Herniation: A Correlative Study of the Neurosensory Diagnosis of Discogenic Pain, American J. of Pain Management, Vol. 10(2):60-65, 2000.

(5) Rendell, M.S., Katims, J.J., Richter, R., Rowland, F. A comparison of nerve conduction velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. J. of Neurology, Neurosurgery and Psychiatry, Vol. 52:502-511, 1989.

(7) Masson, E.A., Veves, A., Fernando, D., Boulton, A.J.M. Current perception thresholds: a new, quick, and reproducible method for the assessment of peripheral neuropathy in diabetes mellitus. Diabetologia,

Vol. 32:724-728, 1989.

(8) Barkai, L., Kempler, P., Vámosi, I., Lukács, K., Marton, A., Keresztes, K. Peripheral Sensory Nerve Dysfunction in Children and Adolescents with Type 1 Diabetes Mellitus. Diabetic Medicine, Vol. 15:228-233, 1998.

(11) Jiang, Y-D, Hsich, S-T, Wu, H-P, Tai, T-Y, Katims, J.J., Chuang, L-M. Characterization of hyperesthetic stage of diabetic neuropathy with current perception threshold, a method for diabetic neuropathy staging. XI Meeting, Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (EASD) NEURODIAB. 2001.

(13) Katims, J.J., Rouvelas, P., Sadler, B.T., Weseley, S.A. Current Perception Threshold: Reproducibility and Comparison with Nerve Conduction in Evaluation of Carpal Tunnel Syndrome. Transactions of the American Society of Artificial Internal Organs, Vol. 35(3):280-284, 1989.

(14) Weseley, S.A., Sadler, B., Katims, J.J. Current Perception: Preferred Test for Evaluation of Peripheral Nerve Integrity. Transactions of the American Society of Artificial Internal Organs, Vol. 34(3):188-193, 1988.

(15) Ro, L.S., Chen, S.T., Tang, L.M., Hsu, W.C., Chang, H.S., Huang, C.C. Current Perception Threshold Testing in Fabry's Disease. Muscle & Nerve, Vol. 22: 1531-1537, 1999.

(20A) Kurozawa, Y., Nasu, Y. Current Perception Thresholds in Vibration-Induced Neuropathy. Archives of Environmental Health, Vol. 56(3):254-256, 2001.

(21) Chu, N.S. Current Perception Thresholds in Toe-To-Digit Transplantation and Digit-To-Digit Replantation. Muscle & Nerve, Vol. 19(2):183-186, 1996.

(23) Takekuma, K., Ando, F., Niino, N., Shimokata, H. Age and gender differences in skin sensory threshold assessed by current perception in community-dwelling Japanese, J of Epidemiology, Vol.10(1):S33-S38, 2000.

(24) Katims, J.J., Naviasky, E., Ng, L.K.Y., Bleecker, M.L., Rendell, M. New Screening Device for Assessment of Peripheral Neuropathy. J of Occ. Med, Vol. 28(12):1219-1221, 1986.

(25) Umezawa, S., Kanamori, A., Yajima, Y., Aoki, C. Current Perception Threshold in evaluating diabetic neuropathy. J. of the Japanese Diabetes Society, Vol. 8(1):711-719, 1997.

(26) Kim, H., Kho, H., Kim, Y., Lee, with., Chung, with. Reliability and Characteristics of Current Perception Thresholds. J. of Orofacial Pain Vol. 14(4): 286-292, 2000.

(28) This is the normative data for various specific body testing sites that is provided with each sNCT device. This normative data was obtained primarily from the following institutions: Johns Hopkins Medical Institution, University of Maryland School of Pharmacology, Creighton University School of Medicine, New York Medical College, New York University Medical Center, and the University of New Mexico School of Medicine. The Formal Request, Appendix E, Reference numbers 6, 19 and 24 contributed to these normative values.

Additional Points of Comparison Between sNCT/CPT and sNCV Evaluations

Page 14 of Neurotron's Formal Request has a table comparing the capabilities and features of the electrodiagnostic sNCT/CPT evaluation to the sNCV (sensory nerve conduction velocity) and ER (evoked response) evaluations - both of which currently receive Medicare coverage. The table illustrates many clinically significant features and capabilities of the sNCT/CPT evaluation that are completely absent from the covered procedures. There was almost no mention of these points of comparison in the *DM*.

The following list expands on some of the points in the table and adds additional comparisons which illustrate clinical and economic advantages of the sNCT procedure compared to currently covered sensory nerve testing procedures.

1 Studies have shown the sNCT/CPT evaluation to be capable of assessing all three basic types of peripheral sensory nerve damage,[1] (Axonal (dying back); Demyelinating; Focal (Compressive - Wallerian)) with equivalent or superior accuracy to the sNCV evaluation

currently covered by Medicare.

2 The sNCT/CPT evaluation assesses the integrity of both myelinated and unmyelinated sensory nerve fibers. The sNCV test only assesses the myelinated sensory nerve fibers. The sNCT/CPT test evaluates over 90% of the nerve fibers. The sNCV test evaluates less than 10 % of the nerves fibers. This is graphically illustrated on page 3 of the Formal Request.

3 The sNCT/CPT evaluation is been documented to be sensitive to radiculopathy and myelopathy. The sNCV test is insensitive to these conditions.

4 The sNCT/CPT evaluation is documented to be sensitive to nerve regeneration. The sNCV test is insensitive to nerve regeneration.

5 The reliability of the automated double-blind sNCT/CPT evaluation measures between different investigators with comparable sensitivity and specificity values has been repeatedly validated over the past sixteen years. A multi-analysis about this point is included with this submission. sNCV measures can not be reliably compared between different healthcare providers.

6 sNCT/CPT normative values have been independently validated. There are no standardized normative values of sNCT measures.

7 The scoring of sNCT/CPT measures has been independently validated. There is no standardized grading for sNCT measures.

8 The sNCT/CPT test is painless and conducive for patient compliance and low stress. The sNCV in not a painless procedure.

9 The sNCT/CPT test offers a diagnostic advantage by permitting testing at the tips of the toes to detect the earliest stage of a distal axonal polyneuropathy. The sNCV cannot detect the neuropathy until it has progressed more proximally.

10 It takes only a day to train a physician in the proper use of the sNCT/CPT procedure to be able to produce reliable and accurate evaluations of sensory nerve integrity. The automated sNCT/CPT procedure does not require the type specialized training needed to learn to how to operate the sNCV equipment and to subjectively interpret its results. The ability of a physician to conduct a sensory nerve evaluation in-office instead of referring patients out for testing represents a potentially huge savings for Medicare. Under the current Medicare system, a referral to a specialist results in a second Medicare covered history and physical evaluation performed prior to the sensory nerve evaluation. A physician conducting an sNCT/CPT evaluation in-office does not generate this second set of charges to Medicare for the second patient history and physical evaluation.

11 The sNCT/CPT evaluation is not distorted by common electromagnetic fields, changes in skin temperature or edema. sNCV measures are distorted by all of those influences. sNCV testing requires an electromagnetically shielded laboratory and a controlled environment for reliable operation. sNCT/CPT does not which results in lower overhead and operating costs.

Evidence Based Medicine Example

The following example illustrates a simplified Evidence Based Medicine approach to choosing between the sNCT/CPT and sNCV for the assessing the sensory nerve integrity for the patient in the case below. The following three premises are supported by extensive external clinical evidence gathered through hundreds of current peer reviewed studies:

1 The sNCT/CPT evaluation is sensitive to both peripheral nerve dysfunction and spinal nerve/cord dysfunction. The sNCV evaluation in sensitive to peripheral nerve/cord dysfunction and completely insensitive to spinal cord sensory dysfunction.
2 The sNCT/CPT evaluation assess the integrity of both large diameter and small diameter sensory fibers. The sNCV evaluation assess the integrity of large diameter sensory fibers only.
3 Both the sNCT/CPT and sNCV tests have comparable sensitivity and specificity within in the limits of the types of sensory nerve fiber(s) each is able to assess.

Case: A patient with an injury that results in a loss of sensation in an extremity and who has an equivocal physical evaluation for sensory impairment.

The differential diagnostic question that a health care provider must answer is whether the injury includes the sensory nervous function and if so, where -the spinal nerve/cord and/or the peripheral nerve? Each type of injury has a different type of medical management. An objective quantitative electrodiagnostic evaluation is required to assist in the diagnosis and management of this patient. Evidenced based medicine would suggest that if a choice existed between conducting an sNCT/CPT or an sNCV evaluation, the sNCT/CPT would be the preferred test for such a patient from both the clinical and financial perspectives. Here's why.

The sNCT/CPT test evaluates both large and small diameter sensory nerve fibers, whereas the sNCV tests evaluates only the large diameter sensory nerve fibers. Neuropathy, however, can selectively impair functioning in either subpopulation of sensory nerve fibers. Evidenced based medicine would suggest that if a choice existed between conducting the sNCV evaluation and the sNCT/CPT evaluation of a suspected large and/or small fiber neuropathy, the sNCT/CPT would be the preferred test. The sNCT/CPT test has a greater potential diagnostic sensitivity because of its ability to assess both large and small fibers as well as its sensitivity to spinal nerve/cord dysfunction. The sNCT/CPT test is, therefore, likely to have a better outcome than the sNCV test.

Cost Savings Associated with the sNCT/CPT Evaluation

The Cost Savings and Diagnostic Advantages Using the sNCT Electrodiagnostic Evaluation section of the Formal Request (pages 17-20) discusses ways that the sNCT/CPT can offer significant cost savings to Medicare compared to the use of currently covered sensory nerve tests. None of these points were mentioned or considered in the *DM* so it may by that they were impacted by the *TLD* problem. Several references listed in Appendix E of the Formal Request also include examples of cost savings:

1 The Vale study (Reference 22) is an example of an outcome study of 1,500 workers sNCT/CPT studies showing a 95% decrease upper extremity cumulative trauma disorders requiring surgical intervention and an associated cost savings of $110,000.
2 The NIH Consensus Conference publication (Reference 12) concludes that periodic sNCT evaluation of dialysis patients could assist in optimizing therapy which, "would reduce morbidity, mortality, and the cost of the ESRD in the United States."
3 The study of organo-phosphate exposure (Reference 16) reports that the sNCT evaluation reduces the need to withdraw blood for detecting toxic exposure levels and that

the sNCT test is easier to manage and more cost effective.

Another section of this submission for reconsideration titled sNCT Evaluation Utilization Guidelines for the Management of Medicare Patient Sub-populations provides numerous examples of cost savings or improved diagnostic sensitivity that may be achieved by using the sNCT evaluation in contrast to other electrodiagnostic nerve conduction studies.

Comparison of sNCT/CPT to Several Diagnostic Procedures

Covered by Medicare

The following table cross references the studies cited in Appendix E of the Formal Request with the type of disease or condition that was evaluated using sNCT/CPT and one or more other types of neurodiagnostic tests. The X symbol indicates that the particular test is not capable of evaluating the disease or condition. The T symbol indicates that although none of the references in Appendix E of the sNCT Formal Request make the comparison in question, other studies have made the comparison and are available upon request. The : symbol indicates that the comparison test is not applicable for the particular disease or condition. Studies have shown that the sNCT/CPT test capable of evaluating all of the diseases and conditions listed in the table. All of the other tests listed are currently covered by Medicare.

sNCT/CPT and Covered Neurodiagnostic Tests Cross Reference

sNCT Evaluation of Disease/ Condition	**Covered Neurodiagnostic Test**					
	sNCV	**MRI**	**BP**	**Blood Chem**	**Biopsy**	**Clinical**
Small nerve fiber neuropathy	X	X	8, 9, 10, 11, 25	8, 10, 11, 12, 15, 16, 17, 18, 25	15A	1, 2, 6, 7, 15, 19, 28
Large nerve fiber neuropathy	5, 7, 13, 14, 15, 17, 20, 25	X	8, 9,10, 11, 25	8, 10, 11, 12, 15, 16, 17, 18, 25	T	1, 2, 5, 6, 7, 8, 10, 11, 15, 18, 19, 28
Spinal dysfunction/ Radiculopathy	X	3, 4	X	X	:	1, 2, 3, 4
Carpal Tunnel Syndrome Hand Arm Vibration Syndrome Cumulative Trauma Disorder	13, 20	X	X	X	:	22
Regeneration/Recovery	X	X	X	X	:	18, 21†
						2, 3, 5, 6,

Test any site	X	4	:	:	T	19, 24, 26, 28
Hyperesthesia	13,14	X	X	15	X	11, 15, 25
Morbidity/Mortality of Uremia	12,13, 14	X	X	12, 15	X	12

[^] only one patient had a biopsy in this study

Sensory nerve dysfunction can occur in one fiber type sparing others. sNCT/CPT findings of the differential susceptibility of different sub-populations of sensory nerve fibers as reflected by the three neuroselective test measures are found in the following references: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 25 and 29 from the Formal Request, Appendix E.

[†] Reference 21 in Appendix E, a nerve regeneration study, provides an example of a publication where a direct comparison of sNCT with the sensory sNCV and somatosensory evoked potential studies is not necessary because previous studies of the same condition indicated that there was a persistent impairment of sensory nerve conduction following nerve repair (References Nos. 3 and 4 within this publication.).

Note: The Formal Request (page 14) includes a Comparison Table of electrodiagnostic sensory nerve studies including the sNCT/CPT, evoked response (ER) and sNCV tests.

Statistical Study Exclusion Criteria Rebuttal

During a phone conversation with CMS, Neurotron asked Dr. Shuren why the *D*M lists as an exclusion criteria studies with less than 10 subjects. He responded that studies with less than 10 subjects were routinely excluded because of associated statistical power problems. Neurotron consulted with two different statisticians and offers the following in rebuttal:

The power of a test is defined as the probability of correctly rejecting the Null hypothesis to avoid a Type II error (accepting the Null hypothesis when it should have been rejected). Whether a study had enough "power" or not depends on a number of factors, one of which is the "effect size". This means simply that if a "treatment" has a large effect, one does not need many subjects to show that a statistically significant difference exists between a "treated" and a "control" group. By the same token, if an "effect" is relatively small, but nonetheless present, more subjects are needed in each group to show this difference statistically. In the case of a small "effect size", insufficient numbers of subjects may not show a statistically significant difference when indeed a difference is present. This would be a Type II error. From this it is apparent, that one does not blindly claim that a study had insufficient power just because the number of subjects was "small". In fact, if a statistically significant difference was obtained, "power" is not even an issue. Therefore, the claim that "studies with less than 10 subjects are routinely excluded because of associated statistical power problems", is untenable. While it is true that less than 10 subjects is a small sample, the stated reason for rejecting it is faulty.

We are certain CMS would recognize that there are situations where the effect of a

treatment is so large that accepting the Null hypothesis is out of the question. For example, how many subjects injected with a local anesthetic need to be compared to those receiving a placebo before you are convinced that the anesthetic eliminates pain? In this case, the effect size of the anesthetic is so large, that not many subjects are needed to show a statistically significant difference between the groups. Another example: It only took one nuclear explosion to convince the United States Government and two to convince the Japanese government that additional nuclear explosions were not required to prove the destructive efficacy of such blasts.

Another point that the statisticians made is that in studies with controlled crossover designs the cross-over, for statistical purposes, effectively doubles the number of measures in such studies. Therefore, a study with an controlled crossover design is statistically considered to have twice the number of measures as a non-crossover study.

Neurotron, Inc. respectfully requests that "10 patient criteria" be reconsidered in light of the preceding analysis.

Menkes (2000) Publication: Supplementary Information

Menkes, D.L., Swenson, M.L., Sander, H.W. Current Perception Threshold: An Adjunctive Test for Detection of Acquired Demyelinating Polyneuropathies. Electromyography and Clinical Neurophysiology, Volume 40; Part 4:195-204, 2000.

The *DM* incorrectly characterized the Menkes article as stating that the sNCT evaluation was an adjunctive test to be conducted only when the sNCV findings were equivocal. While it is true that the publication and its title referred to the sNCT/CPT test as being an "adjunctive test" to SNCV, it was in the context of it being adjunctive to *motor* SNCV (mNCV) tests, not to the *sensory* SNCV (sNCV) tests. Depending upon the condition being evaluated, it would also be true that the mNCV could be an adjunctive test to be conducted only when sNCT findings were equivocal. (Note: See Letter from Dr. Menkes to CMS for a copy of Dr. Menkes' communication to CMS.)

This Menkes (2000) publication also references the impact of the sNCT/CPT evaluations on outcomes and expenses by making the following points:

1 Differentiating demyelinating from axonal polyneuropathies permits the clinician to decide whether or not an expensive treatment would be indicated.
2 Earlier treatments minimizes morbidity by reducing the degree of irreversible nerve damage.
3 The painful sensory sNCV test has patient compliance problems. There have been no publications mentioning any patient compliance problems with the painless sNCT test.

The publication cites several critical diagnostic advantages of the sNCT/CPT evaluation over the sensory sNCV evaluation for this type of study. The limitations of sNCV studies are well documented, forming the basis for the authors of this publication to make the following points:

1. The ability to test neurological function within the tips of the digits as well as proximally permits the sNCT/CPT test to detect dying back distal *axona*l polyneuropathies earlier than the sensory sNCV.

Note: The sNCV test can not test sensory function within the digits. The sensory sNCV

can not test proximally in the area of the dorsal root ganglia where *demyelinating* polyneuropathy often begins.

2. The ability to test sensory nerve function in *small* as well as *large* diameter myelinated fibers engenders the sNCT test with superior diagnostic sensitivity in comparison to the sensory sNCV test since dysfunction can occur in one fiber type sparing others as "axonal polyneuropathies tend to affect small fibers before large fibers".

Note: The sensory sNCV evaluation does not test small diameter myelinated or unmyelinated sensory nerve fibers.

Other advantages of the sNCT to sensory sNCV tests cited include the "noninvasive and painless" nature of the test and the fact that it requires "less technical expertise, is unaffected by skin temperature or resistance, and it can evaluate a large variety of skin surface sites".

The Menkes paper points out limitations of the sNCT/CPT evaluation as well:

1 Only tests sensory fibers.
2 Requires an alert patient
3 Requires a cooperative patient.

The publication stated that the sNCT test is at least as sensitive as the sensory sNCV test in differentiating axonal from demyelinating polyneuropathy. The study also indicates advantages of the sNCT test in contrast to the evoked potential test (SSEP). Dr. Menkes wrote an email on this topic to CMS which can be found in the Letter from Dr. Menkes to CMS section of this submission.

sNCT Evaluation and Outcome Among Kidney Dialysis Population: NIH Consensus Conference Publication

Avram, M.M. Neurological Complications in Chronic Uremia Management. Morbidity and Mortality of Dialysis NIH Consensus Development Conference, pp. 123-128, National Institute of Health (USA), Bethesda, MD, 1993.

Kidney dialysis filters are not perfect and do not completely filter the so-called "middle molecules" from the blood that are presumably responsible for the morbidity and mortality of uremia. Middle molecules have not yet been clearly defined or characterized. There is no laboratory test for middle molecules and they are only evaluated by indirect measures. Dialysis clinics utilize a variety of serum biochemistries and other measures in effort to indirectly assess the adequacy of dialysis and other therapeutic interventions (Ref: The Agency for Health Care Policy)

The NIH Consensus Conference (Formal Request, Appendix E #12) included 12 different serum biochemistries and other outcome adequacy measures among a population of hemodialysis patients. The presence of severe neuropathy as detected by the sNCT/CPT evaluation was associated with a significantly higher percentage of mortality among the non-diabetic uremics. The report indicates that patients with "adequate" dialysis and "favorable" lipid profiles that had severe neuropathy had significantly higher 1 year mortality. The study demonstrated no gender effects with respect to neuropathy. Significant differences in

the prevalence of neuropathy was noted between the black (45%), white (6%) and Hispanic (30%) uremic patient populations. This study demonstrated that the sNCT/CPT measure provided more valuable information about the long term outcome of dialysis patients than several serum chemistries. Other dialysis outcome studies are cited in the sNCT Formal Request appendix pages E-6 and E-7.

This study is not cited to imply that the sNCT evaluation would be indicated as a standard test for all dialysis patients, but instead it demonstrates the clinical utility of the sNCT procedure as a diagnostic instrument for measuring sensory nerve functions. The indications for the sNCT evaluation as prescribed by nephrologists is discussed in the Formal Request for a National Coverage Decision for the sNCT CPT Procedures, Appendix C, pages C-1 and C-2.

Sensitivity for Diagnosing Sensory Neuropathies: sNCT/CPT vs. sNCV

A number of studies and references included with Neurotron's Formal Request in Appendix E document the relative sensitivity of the sNCT/CPT and sNCV evaluations for detecting sensory neuropathies within the same patient group. Other studies document the ability of the sNCT to evaluate sensory neuropathies in conditions for which it is well documented that the sNCV is insensitive. The following listing cross references conditions associated with sensory neuropathy with the studies listed in Appendix E of Neurotron's Formal Application that address the sensitivity of the sNCT/CPT and sNCV for that particular condition.

Spinal Evaluation

Formal Request Appendix E, references 1, 2, 3 and 4 and references 26 and 27 in the Recent References section of this document: The sensory sNCV test is insensitive to spinal anesthesia, epidural anesthesia, syringomyelia and common radiculopathies[2,3,4]. The sensitivity of the sNCT/CPT measures for these conditions is discussed in these references.

Diabetic Neuropathy

Formal Request Appendix E, reference 5: sNCT vs CPT - (Figures 1 and 2): The sural and median nerve sNCV measures only indicated abnormalities correlating with physical scores and the symptom scores from the very abnormal diabetic group only. The sNCT/CPT evaluation detected significant sensory impairments that correlated with these both of these scores in both the relatively abnormal diabetic group and the very abnormal groups of diabetics.

Formal Request Appendix E, reference 6: Mapping Diabetic Neuropathy - It is impossible to conduct the sNCV evaluation from the tip of the finger or the toe where dying back neuropathy begins. sNCT/CPT studies from these sites are presented.

Formal Request Appendix E, reference 7: sNCT/CPT and sNCV measures only shows a correlation only at 2 kHz - the sNCT/CPT frequency of stimulus that excites the large myelinated sensory fibers.

Uremic Neuropathy

Formal Request Appendix E, reference 13: The detection sensitivity for uremic polyneuropathy: CPT 92%, sNCV 79%.

Kimura, J. Electrodiagnosis in Diseases of Nerve and Muscle. Edition 2, page 448, F.A. Davis Co. Philadelphia., PA, 1989.

[3] Goodgold, J. Rehabilitation Medicine. page 53, C.V. Mosby Co. St. Louis, MO, 1988.

[4] Electrodiagnosis in Clinical Medicine. 2nd edition, edited by Michael J, Aminoff, Churchill Livingstone, New York, 1986.

Formal Request Appendix E, reference 14: Table 5 has a sensitivity comparison showing the initial test sensitivity: CPT 76%, sNCV 65%; and the follow-up sensitivity: CPT 87%, sNCV 78%.

Large and Small Fiber Neuropathy Formal Request Appendix E, reference 15: Fabry disease - All sNCVs were normal in this selective small fiber polyneuropathy. sNCT had 50% low frequency CPT detection sensitivity. All high frequency (2000 Hz) CPTs were normal. Both hyperesthetic and hypoesthetic low frequency CPTs were detected.

Formal Request Appendix E, reference 17: Menkes study. Discusses demyelinating lesions. Robbins[5] reports that acute demyelinating polyneuropathies show "some predilection for the proximal nerve trunks" (top right paragraph on page 1430). Proximal lesions are not detected with sNCV.

Formal Request Appendix E, reference 18: Improvement following Iv. Ig therapy, historically is not noted detectable with sNCV studies but improvement was observed in this study using the sNCT/CPT evaluation.

Formal Request Appendix E, reference 20: CPT (2 kHz) and sNCV both had the same significance for correlation of impairment detection of vibration syndrome polyneuropathy. This neuroselectivity is also replicated in reference 9 in the Recent Publications section of this document.

Nerve Regeneration and Recovery of Function Formal Request Appendix E, reference 21: Regeneration study cites two references (3 and 4) showing persistent impairment of nerve conduction by sNCV and ER following regeneration. In contrast the sNCT/CPT demonstrated a recovery of function and change in transplanted toe sensory sensitivity to become more like the finger. The finger normally has significantly lower CPT measures than the toe.

Statistical Demonstrations of Equivalence and Superiority of sNCT/CPT to sNCV Evaluations

The following list presents the results of statistical analyses of the sensitivity for

diagnosing sensory neuropathies of the sNCT/CPT test compared to the sNCV test. The additional information presented below is the result of statistical analyses performed at CMS' request that were conducted by a professional statistician using the SPSS statistical program. (**Note**: Eight studies were originally submitted with the Neurotron's Formal Request that compared the sNCT/CPT test to the sNCV test. The sensitivity and specificity of the sNCT/CPT electrodiagnostic evaluation is discussed in the Formal Request, Appendix D.)

These analyses demonstrate that there was no statistically significant difference between the sensitivity of the sNCT/CPT measures of large fiber nerve pathology as compared with the sensory nerve conduction velocity evaluation. These analyses lead to the conclusion that, for the evaluation of large fiber pathology, the sNCT/CPT and sensory nerve conduction velocity evaluations were substantially equivalent in their clinical efficacy. However, for the evaluation of small fiber neuropathy, the sNCT/CPT evaluation is superior to the sNCV evaluation. Sensory nerve impairments can effect small and/or larger diameter sensory nerve fiber function.

1. Ro, L.S., Chen, S.T., Tang, L.M., Hsu, W.C., Chang, H.S., Huang, C.C. Current Perception Threshold Testing in Fabry's Disease. Muscle & Nerve, Volume 22: 1531-1537, 1999. Formal Request, Appendix E., Reference 15.

A chi-square SPSS statistical analysis was conducted to compare the detection sensitivity of neuropathy by sNCT/CPT and sNCV tests in this study. The CPT detected neuropathy in 50% of the patients. The sNCV detected neuropathy in 0% of the patients. There was a significant superiority of the detection sensitivity of the sNCT/CPT electrodiagnostic test over the sNCV test in this study ($p<0.001$, $df=1$).

2. Katims, J.J., Rouvelas, P., Sadler, B.T., Weseley, S.A. Current Perception Threshold: Reproducibility and Comparison with Nerve Conduction in Evaluation of Carpal Tunnel Syndrome. Transactions of the American Society of Artificial Internal Organs, Volume 35(3):280-284, 1989. Formal Request, Appendix E., Reference 13.

A chi-square SPSS statistical analysis was conducted to compare the detection of neuropathy by sNCT/CPT measure and sNCV measures in the median nerve and in the peroneal nerve. The tests were equally sensitive in their detection sensitivity for neuropathy ($p<0.193$, $df=1$, median nerve and $p<0.707$, $df=1$, peroneal nerve).

1 Weseley, S.A., Sadler, B., Katims, J.J. Current Perception: Preferred Test for Evaluation of Peripheral Nerve Integrity. Transactions of the American Society

of Artificial Internal Organs, Volume 34(3):188-193, 1988. Formal Request, Appendix E., Reference 14.

A chi-square SPSS statistical analysis was conducted to compare the detection of neuropathy by sNCT/CPT measure and sNCV measures in the median nerve and in the peroneal nerve. The tests were equally sensitive in their detection sensitivity for neuropathy ($p<0.119$, median nerve and $p<0.701$, peroneal nerve).

4. Kurozawa, Y., Nasu, Y. Current Perception Thresholds in Vibration-Induced Neuropathy. Archives of Environmental Health, Volume 56(3):254-256, 2001.

A. A chi-square SPSS statistical analysis was conducted to compare the detection of stage 3 vibration neuropathy by sNCT/CPT measure and sNCV measures. The tests

were equally sensitive in their detection sensitivity for this stage of vibration neuropathy ($p<0.308$, df = 1).

B. A chi-square SPSS statistical analysis was conducted to compare the detection of stage 2 vibration neuropathy by sNCT/CPT measure and sNCV measures. There was a significant superiority of the detection sensitivity of the sNCT/CPT electrodiagnostic test over the sNCV test in the detection of this stage of neuropathy($p<0.000$, df=1).

5. Rendell, M.S., Katims, J.J., Richter, R., Rowland, F. A comparison of nerve conduction velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. Journal of Neurology, Neurosurgery and Psychiatry, Volume 52:502-511, 1989. Formal Request, Appendix E., Reference 5.

A. Among the diabetic subjects in this study classified by both Physical Score and Symptom Score as normal, the 5 Hz CPT measures were the most "effective discriminator" of these "normal" patients in comparison with the sNCV and other measures in the study ($p<0.05$, Tables 6 and 7). This finding is a indication of the specificity of the CPT evaluation based on clinical findings.

B. Lower extremity sensory sNCV measures were unable to discriminate between the normal and abnormal subjects as classified by both Physical Score and Symptom Score. All three frequency CPT measures were able to discriminate between these same two groups of subjects. The significance of these observations ranged from $p<0.01$ (5 Hz and 250 Hz) to $p<0.05$ (2 kHz). This finding demonstrates that the CPT evaluation is a more effective discriminator than the sensory sNCV. See Table 7.

C. A strong correlation is defined as a correlation coefficient > 0.5. Correlations of the upper and lower extremity Physical and Symptom Scores with the CPT and sensory sNCV measures were significant, with p values ranging from 0.001 to 0.05. The strongest correlation was observed with physical evaluation and the 250 Hz CPT from the lower extremity (Spearman correlation coefficient = 0.57, $p<0.001$). The sensory sNCV from the same extremity showed a very weak correlation (Spearman correlation coefficient = 0.15, $p<0.05$). See Tables 4 and 5.

D. When the electrodiagnostic measures were further divided into "Relatively Abnormal" and "Very Abnormal Groups", the sensory sNCV was unable to discriminate between the normal and relatively abnormal groups Physical or Symptom scores in either the upper or the lower extremity. In contrast, the CPT measures were able to discriminate between the normal and relatively abnormal groups Physical or Symptom scores in either extremity ($p<0.01$). These findings indicate that the sensory sNCV is not effective for discriminating moderate neuropathy, but is effective for discriminating severe neuropathy. In contrast the CPT measures are effective for discriminating both moderate neuropathy, and severe neuropathy.

6. Masson, E.A., Veves, A., Fernando, D., Boulton, A.J.M. Current perception thresholds: a new, quick, and reproducible method for the assessment of peripheral neuropathy in diabetes mellitus. Diabetologia, Volume 32:724-728, 1989. Formal Request, Appendix E., Reference 7.

A. This publication does not permit a direct comparison of the detection sensitivities of the sNCT/CPT and the mNCV or sNCV measures.

B. A significant correlation between the 2000 Hz CPT measures and the mNCV or sNCV measures (Spearman correlation coefficient -0.66, $p<0.005$) was reported in Table 2.

C. A significant correlation between the 5 Hz CPT measures and the thermal measures (Spearman correlation coefficient .34, $p<0.005$) was reported in Table 2.

D. No significant correlation was observed between the mNCV or sNCV and the thermal end-organ sensory threshold test as reported in Table 2. This was expected as the mNCV or sNCV is a large fiber test and thermal end-organ stimulation is conducted by the small fibers. As neuropathies can selectively effect the large or small diameter nerve fibers the ability of the sNCT evaluation to test the function of both sub-populations of nerve fibers makes this test a more effective tool for the evaluation of neuropathy than the mNCV or sNCV test.

Pathological Definitions of Neuropathies Evaluated by sNCT/CPT

Appendix B of the Formal Request lists the following 4 types of nerve impairment that may be evaluated using the sNCT/CPT evaluation:

1 Distal symmetrical polyneuropathy
2 Asymmetric polyneuropathy
3 Radiculopathy
4 Compressive and focal lesions

The classification of these conditions is consistent with the classic medical pathology approach as described in the pathology textbook by Robbins et. al.[6]. Robbins has a section on peripheral neuropathy. The Formal Request goes into additional detail to distinguish the sNCT study from the sensory nerve conduction velocity (sNCV) study. For example, the diagnostic applications of the sNCT study is discussed for specific small and or large fiber neuropathy, regeneration, radiculopathy and proximal lesions because these conditions are not capable of being evaluated by the sNCV study.

Robbins' second paragraph (page 1429) begins discussing "both diffuse demyelination and axonal degeneration" neuropathy. The axonal degeneration neuropathy results in a distal symmetrical dying back polyneuropathy as illustrated in Fig. 29-44. Diffuse demyelination, also shown in this illustration, may occur anywhere along the length of the nerve and present clinically with an asymmetric distribution. Robbins reports that acute demyelinating polyneuropathies show "some predilection for the proximal nerve trunks" (top right paragraph on page 1430).

Robbins also reports in the first sentence of the 3rd paragraph of page 1429 that there are also focal nerve lesions. This would include radiculopathy and compressive lesions.

Independent Validation of Normative sNCT/CPT Values and Scoring

Scientific evidence provides the basis of the validation of the sNCT/CPT electrodiagnostic evaluation measure. There are more than 300 sNCT/CPT studies of statistically expressed normative sNCT/CPT values from around the world as well as the normative sNCT/CPT values provided to the FDA in 1985. This information is cited and reviewed in the Formal Request as well as in the following documents:

1 Specific normative sNCT/CPT value peer reviewed references were discussed in the Formal Request Appendix E, Section 8, page E-12, titled, "Selected sNCT Normative Value References".
2 Appendix H of the Formal Request explains the evaluation and grading of CPT measures based upon those related publications from Appendix E. A selection of additional peer-reviewed publications related to the evaluation of sNCT/CPT measures is available upon request.
3 Appendix D of the Formal Request is related to the statistical validation of normative sNCT/CPT values.
4 The recent publication cited in the Recent Documents section of this document provides further independent validation of the sNCT/CPT evaluation,

sNCT/CPT studies follow a standardized, automated double-blind procedure to generate objective, sensitive and reliable measures of sensory nerve function. Measures are obtained using microprocessor controlled constant alternating current (AC) sinusoid waveform stimuli presented at intensities ranging from 0.001 mAmperes to 9.99 mAmperes and at frequencies of 2000 Hz, 250 Hz and 5 Hz frequencies with durations of 1.65 second, 1.65 seconds and 2.88 seconds respectively. The measures are in the form of Current Perception Threshold (CPT) values, each of which represents the minimum intensity of a neuroselective, transcutaneous constant electrical current required to reproducibly evoke a sensation with a resolution of +/- 20 microAmperes and a $p<0.006$.

The electrical stimulus produced by the sNCT equipment is self-calibrating and able to maintain a constant current output regardless of normal variations in skin thickness and impedance. The system monitors the impedance at the skin electrode interface and instantly warns operators when conditions cause excessive impedance that could distort the accuracy of the measures. The system also monitors the consistency of a patient's responses to guard against false readings due to improper procedures or non-compliance. sNCT studies follow a double blind, forced choice testing paradigm at standardized testing sites to determine Current Perception Threshold (CPT) measures with a resolution of +/- 20 μAmperes to a $p<0.006$[7,8].

[7] Katims, J.J. Electrodiagnostic Functional Sensory Evaluation of the Patient with Pain: A

(continued...) Neurotron,

sNCT studies are conducted using equipment that is battery powered and portable and

doesn't require any special electrical shielding for safe and reliable operation. Patients can be evaluated almost anywhere they can be made comfortable and in an environment free from interruptions. Studies have demonstrated the reliability of sNCT evaluations conducted under a wide range of conditions, both in and out of clinical settings. (Appendices D and E of the Formal Request review related publications.)

The standardization of the sNCT evaluation removes tester and testing method factors from effecting CPT measures obtained from different populations at different locations and time periods. In contrast, these factors represent major confounding variables for sNCV studies[9][10][11]. Numerous studies from the past 16 years have evaluated CPT measures from healthy individuals from various populations and the following table summarizes findings from a representative example of these studies. The most commonly tested sites are the fingers and the toes.

Healthy Mean CPT Values (SD) , (1 CPT = 10 microAmperes)

	Face (Trigeminal Nerve)		**Finger**(Median Nerve)			**Toe** (Peroneal Nerve)	
CPT Frequency	USA[28] (n=338)	Korea[26] (n=400)	USA (n=334)	Japan[23] (n=1632)	Taiwan[15] (n=50)	USA (n=310)	Taiwan[15] (n=50)
5 Hz	10 (10)	11 (8)	46 (27)	61 (30)	50 (25)	73 (34)	74 (30)
250 Hz	19 (14)	21 (12)	81 (42)	93 (44)	78 (30)	125 (52)	126 (50)
2000 Hz	118 (52)	99 (28)	226 (80)	236 (62)	230 (70)	322 (110)	325 (106)

[**Note**: The superscripted numbers in the following tables reference the studies from which the data was gathered listed in Accuracy Analysis References on pages 5-6 of this submission. They are not footnotes.]

Appendix D of the Formal Request discusses the coefficients of variation of repeated CPT measures and their sensitivity and specificity as an index of the reliability of the sNCT study evaluation. The studies cited in Appendix D were included with the application and are summarized in Appendix E. Appendix H discusses the evaluation and grading of CPT measures

[7] (...continued)

Review of the Neuroselective Current Perception Threshold (CPT) and Pain Tolerance Threshold (PTT). Pain Digest Volume 8(5), 219-230, 1998

[8] Pain Tolerance Threshold (PTT). Pain Digest Volume 8(5), 219-230, 1998

[9] Chaudry, V. et al. inter- and Intraexaminer reliability of nerve conduction measurements in patients with diabetic neuropathy. Neurology. Volume 44;1459-1462, 1994.

[10] Chaudry, V. et al. inter- and Intraexaminer reliability of nerve conduction measurements in normal subjects. Annals of Neurology, Volume 30(6):841-831, 1991

[11] Annals of Neurology, Volume 30(6):841-831, 1991

Section 8 of Appendix E of the Formal Request reviews how standardized ranges of

healthy sNCT/CPT measures have been established for dozens of body sites through clinical studies conducted at several major institutions. . Those studies which contributed to the healthy base measures as well as some that established their own normal base measures are included in Appendix E. They are publication numbers 6, 7, 8, 9, 16, 19, 23, 24, 25 and 26.

Neuropathological Conditions Evaluated by sNCT/CPT

The following is a list of the top eight neuropathological conditions that may be appropriately evaluated by the sNCT/CPT evaluations. This information may be relevant for CMS for comparison of the sNCT/CPT evaluation to currently covered sensory neurodiagnostic procedures. An extended list of neuropathological conditions appropriately evaluated by sNCT/CPT is available upon request.

1 Axonal polyneuropathy
2 Demyelinating polyneuropathy
3 Entrapment Neuropathy (e.g. Carpal Tunnel Syndrome)
4 Focal nerve lesion
5 Radiculopathy
6 Myelopathy
7 Metabolic neuropathy
8 Toxic neuropathy

Neuropathy Experts Available for CMS to Contact

Following publication of the *DM*, Dr. Shuren invited Neurotron to submit a list of experts in neuropathy who are also familiar with the sNCT/CPT evaluation who could be interviewed by CMS when evaluating this Request for Reconsideration of the Decision Memorandum. Most of these physicians have also published studies using the sNCT/CPT evaluations. Additional information is available upon request.

1 Dr. Norman Latov (Cornel/Columbia University) (212)888-8516
2 Dr. Margit Bleecker (AMA Guides for Disability Evaluation of the Nervous System) (410)669-1101
3 Dr. Daniel Menkes (University of Tennessee) (901)448-6780
4 Dr. Marc Rendell (Creighton University) (402)280-4319
5 Dr. Sarala Palliyath, (VAMC & Tulane University) (504)589-5227
6 Dr. Neil Spielholz (University of Miami) (305)284.4535
7 Dr. Alan Hirsch (Rush Presbyterian Medical Center, Chicago)(312)649-5829
8 Dr. Levar Best (Craig Hospital, Englewood, CO) (303)797.1872

Pharmaceutical Publications

Following publication of the *DM*, Dr. Shuren indicated that he would be interested in knowing about any studies that showed that the sNCT/CPT evaluation could be used monitor

the efficacy of any pharmaceutic therapy. The following is a bibliography of peer reviewed publications that address that topic. The Recent Publications section of this document lists additional pharmaceutical related publications. Copies of any of these publications are available upon request

1 Winkler, G., Pal, B., Nagybeganyi, E., Ory, I., Porochnavec, M., Kempler, P. Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. Arzneim.-Forsch./Drug Reseach, Volume 49:220-224, 1999.

2 Appenzeller, O., Wood, S.C., Appenzeller, T. Pentoxifylline, Altitude, and Peripheral Nerve Function. Annals of Sports Medicine, Volume 4(4):286-288, 1988.

3 Kiso, T., Nagakura,, Y., Toya, T., Matsumoto, N., Tamura, S., Ito, H., Okada, M., Yamaguchi, T. Neurometer measurement of current stimulus threshold in rats. The Journal of Pharmacology and Experimental Therapeutics,, Volume 297(1):352356, 2001.

4 Kudoh, A., Ishihara, H., Matsuki, A., Current Perception Threshold and Postoperative Pain in Schizophrenic Patients, Regional Anesthesia and Pain Medicine, Volume 25(5):475-479, 2000.

5 Kudoh, A., Matsuki, A. Current perception thresholds of epileptic patients treated with valproate. Seizure, Volume 9; Part 7:498-501, 2000.

6 Wallace, M.S., Dyck, J.B., Rossi, S.S., Yaksh, T.L. Computer Controlled Lidocaine Infusion for the Evaluation of Neuropathic Pain after Peripheral Nerve Injury. Pain, Volume 66:69-77, 1996.

7 Liu, S.S., Gerancher, J.C., Bainton, B.G., Kopacz, D.J., Carpenter, R.L: Effects of Electrical Stimulation at Different Frequencies on Perception and Pain in Human Volunteers: Epidural Versus Intravenous Administration of Fentanyl. Anesthesia & Analgesia, Volume 82:98-102, 1996.

8 Tay, B., Wallace, M.S., Irving, G. Quantitative Assessment of Differential Sensory Blockade after Lumbar Epidural Lidocaine. Anesthesia and Analgesia, Volume 84:1071-1075, 1997.

9 Lee, Y., Robinson, M., Wong, N., Chan, E., Charles, M. A. The effect of pentoxifylline on current perception thresholds in patients with diabetic sensory neuropathy. Journal of Diabetes Complications, Volume 11(5):274-278, 1997.

10 Sakura S, Sumi M, Yamada Y, Saito, Y., Kosaka, Y. Quantitative and Selective Assessment of Sensory Block During Lumbar Epidural Anaesthesia with 1% or 2% lidocaine. British Journal of Anaesthesia, Volume 81:718-22, 1998.

11 Sakura, S., Sumi, M., Kushizaki, H., Saito, Y., Kosaka, Y. Concentration of Lidocaine Affects Intensity of Sensory Block During Lumbar Epidural Anesthesia. Anesthesia and Analgesia, Volume 88(1):123-7, 1998.

12 Angst, M.S., Drover, D.R., Lötsch, J., Ramaswamy, B., Naidu, S., Wada, D.R., Stanski, D.R. The pharmacodynamics of orally administered sustained release hydromorphone in humans. Anesthesiology, Volume 94:63-73, 2001.

13 Sakura, S., Sumi, M., Morimoto, N., Saito, Y. The Addition of Epinephrine Increases Intensity of Sensory Block During Epidural Anesthesia with Lidocaine, Regional Anesthesia and Pain Medicine. Volume 24(6): 541-546, 1999.

14 Finkel, J.C., Yang, C.I. Yarvitz, J.L. Patel, K.M. Neuroselective sensory electrodiagnostic evaluation of 4% liposomal lidocaine. Anesthesia Analgesia, Volume 94,:1259-62, 2002.

15 Gustorff, B., Nahlik, G., Klaus, Hoerauf, K.H., Kress, H.G. The Absence of Acute

Tolerance During Remifentanil Infusion in Volunteers. Anesthesia and Analgesia, Volume 94: 1223-8, 2002.

Updated Government, Insurance and Legal Citations

Appendix G of Neurotron's Formal Request references various government decisions related to the sNCT/CPT evaluation. Presently, the sNCT evaluation is being employed for non-investigational, clinical purposes under the supervision of physicians at more than five thousand locations in the United States and overseas. Appendix K of the Formal Request provides a partial listing of medical institutions at which sNCT studies have been employed, including the United States Air Force and eleven Veteran Administration Medical Center facilities as well as the Japanese, Taiwanese and Chinese military.

State of Texas

In 2000, the Texas Workers Compensation Commission (TWCC) performed its own independent review of the Neurometer CPT sensory Nerve Conduction Threshold (sNCT) procedure and concluded that procedure is not only a valid and valuable procedure, but that it also offers significant advantages over traditional Nerve Conduction Velocity (SNCV) tests. Recognizing the impact and importance of early detection on workers' health and the costs of treatment, the TWCC incorporated the sNCT studies into their guidelines[12]

The Spinal Treatment Guidelines (STG) group reviewed SNCV, sNCT/CPT and somato sensory evoked potential responses (ER) studies. The workgroup and staff concluded that SNCV and sNCT studies were deemed to be appropriate diagnostic tools and have been included in the list of Diagnostic Interventions, Subsection F. of the STG as EMG/Nerve Conduction Studies. The workgroup review of sNCT/CPT, a type of sensory conductive test, indicated that there was supporting literature for its effectiveness in some medical conditions but there was little evidence to warrant its use for musculo-skeletal conditions. However, the staff's review of the literature supplied by commenters supported the efficacy of sNCT/CPT testing for peripheral sensory impairments that are not clinically detectable through sensory SNCV studies. Staff review of the literature also supported the efficacy of CPT testing for the evaluation of radiculopathy and as an appropriate diagnostic tool for the quantitative measure of the functional integrity of sensory nerve fibers. CPT is considered a nerve conduction study and is therefore included in the STG.

Japanese National Health Coverage

In 1998, the Japanese government, Ministry of Health, authorized reimbursement for the automated neuroselective sNCT evaluation. The reimbursement rate for this electrodiagnostic evaluation is the same as for the sensory nerve conduction velocity (SNCV) procedure. Further information is available upon request.

12 Spine Treatment Guideline, Preamble, page 14 and Adopted amendment to §134.1001, page 77, effective February 1, 2000. Downloadable at <http://www.twcc.state.tx.us/rules/preambledrules/preambledtoc.html#Chapter>.8

Washington State

In March 1999, an Industrial Appeals Judge before the Board of Industrial Insurance Appeals, State of Washington concluded in a hearing related to the utility of the sNCT/CPT electrodiagnostic evaluation of Carpal Tunnel Syndrome: "The CPT Neurometer provides proper and necessary medical services within the meaning of RCW 51.36.010 and it was not improper to bill using procedure code 95904 "..."and that providers are not precluded from submitting billings for diagnostic testing using the CPT Neurometer". (Docket No. 98 P0056)

The Commonwealth of Massachusetts

On April 10, 2002, The Commonwealth of Massachusetts, Department of Industrial Accidents, Administrative Judge James L. Lamothe Jr. ruled that the Argonaut Insurance Company acting upon a claim processed by CONCENTRA Managed Care Services, Inc., an accredited Utilization-Review Accreditation Commission, also known as the American Accreditation Health Care Commission, must reimburse for the neuroselective sensory Nerve Conduction Threshold (sNCT) electrodiagnostic evaluation with Current Perception Threshold (CPT) measures. The Order specifically states "The Insurer shall pay for the CPT test." A determination was made that the sNCT/CPT evaluation was reasonable and necessary. The physician requested the sNCT/CPT evaluation because the MRI and EMG evaluations although both negative are insensitive to small fiber sensory nerve impairments capable of causing the patients pain that may be detected and evaluated by the sNCT/CPT measures.

Allstate Insurance Company

On April 3, 1995 at the US District Court, Eastern District of New York, Mario Introna vs. Allstate Insurance Company, 93-CV-2870, Judge Bartels, based upon recommendations by the expert from the Allstate Insurance Company, determined that the correct procedure code to be utilized for the sensory Nerve Conduction Threshold (sNCT) electrodiagnostic evaluation Current Perception Threshold (CPT) evaluation be the same code that is used for the sensory nerve conduction velocity evaluation - 95904.

Nationwide Insurance Company

In January 1998, Nationwide Insurance Company reported that the sNCT/CPT evaluation "proved to have clinical applications. Independent neurologists contacted stated CPT was a reimbursable procedure. These opinions, and discussion with area physicians on the effectiveness if a CPT evaluation in their practices resulted in the reimbursement of the CPT procedure"..."With the 1997 coding revisions, CPT is being submitted under the 95904 procedure code."

Additional Legal Citations Involving the sNCT/CPT Evaluation

1 Herman Leblanc, Jr. vs Aetna Life and Casualty Co., OWC #90-01163, District 5.

2 Kenneth Atkinson vs Ethyl Corporation, et. al., District Court of Harris County Texas, 152nd Judicial District.

3 Lilburn Levay Fuller and Gary James Darby vs Union Equity Cooperative Exchange,

et. al.
4 Lilburn Levay Fuller vs Gulf Stream Maritime and Aetna Casualty and Surety Co., OWC #8-91011.
5 Gary James Darby vs Gulf Stream Maritime and Aetna Casualty and Surety Co., OWC #8-91032.
6 Ruth Theirry Bird vs Jimmy D. Qualle and Jonathon Kaizer. Okmulgee District Court, Okmulgee, Oklahoma.
7 Jack L. Pope vs Hinz Trucking-a foreign corporation & Allan Zuckert-an individual, Okmulgee District Court, Okmulgee, Oklahoma.
8 Stacy Null vs Ruben Gomez Superior Court for the County of Ventura, California, Case #123736 (1/31/94).
9 GTE vs. Wilson-Briton, before the State of Washington Board of Industrial Insurance Appeals, Claim T579020 Docket #924082. Proposed decision and order, re: Judith M. Wilson, July 15, 1993.
10 Onamura vs Weisman, Case No.92-3169-09, Circuit Court of the First Circuit of the State of Hawaii, Honolulu, August, 1995.
11 Louise Jones vs Nationwide Ins. Co. / Solomon, Docket 64834-6 T.D., Shelby County, TN. Circuit Court, October, 1997.
12 Havsy, S.L., D.O. and Pain Diagnostics and Rehabilitation Associates, P.S., Before the Board of Industrial Insurance Appeals State of Washington, Docket No. 98.P0056, Provider No. 55001 & 56000, Industrial Appeals Judge: Kathryn Guykema, March 1999.
13 Christopher Dial and Angeline Taylor v. Grave Rigsby, Order CCG-N002, IL, 97 M4 704, Fourth Municipal District Circuit Court of Cook County, Judge James V. Murphy, May 24, 2000. Aurelia Pucinski, Clerk of the Circuit Court.

Letter from Margit Bleecker, M.D., Ph.D. to CMS

The letter on the following two pages was submitted by Margit Bleecker, M.D., Ph.D. to CMS in support of a National Coverage Decision for the sNCT/CPT evaluation. Dr. Bleecker is a world renowned and AMA expert in peripheral neuropathy. Dr. Bleecker was the Chapter Chair of the chapter "The Central and Peripheral Nervous System" on the AMA Guides to Disability Evaluation, 5th edition, 2001. Dr. Bleecker has over 20 years of clinical experience with the sNCT/CPT evaluation. Neither the letter nor endorsement were cited or mentioned in the *DM* and were presumably never reviewed by the *DM*'s author(s) due to the TLD problem.

C O E N Center for Occupational and Environmental Neurology

MEDICAL-ERGONOMIC PROGRAM

Occupational Neurology & Neuropsychiatry
Margit L. Bleecker, MD, PhD
D. Patrick Ford, MD, MPH, CIH

Clinical Psychology & Occupational Stress Management
Karen N. Lindgren, PhD
Valerie L. Masten, PhD
Daniel R. Malone, PhD
Karin Scheetz, MA

Occupational Therapy
Shari K. Barnes, OTR

November 15, 2001.

Dr. John Whyte
Director of Items and Devices
Coverage and Analysis Group
HCFA
7500 Security Blvd.
Baltimore, MD 21244

Re: Letter of support for sNCT/CPT evaluation

Dear Dr. White:

At the request of Dr. Jefferson Katims I am writing you to provide my opinion and experience with the sNCT examination. As a neurologist and the Director for the Center for Occupational and Environmental Neurology there have been numerous opportunities to publish on the quantitative neurological examination needed to detect changes in the nervous system from a variety of insults; most recently as the Chapter Chair for the chapter, "The Central and Peripheral Nervous System" in the AMA Guides to the Evaluation of Permanent Impairment, 5th edition, 2001 and "The Role of the Quantitative Neurological Examination" in Neurologic Clinics-Clinical Neurobehavioral Toxicology, JW Albers and S Berent editors, August 2000.

The need to document change in the nervous system both for disease onset and progression and for response to treatment is critical. One test used to document sensory change in the peripheral nervous system is the sensory nerve conduction velocity and amplitude study. However this test only reflects pathology in the fastest conducting, large myelinated A-beta fibers. Toxic neuropathies may compromise the smaller A-delta and C nerve fibers that carry the sensory information for temperature and pain. However pathology in the A-delta and C nerve fibers cannot be detected by sensory nerve conduction velocity studies. The sNCT has the ability to examine A-beta, A-delta and C nerve fibers and thereby provide more fully the extent of the underlying pathology. This was elegantly demonstrated in an ongoing case of arsenic neuropathy that involved all three fiber populations. Follow-up with sNCT examination showed improvement by proximal-distal anatomical location and through the differential recovery by specific nerve fiber population.

Toxic neuropathies whether from exposures in the workplace or other metabolic dysfunction usually begin at the most distal end of the sensory nerve fibers, an area easily studied with sNCT but not accessible to sensory nerve conduction velocity studies. This feature is important for detection of neuropathies early in their development.

Residents in the Occupational Medicine program at Johns Hopkins School of Public Health receive their training in Occupational Neurology at the Center for Occupational and Environmental Neurology. Learning how to use and interpret sNCT is part of that training. These residents must be able to detect the earliest evidence of neuropathy onset in the workplace in order to provide early intervention and thereby protect the health of the worker. sNCT is the perfect tool for this purpose with the ability to measure change whether hyperesthetic or hypesthetic, at the distal or proximal site of onset and of all fiber populations.

Sincerely,

Margit L. Bleecker, MD, PhD
Director
Center for Occupational and Environmental Neurology

Letter from Daniel Menkes, M.D. to CMS

The following email was sent to CMS by Daniel Menkes, M.D., Assistant Professor of Neurology at University of Tennessee, Memphis. This letter had two primary purposes. The first was to clear up CMS' confusion over meaning of the title of the following publication:

Menkes, D.L., Swenson, M.L., Sander, H.W. **Current Perception Threshold: An Adjunctive Test for Detection of Acquired Demyelinating Polyneuropathies**. Electromyography and Clinical Neurophysiology, Volume 40; Part 4:195-204, 2000.

(Note: See Menkes (2000) Publication: Supplementary Information earlier in this document for additional information.)

The second purpose of the Menkes letter was to urge CMS to "approve the sNCT as being "reasonable and necessary" for the evaluation of sensory disturbances in the Medicare population." and he also offered to speak with CMS. The *DM*, however, failed to consider Menkes' clarification of the title of his publication that Dr. Menkes provided and so repeated its error in the *DM*. Also, neither his letter nor endorsement were cited or mentioned in the *DM* and all were apparently never reviewed by the *DM*'s author(s) due to the TLD problem.

Date: Sun, 19 Aug 2001 09:44:20 -0400 (EDT)
Message-Id: <200108191344.JAA02896@web2.po.com>
From: Daniel Menkes <menkes@pol.net>
To: jwhyte@hcfa.gov
Subject: Neurometer CPT application

Dr. John Whyte
Director of Items and Devices
Coverage and Analysis Group
HCFA
7500 Security Blvd.
Baltimore, MD 21244
(410)786-9668
email: jwhyte@hcfa.gov

Dear Dr. Whyte,

Dr. Jefferson Katims has informed me that CMS is evaluating a formal application to determine whether current literature supports the clinical use of the sNCT exam as being considered "reasonable and necessary" for the Medicare population. I understand that one of my publications was referenced. For that reason, I respectfully request that I clarify my perspectives on the Neurometer CPT and its sNCT examination.

While the title of my publication used the word "adjunctive", I can assure you that the sNCT test should not be viewed in that context. Medical journals tend to be conservative by nature and expect new

ideas to be introduced slowly and deliberately. In clinical practice, I have found the sNCT to be an important electrodiagnostic method for evaluating disorders affecting any and all portions of the sensory nervous system.

As you are aware, diagnostic testing has replaced physical examination as the gold standard for the diagnosis of most medical conditions. While cardiac auscultation is still important, few cardiologists would make important clinical decisions without the data obtained from an electrocardiogram or an echocardiogram. These tests provide an electrical and anatomic description of the heart that a physical examination simply cannot provide. Therefore, all of these modalities are important.

Neurological disturbances of the sensory nervous system are no exception to this rule. While a sensory examination can provide some information, electrodiagnostic testing provides objective quantification of the location and degree of the sensory deficit. There are three important and complimentary tests that are important in this regard; sensory nerve conduction velocities (sNCV), somatosensory evoked potentials (SSEPs) and the Neurometer sensory nerve conduction threshold (sNCT).

Sensory information is conveyed in three main types of sensory fibers designated A-beta, A-delta and C fibers. The A-beta fibers are large and thickly myelinated. A-beta fibers relay information regarding vibration and position. A-delta fibers are thinly myelinated and relay visceral afferent information. C fibers are unmyelinated and convey pain and temperature sensation. However, sNCV and SSEPs are only capable of analyzing the A-beta fibers. They provide no information whatsoever regarding A-delta of C fiber function. By contrast, the Neurometer sNCT is able to evaluate all three fiber types. This information should be contained in Dr. Katim's application.

As an Assistant Professor of Neurology at the University of Tennessee who is the Director of the Clinical Neurophysiology Service, I am often asked to define the location and severity of a sensory deficit. This requires the ability to quantify sensory function in all three fiber subtypes. The anatomic distribution and the pattern of sensory dysfunction of the three main subtypes provides the best means of achieving an accurate diagnosis.

I respectfully request that you approve the sNCT as being "reasonable and necessary" for the evaluation of sensory disturbances in the Medicare population. If you have any more questions, please do not hesitate to contact me.

Sincerely,

Daniel L. Menkes, M.D. Assistant Professor of Neurology University of Tennessee, Memphis

Recent Publications

The following is a list of recent publications published subsequent to the Neurotron's Formal Request in March 2001 that are being submitted for CMS' consideration. Copies are available upon request.

Note: The following recent publication was requested by and submitted to CMS in November 2001 along with an accompanying PowerPoint presentation: Jiang, Y-D, Hsieh, S-T, Chen, TH, Wu, H-P, Tai, T-Y, Katims, JJ, Chuang, L-M. Characterization of the hyperesthetic and hypoesthetic stages of diabetic neuropathy by current perception threshold evaluation. Submitted for publication, Diabetologia, 2001. A copy is available upon request. Neither this publications nor it findings were cited or mentioned in the *DM* and presumably were never reviewed by the *DM*'s author(s) due to the TLD problem.

Animal Studies: Pain, Pharmacology and Physiology

1) Kiso, T., Nagakura,, Y., Toya, T., Matsumoto, N., Tamura, S., Ito, H., Okada, M.,

Yamaguchi, T. Neurometer measurement of current stimulus threshold in rats. The Journal of Pharmacology and Experimental Therapeutics., Volume 297(1):352-356, 2001.

This Neurometer® Animal Response Threshold (ART) research is from the Yamanouchi Pharmaceutical Co., Ltd. research institute in Tsukuba, Japan. A total of 87 rats were used for several studies:

a) Repeated ART Measures: Eight rats were repeatedly tested over a 3 hour period and over 3 days. The measures were extremely reliable and researchers reported that "The rats showed almost constant current stimulus thresholds during the 3 h"...., "The rats showed hardly any variation in the current stimulus threshold with respective stimulations over a 3-day period."

b) Capsaicin Study - "Repeated topical application to the area around the stimulating electrode of a high concentration of capsaicin, which acts on small-diameter fibers, increased the thresholds at 250 and 5 Hz, but did not affect the 2000 Hz" ART measures.

c) Morphine - Intravenous morphine (2-5 mg/kg) increased all three ARTs, whereas intrathecal morphine (20 or 80 mg) increased only the 5-Hz ART. This finding is consistent with observations made with the following human study:

Liu, S.S., Gerancher, J.C., Bainton, B.G., Kopacz, D.J., Carpenter, R.L: Effects of Electrical Stimulation at Different Frequencies on Perception and Pain in Human Volunteers: Epidural Versus Intravenous Administration of Fentanyl. Anesthesia & Analgesia, Volume 82:98-102, 1996. (Note: This study also demonstrated that the opiate, fentanyl, had no effect on the painless Current Perception Threshold (CPT) measures and a neuroselective effect on Pain Tolerance Threshold (PTT) measures)

d) Diazepam - Intravenous injection of a diazepam, at 1 mg/kg raised the ARTs at 2000 and 250 Hz, but did not affect the 5-Hz ART. Higher dose of diazepam increased all three frequencies ARTs.

The publication concludes that, "The Neurometer makes possible selective examination of sub-sets of nerve fibers that differ in diameter not only in humans but also in animals." Another recent related publication by these researchers was:

Yamaguchi, T., Toya, T., Tamura, S., Takemoto, Y., Nagakura, Y., Kohara, A., Kiso, T., Kakimoto, S., Iwai, A., Akuzawa, S., Effects of NMDA receptor antagonists on the current stimulus threshold with the neurometer in rats. Japanese Journal of Pharmacology. Volume 88(Sup 1.):230P, 2002.

2) Song, E.B., Yang, J.H., Kang, Y.K., Kim, S.J. Usefulness of Current Withdrawal Threshold on Evaluation of the Neuropathic Pain on Animal Model. Journal of the Korean Academy of Rehabilitation Medicine, Volume 25(1):117-121, 2001.

This research, from Korea University Medical Center, was a controlled study of the rat model of neuropathic pain. Neurometer® Animal Response Threshold (ART) measurers were obtained from 36 rats using the 5 Hz measures only. This neuropathic pain condition was associated with a significant decrease in the 5 Hz ART measures. The systemic administration of betamethasone resulted in the abnormal ART measures returning to baseline levels.

3) Mamiya, K., Yokohama, H., Mamiya, N., Takahata, O. Iwasaki, H. Pregnancy Increases Cutaneous Pain Thresholds to Electrical and Chemical Stimuli in the Rats. American Society of Anesthesiology, Abstract A-748, 2001.

This research, from Asahikawa Medical College, Japan, was a controlled study that included 24 rats. Pregnancy resulted in significantly higher Neurometer® Animal Response Threshold (ART) measures with the 5 Hz, 250 Hz and 2000 Hz measures. Pregnancy also increased the threshold to chemical (formalin) stimuli. (Note: This animal pregnancy study is complimentary to the human pregnancy related publication below #24.) Another recent related study by these researchers was:

a) Mamiya, K, Okaoda, H., Yokohama, K. Sengoku, K., Takahata, without., Iwazi, H. The effects of pregnancy-induced analgesia on sensory processing of the peripheral nerves in rats. Japanese Society of Anesthesiology. Annual Meeting, Poster Pd2N01, 2001.

4) Miyabe, T., Kitagawa, N., Oda, Y., Sakutrata, T., Morimoto, T. Quantitative evaluation of lidocaine neurotoxicity by current perception threshold in rat. Japanese Society of Anesthesiology. Annual Meeting, Poster P2A05, 2001.

Endocrinology: Diabetes, Autonomic Dysfunction, Hyperesthesia

5) Jiang, Y-D, Hsich, S-T, Wu, H-P, Tai, T-Y, Katims, J.J., Chuang, L-M. Char-acterization of hyperesthetic stage of diabetic neuropathy with current perception threshold, a method for diabetic neuropathy staging. XI Meeting, Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (EASD) NEURODIAB. 2001.

This research, from National Taiwan University and New York University, studied 2360 type 2 diabetic patients. Hyper, hypo and normoesthetic Neurometer® Current Perception Threshold (CPT) measures from diabetic patients were compared to other sensory tests and clinical measures. This study demonstrated a hyperesthetic stage lying between normal sensory function and hypoesthesia during the development of overt diabetic neuropathy.

6) Várkoni, T.T., Lengyel, C., Madácsy, L., Velösy, B., Kempler, P., Fazekas, T., Pávics, L., Csernay, L., Lonovics, J. Gallbladder Hypomotility in diabetic neuropathy. Clinical Autonomic Research, Volume 11:377-381, 2001.

This study, from the University of Szeged and Semmelweis University in Hungary, was of 10 type 1 diabetic patients. The findings demonstrated a significant correlation between the impairment of gallbladder motility, cardiac autonomic dysfunction and Neurometer® Current Perception Threshold (CPT) measures of polyneuropathy. These findings were consistent with the following previous publication by this group:

a) Lengyel, C., Török, T., Várkonyi, T., Kempler, P., Rudas, L. Baroreflex Sensitivity and Heart-Rate Variability in Insulin-Dependent Diabetics with Polyneuropathy. The Lancet Volume 351(1823):1436-1437, 1998.

7) Várkoni, T.T., Tóth, F., Róvo, L., Lengyel, C, Kiss, J.G., Kempler, P., Lonovics, J. Impairment of the auditory brainstem function in diabetic neuropathy. Diabetes Care, Volume 25(3):631-632, 2002.

This study, from the University of Szeged and Semmelweis University in Hungary, included 12 patients with long standing type 1 diabetes with normal hearing. The patients had auditory brainstem evoked potential abnormalities that correlated with 2000 Hz and 250 Hz Neurometer® Current Perception Threshold (CPT) measures of diabetic polyneuropathy. Both the brainstem potential studies and the 2000 Hz and 250 Hz CPT measures reflect the functioning of the larger diameter nerve fibers.

8) Other recent diabetes related publications from Japan include the following:

a) Ishida, K., Okanishi, A., Shiraishi, Y. The evaluation of the effects of epalrestat on diabetic peripheral by using the Current Perception Threshold (CPT) electrodiagnostic evaluation. Journal of the Japan Diabetes Society. Volume 44:S177, 2001.

b) Isotani, H., Ishida, S., Yamamoto, N., Kameoka, K., Furukawa, K., Hanabusa, T. Usefulness of simultaneous screening of diabetic foot lesion and neuropathy. Journal of the Japan Diabetes Society Volume 44:S-176, 2001.

c) Okanishi, A., Ishida, K., Shiraishi, Y. The relationship of diabetic peripheral neuropathy to peripheral circulatory function. Journal of the Japan Diabetes Society. Volume 44:S-75, 2001.

Occupational Medicine / Vibration Neuropathy

9) Kurozawa, Y., Nasu, Y. Current Perception Thresholds in Vibration-Induced Neuropathy. Archives of Environmental Health, Volume 56(3):254-256, 2001.

This research from Tottori University and San-in Rosai Hospital of Yonago, Japan, was of 59 men officially recognized by the Japanese Ministry of Labor with hand-arm vibration syndrome that was documented by clinical and laboratory tests. There were 20 matched control subjects. The sensory nerve conduction velocity evaluation was used to confirm Stage 3 vibration neuropathy. Stage 3 is the most advanced stage based upon the international Stockholm classification system. The sensory nerve conduction velocity evaluation is insensitive to the earlier Stages 1 and 2 of vibration neuropathy when intervention is less expensive and more beneficial. The Neurometer CPT evaluation was able to detect sensory impairments in all 3 stages of vibration neuropathy neuroselectively by showing impairments confined to large and small myelinated fiber function only, a finding consistent with histological studies. These findings are also consistent with the following report by Canadian researchers of a study of 173 vibration neuropathy related subjects which also included CPT and sensory nerve conduction velocity studies:

a) Pelmear, P.L. and Kusiak, R. Clinical Assessment of Hand-Arm Vibration Syndrome. Nagoya Journal of Medical Science, Volume 57:27-41, 1994).

Another related recent publication includes the following:

b) Nonomura, H., Early stages of carpal tunnel syndrome patients shows sensory disturbance as not only hypoesthesia but also hyperesthesia by quantitative sensory evaluation using current perception threshold testing. Japanese Society for Surgery of the Hand. Volume 18 (Part 4):page S44, 2001.

Pain Pharmacology

10) Angst, M.S., Drover, D.R., Lötsch, J., Ramaswamy, B., Naidu, S., Wada, D.R., Stanski, D.R. The pharmacodynamics of orally administered sustained release hydromorphone in humans. Anesthesiology, Volume 94:63-73, 2001.

These researchers from Stanford University, USA, used Neurometer® PTT measures to evaluate analgesia associated with different analogs of the analgesic, hydromorphone, in 12 subjects in a double blind cross-over design. The study demonstrated the dose dependent effect of the drugs ($p<0.001$) and that the sustained release hydromorphone has analgesic effects of approximately ten times the duration of the immediate release version of this drug.

11) Radwan, I.A., Saito, S. Goto, F. High-concentration tetracaine for the management of trigeminal neuralgia: quantitative assessment of sensory function after peripheral nerve block. Clinical Journal of Pain. Volume 17:323-326, 2001.

This study, from Gunma University School of Medicine, Japan, included five elderly patients with trigeminal neuralgia receiving infraorbital nerve blocks using 4% tetracaine dissolved in saline or 0.5% bupivacaine. Neurometer® CPT measures demonstrated that the high-concentration tetracaine peripheral nerve blocks were relatively safe with no adverse sensory functional impairments. A related report by these researchers was:

a) Goto, F. , Radwan, I.A. Current perception threshold following trigeminal nerve block. 6th Biennial Congress, Asian and Oceanic Society of Regional Anesthesiology. PS1-01, page 229, 2001.

12) Gustorff, B., Nahlik, G., Klaus, Hoerauf, K.H., Kress, H.G. The Absence of Acute Tolerance During Remifentanil Infusion in Volunteers. Anesthesia & Analgesia, Volume 94: 1223-8, 2002.

This paper was awarded the 2002 Scientific Prize of the Austrian Pain Society. This prospective double blind placebo controlled double-blinded cross-over study, from the University of Vienna, included 17 subjects. Neurometer® Pain Tolerance Threshold (PTT) 250 Hz and 5 Hz measures were used to evaluate constant remifentanyl infusion during a 3 hour period. The study concludes that this course of administration does not lead to a rapid development of opiate tolerance. Additional recent publications by these researchers from the University of Vienna include the following:

a) Gustorff B., Nahlik G., Hoerauf K., Kress H.G. No early tolerance during Remifentanil infusion in volunteers. European Journal of Anaesthesiology, Volume 18: S138, 2001

b) Sycha T., Voller, B., Gustorff B., Auff, E., Schnider, P. Towards the analgesic effects of botulinum toxin A: a randomized, double blind, placebo controlled study. British Journal of Anaesthesiology. Volume 87:S 39, 2001.

c) Voller, B., Sycha, T., Gustorff, B., Auff, E., Schnider, P. Botulinum Toxin in der Schmerzbehandlung: Wirkung an der C und A-delta Faser an gesunden Probanden. 9th Annual Meeting of the Austrian Pain Society, Abstract-Suppl, Velden, 2001.

13) Okada, T., et al. Long-term efficacy of topical 0,05% capsaicin in post herpetic neuralgia. Pain Clinic (Japan), Volume 22(2)219-222, 2001.

Pain Physiology

14) Raj, P.P., et al. Painless Electrodiagnostic Current Perception Threshold and Pain Tolerance Threshold Values in CRPS Subjects and Healthy Controls: A Multi-Center Study. Pain Practice, Volume 1(1);53-60, 2001.

This multi-center study (USA, Australia) of 36 chronic pain CRPS patients with allodynia and 57 healthy controls had a detection sensitivity of the Neurometer® Pain Tolerance Threshold (PTT) measure of 78% at the symptomatic test site. The painless Current Perception Threshold (CPT) measures had a detection sensitivity of 47% at the same site. Selective large myelinated, small myelinated and/or unmyelinated fiber pathology was detected. PTT measures are reported to provide additional valuable information for the assessment of the chronic pain patient. Normative PTT values for the fingers and the toes were established by this study

15) Sakai, T., Tomiyasu, C., Ono, T., Yamada, Y., Sumikawa, K. The Evaluation of Dynamic Allodynia and Pain Associated with Postherpetic Neuralgia Using Current Perception Threshold Testing Device. American Society of Anesthesiology, Abstract A-800, 2001.

This study from the Nagasaki University School of Medicine, Japan, conducted Neurometer® Current Perception Threshold (CPT) evaluations of 15 patients with thoracic Postherpetic Neuralgia (PHN) and dynamic allodynia. The study concluded that the intensity of dynamic allodynia is dependent upon the preserved functions of the small myelinated and unmyelinated sensory nerve fibers. The data was consistent with the idea that the activity of unmyelinated fibers, such as ectopic impulses associated with nerve injury, induces a central sensitization in the spinal cord, resulting in the production of allodynia mediated by large myelinated fibers. A lack of correlation between intensity of ongoing pain and dynamic allodynia suggested that ongoing PHN pain is not only caused by ectopic impulse production, but also deafferentation mechanisms. This conclusion was supported by the observation that the intensity of ongoing PHN pain is independent of the preserved unmyelinated fiber function.

16) Sakura, S., Imamachi, N., Kushizaki, H., Hashimoto, T., Saito, Y., et al. Effect of Ambient Temperature on Current Perception Thresholds in Healthy Volunteers. American Society of Anesthesiology, Abstract A-838, 2001.

This study from Shimane Medical University studied the effects of ambient temperature on Neurometer® Current Perception Threshold (CPT) measures from 14 healthy volunteers. The subjects were randomly exposed for one hour intervals to two different ambient temperatures: 25°C and 8°C. In the colder environment the skin temperature was significantly lower and the 2000 Hz CPT measures and systolic blood pressure measures were significantly higher than at the warm ambient temperature. No differences were observed between the 250 Hz and 5 Hz CPTs between the two environments. The authors conclude that since 2000 Hz CPTs reflect large fiber function, that a cold environment selectively suppresses the function of these fibers. Related publications by these researchers includes the following:

a) Imamachi, N., Sakura, S., Sato, N., Kanata, K., Saito, Y., et al. Ambient Temperature Affects Current Perception Thresholds in Patients with Neuropathic Pain. American

Society of Anesthesiology, Abstract A-837, 2001.

This study of 8 patients with neuropathic pain (including 5 with post herpetic neuralgia) demonstrated that ambient temperatures affected all three CPTs in the area of neuropathic pain but not in the area free of pain. Cold temperature affected both large and small diameter sensory nerve fibers in patients with neuropathic pain. The authors conclude that these results may their clinical experiences that complaints by chronic pain patients varies depending on the weather.

b) Imanachi, N., Sakura, with., Yokokawa, N., Doi, K., Nakatani, T., Saito, Y. Effects of ambient temperature on current perception threshold in patients with neuropathic pain. Regional Anesthesia and Pain Medicine, Volume 26(2);46, 2001

Additional related recent publications include the following;

c) Maeda, S., Sasaki, U., Nagasawa, H., Shimizu, S., Tanaka, K., Obuchi, S., Shiba, Y., Hoka, C. Changes in the Current Perception Threshold (CPT) Due to Artificial High Concentration CO.2 Water Warm Bathing. Journal of the Japanese Association of Physical Medicine Balneology and Climatology. Volume 64, Part 4:191-198, 2001.

17) Morell, R.C., Prielipp, R.C., Butterworth, J.F., Harwood, T.N., Vriesema, M.L. Ulnar Nerve Dysfunction Induced by Pressure or Flexion. American Society of Anesthesiology, Abstract A-1182, 2001.

This prospective study from the Wake Forest University School of Medicine, NC, USA, included 80 female and 80 male volunteers. Ulnar nerve dysfunction by direct pressure and also by flexion was evaluated. Both direct pressure and flexion produced highly significant decrements in 5 Hz © fiber) Neurometer® Current Perception Threshold (CPT) measures. Significant effects on 250 Hz (A delta) CPT measures were reported with direct pressure but not with flexion. Neither flexion nor direct pressure significantly altered CPT measurements at 2000 Hz (Abeta). Interestingly, a previous report by these researchers and reports from other researchers including those at the University of Texas and the Queen Alexandria Hospital in the UK have shown that tourniquet ischemia selectively increases 2000 Hz CPT measures while sparing the 250 Hz and 5 Hz CPT measures. All of these findings are consistent with known physiological differences between the various sub-populations of sensory nerve fibers. These other studies are:

a) Morell, R.C., Prielipp, R.C., Butterworth, J.F., Harwood, T.N. Walker, F.O. Males Appear More Susceptible to Ulnar Nerve Ischemia Than Females. American Society of Anesthesiology, Abstract 1124, 2000.

b) Savidge, M.J., Fahmy, B., Price, C.M., Rodgers, P.D. Quantitative changes in sensory nerve threshold potentials, induced by a tourniquet and measured by a Neurometer® device. The Pain Society. The British and Irish Chapter of the International Association for the Study of Pain. Abstract, 1999.

c) Baron, G.C., Irving, G.A. Effects of Tourniquet Ischemia on Current Perception Thresholds in Healthy Volunteers. Pain Practice, Volume 2(2);129-133, 2002. (This publication is described in reference number 25 below.)

Intercostal Nerve Damage Associated with Chronic Post-Thoracotomy Pain. American Society of Anesthesiology, Abstract A-964, 2001.

This study from the Nagasaki University School of Medicine, Japan, was conducted to evaluate the primary afferent nerve damage 1 month after thoracotomy using Neurometer® current perception threshold (CPT) testing. Fourteen patients were studied. Significantly increased 2000 Hz and 250 Hz CPTs were detected, but no changes were observed with the 5 Hz CPTs. The percentage of the change correlated with the severity of the post-thoracotomy pain reported by the patients. The authors conclude that selective damage to the peripheral myelinated fibers plays a significant role in the development of chronic post-thoracotomy pain.

19) Lee, K-S., Kim, L-S., A Clinical Evaluation of DITI and Neurometer® for the Diagnosis of Cold Hypersensitivity. American Academy of Thermology, 29th Annual Meeting, page 49, 2001.

This study from Kyung Hee University in Seoul, South Korea, evaluated 30 female patients with cold hypersensitivity. Significant thermographic abnormalities were observed in these patients. Additionally, significant Neurometer® Current Perception Threshold (CPT) abnormalities were observed in 85% of the patients. The authors conclude that the detection of cold hypersensitivity by both thermographic imaging and CPT evaluation permits earlier therapeutic intervention, thereby improving the prognosis, with the potential of limiting more severe damage and reducing the cost of care.

20) Finkel, J.C., Yang, C.I. Yarvitz, J.L. Patel, K.M. Neuroselective sensory electrodiagnostic evaluation of 4% liposomal. Anesthesia & Analgesia, Volume 94:1259-62, 2002.

This publication from the Children's National Medical Center (USA) and George Washington University, utilized the Neurometer® Pain Tolerance Threshold (PTT) to evaluate the effects of the cutaneous application of 4% liposomal lidocaine. Blockade of unmyelinated © fiber function was observed earlier than small myelinated fiber (A delta) function which occurred before large myelinated fiber (A beta) function. This observation of the neuroselectivity of the effects of lidocaine has been reported in numerous other Neurometer® sensory Nerve Conduction Threshold (sNCT) electrodiagnostic evaluation publications which are available upon request. These researchers reported the mean onset time of approximately 4 minutes for unmyelinated fiber transmission and 6 minutes for small myelinated fiber transmission which suggested that painful stimuli such as venipuncture may be attenuated as early as 7 minutes by the cutaneous application of 4% Liposomal Lidocaine. Other related publications by these researchers include the following by this research group as well as number publication number 21 below:

a) Finkel, J.C., Yang, C.I., Yarvitz, J.L., Patel, K.M. Neuroselective Electrodiagnostic Current Perception Threshold Evaluation of 4% Liposomal Lidocaine (free paper). Presented at 1st World Congress on Regional Anaesthesia and Pain Therapy. Barcelona, Spain. May 31, 2002.

b) Finkel, J.C., Yang, C.I., Yarvitz, J.L., Patel, K.M. Neuroselective sensory electrodiagnostic evaluation of 4% liposomal lidocaine. Anesthesia Analgesia, Volume 94:S218, 2002.

c) Finkel J.C, Yang, C.I., Yarvitz, J.L., Patel, K.M. The influence of an occlusive dressing on onset time of topical anesthesia with 4% liposomal lidocaine as determined by

neuroselective pain tolerance thresholds. Anesthesia and Analgesia, Volume 94:S219, 2002.

d) Finkel, J.C., Yang, C.I., Yarvitz, J.L., Patel, K.M. The Influence of an Occlusive Dressing on Onset Time of Topical Anesthesia with 4% Liposomal Lidocaine as Determined by Neuroselective Current Perception Thresholds and Pinprick (poster). Presented at 1st World Congress on Regional Anaesthesia and Pain Therapy. Barcelona, Spain. May 31, 2002

21) Egi, A.; Sanuki, M.; Kinoshita, H.; Fujii, K. Evaluation of adhesive tape containing lidocaine using current perception threshold measurement. Masui, Volume 50(7):731735, 2001.

This study from Hiroshima Hospital, Hiroshima, Japan, used the Neurometer® Current Perception Threshold (CPT) electrodiagnostic evaluation to evaluate the efficacy of lidocaine adhesive tape (Penles; Wyeth Lederle Japan, Ltd, Tokyo, Japan) for pain. The peak efficacy for analgesia, as measured by increased 5 Hz CPT measures, was observed at 6 hours following placement of the tape.

22) Sung, C.H. Neural blockade treatment for cervical dystonia, especially for spasmodic torticollis and benign essential blepharospasm. 6th Biennial Congress, Asian and Oceanic Society of Regional Anesthesiology. SL VIII-2, page 92; supplemental pages 1-10, 2001.

This report from the St. Mary's Hospital Catholic University Medical College in Seoul, Korea, included 7 patients with benign essential blepharospasm, eye pain and dry eye. All of the subjects had Neurometer® Current Perception Threshold (CPT) trigeminal nerve abnormalities. Following stellate ganglion block therapy all the patients had a short term immediate improvement in their pain symptomatology. Two patients had complete remission to normal CPT measures and 4 others showed some improvement in their CPT measures and their pain did not progress. One patient had no long term benefit from this intervention and continued to deteriorate. Although trigeminal CPT evaluations of healthy individuals do not evoke blepharospasm, it is interesting to note that in this study, the trigeminal CPT evaluation evoked blepharospasm in several patients. The Neurometer CPT evaluation was able to provide an objective quantitative measure of the efficacy of the stellate ganglion blocks in these pain patients.
Medical School Volume 69(1):19-23, 2002).

This Nippon Medical School study included 24 pregnant and 22 non-pregnant women. It reported a significant increase in the 250 Hz and 2000 Hz Neurometer® Current Perception Threshold (CPT) measures associated with pregnancy. A discrepancy between this clinical study and the animal pregnancy study discussed above in number 3, was that this human study utilized the painless CPT measure and not the painful Pain Tolerance Threshold (PTT) measure. The animal study, in contrast, was measuring the Animal Response Threshold (ART) which is understood to be an adverse stimulus.

Urology

24) Ukimura, O., Iwata, T., Inaba, M., Honjo, H., Kawauchi, A., Kojima, M.; Miki, T. Quantitative measurement of urinary sensory function assessed by current perception

threshold in the bladder using a Neurometer. Neurourology and Urodynamics, Volume 20 (Part 4):124, 2001.

This research from the Kyoto Prefectural University of Medicine, Japan, used the Neurometer® CPT/C device and an electrophysiology catheter to obtain Current Perception Threshold (CPT) measures from the bladders of 30 patients. Three additional patients who had no sensation as a result of complete spinal injury were unable to provide any bladder CPT measures. In normoactive bladders, the bladder CPT values were approximately half of CPT values on the skin of the index finger. In the 6 patients with detrusor hyperreflexia due to incomplete cervical or thoracic spinal diseases, diagnosed by the presence of uninhibited contraction and/or positive ice-water test, the bladder 5 Hz CPT value was significantly lower than the normoactive bladder 5 Hz CPT measures. In the neurogenic bladder determined to be underactive (n=11), including post pelvic surgery and diabetic patients, relatively higher CPT values were reported at all three CPT frequencies compared to those in the normoactive bladder. The authors conclude that the quantitative evaluation of the three major sub-populations of sensory nerve fibers in the bladder may "contribute to the appropriate selection of therapeutic strategy in individual patients with neurogenic bladders." An additional publication by this group is the following:

a) Ukimura, O., Miki, T., Kawauchi, A., Iwata, T., Iwata, M., Honjo, H. Preliminary results of quantitative measurement of urinary sensory function assessed by current perception threshold in the bladder. Journal of Urology, Volume 165(5 Suppl.):299, 2001.

Neurophysiology, Neuroselectivity

25) Baron, G.C., Irving, G.A. Effects of Tourniquet Ischemia on Current Perception Thresholds in Healthy Volunteers. Pain Practice, Volume 2(2);129-133, 2002.

This Neurometer CPT study from The University of Texas-Houston Health Science Center Medical School confirms an earlier British report that the 5 Hz CPT measures are unaffected by 30 minutes of tourniquet ischemia, whereas the 2 kHz CPT measures were significantly elevated for the last 25 minutes of this ischemia. This observation obtained from 10 healthy individuals is consistent with the understanding that the smaller diameter sensory fibers are more resistant to the effects of ischemia than the larger diameter fibers. [Note: This paper is cited in point 17) c) above.

Radiculopathy, Spine, Neurosurgery, Pain

26) Falci, S.P., Best, L.G, Bayles, R., Cown, C. Dorsal Root Entry Zone (DREZ) microcoagulation for central pain of spinal cord injury: operative intramedullary electrophysiological guidance and clinical outcome. Journal of Neurosurgery (Spine 2), Volume 97:193-200, 2002.

This paper from the Craig Hospital in Denver, Colorado, includes 52 patients. It reports that 5 Hz CPT measures correlated well with neurophysiologic abnormalities as monitored intraoperatively from the substantia gelatinosa (lamina II) area of the spinal dorsal horn innervated by C fiber afferents. The 5 Hz CPT measures were more sensitive in identifying pathologic spinal segments than the intraoperative neurophysiologic measures (approximately 84% for CPT versus 56% for neurophysiologic). This publication clearly demonstrates the ability of the CPT evaluation to localize the dermatome level of a spinal

cord lesion. A previous related publication by these researchers includes:

a) Falci, S., Best, L., Lammertse, D., Starnes, C. Surgical Treatment of Spinal Cord Injury (SCI) Pain Using A New Technique of Intramedullary Electrical Analysis. Journal of Spinal Cord Medicine. Volume22(1):39, 1999.

27) Yamashita, T., Kanaya, K., Sekine, M., Takebayashi, T., Kawaguchi, S., Katahira, G. A quantitative analysis of sensory function in lumbar radiculopathy using current perception threshold testing. Spine, Volume 27(14:1567-70;2002.

This study from the Sapporo Medical University and the Sapporo Kiyota Orthopedic Hospital appears in the official international journal of many spine societies, including those from Asia, Europe, North and South America. This paper documents the ability of the sNCT/CPT evaluation to document sensory nerve dysfunction in dermatomes associated with pain and unequivocal disc dysfunction as shown by magnetic resonance imaging. A total of 48 patients were studied and 11 healthy subjects were used as control subjects. In the control group , there was no significant difference in sNCT/CPT values between the left and right legs. In the patient group, the sNCT/CPT measures in the effected leg dermatome test sites were significantly higher than in the contralateral matched test sites ($p<0.01$). the authors conclude that the sNCT/CPT evaluation is useful in quantifying sensory dysfunction resulting from radiculopathy.