# Differences in Current Perception Threshold between Individuals with and Without Diabetes Mellitus

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## Abstract

**Objective:** The dental research field has little evidence about sensation in individuals with Diabetes Mellitus (DM). Thus, we conducted study to verify our questions as following: 1) whether there are any differences of Current Perception Threshold (CPT) between DM and non-DM (NDM) groups, which was totally evaluated top-to-toe organs as represented by foot, hand, and oral cavity; 2) whether CPTs obtained from oral cavity, hand and foot differed from each other; 3) whether CPTs obtained from three current frequencies used for testing (2000Hz, 250Hz, and 5Hz) differed from each other. **Methods:** CPT measurements were obtained from the oral mucosa and the tips of fingers and toes of fifty six volunteers: 21 individuals with DM (12 male and 9 female, average age = 72.1 ± 4.7 years) and 35 individuals with NDM (17 male and 18 female, average age = 51.2 ± 23.9 years) using electrical stimulation at frequencies of 5, 250, and 2000 Hz. **Results:** The individuals with DM had significantly lower CPT value than those without DM. The CPT values of oral cavity, hand and foot significantly differed from each other (foot > hand, foot > oral cavity, hand > oral cavity). There was significant difference in the CPT values of 5Hz and 2000Hz as well as 5Hz and 2000Hz.

*Key Words: Diabetes mellitus, Foot, Hand, Hyperesthesia*

## Introduction

The World Health Organization reported that people with Diabetes Mellitus (DM) has risen from 108 million in 1980 to 422 million in 2014 [1]. The 2003–2012 Japanese National Health and Nutrition Surveys obtained from 51,128 individuals aged ≥ 20 years showed that the age-standardized prevalence of diabetes remained constant at approximately 8%, and the proportion of individuals receiving treatment for DM increased significantly from 41.8% in 2003 to 54.9% in 2012 [2].

The DM cause peripheral neuropathy, which is a common serious complication of diabetes and cause of disability and reduced quality of life, due to sensory loss, pain, gait disturbance, fall-related injuries, and foot ulceration and amputation [3]. The neuropathy is often a major component in the critical pathway for the development of diabetic ulcers and amputations. Foot ulcers are among the most common complications of diabetes, which induced by repetitive pressure [4-6]. Collin et al. reported that repetitive pressure induced by occlusal force causes denture-related lesions on the pressure-supporting oral mucosa occur more often in denture wearers with DM than in those without DM [7]. This report was in agreement with our clinical experience with denture wearers of DM patients, treatment of which tend to be extended for a long period of time due to severe ulcers on oral mucosa. We thought this might be attributed to diabetic neuropathy. Perception is one of the primary natural warning systems to alert danger to individuals. If this early warning system fails to function normally, individuals with diabetic neuropathy can sustain injuries that are not recognized until they are so severe that full-thickness wounds result [8]. The susceptibility of DM patients to ulcers in the oral mucosa covered by dentures might be contributed by neuropathy occurring in oral mucosa. As denture wearing as well as the prevalence of DM is increased in an aging society, it is therefore important to investigate relation between oral sensation and DM.

The neuropathy in DM has been evaluated by several methods [9-14], including transcranial direct current stimulation. The Current Perception Threshold (CPT) as determined using a Neurometer® has been proposed to be a useful quantitative parameter for assessing peripheral sensory nerve function in body such as hand, foot, and head [15]. The current frequencies of 2000, 250, and 5 Hz selectively evaluate the large myelinated A-beta fibers, small myelinated A-delta fibers, and unmyelinated C fibers respectively. The validity of the method was proven by comparison to standard sensory testing techniques that have popularly been used for diagnosis of neuropathy in DM, including thermal and vibration detection thresholds [16,17]. We have developed an approach to apply transcranial direct current stimulations for oral sensory measurements and have previously reported in several manuscripts that the CPT can be useful for assessing changes in oral sensation in denture wearers [18-20]. The CPT as measured by the Neurometer® may also be useful for oral sensory measurements in patients with DM. This study aimed that the sensation in intraoral sensation between individuals with and without DM.

## Methods

### Participants

This study was approved by the Human Ethics Committee of Nihon University School of Dentistry at Matsudo (IRB project number: 15-003). Fifty-six volunteers, including 21 individuals with DM (DM group, 12 men and 9 women, average age = 72.1 ± 4.7 years), and 35 individuals without DM (NDM group, 17 men and 18 women, average age= 51.2

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± 23.9 years), were recruited for the study. These individuals were patients at the Nihon University School of Dentistry at Matsudo Affiliated Hospital or were workers or students at the Nihon University School of Dentistry at Matsudo, respectively, and provided written informed consent prior to enrollment. Individuals meeting the following conditions were excluded:

- The presence of general health problems that could affect the measurement of nerve activity (e.g., trigeminal neuralgia or postherpetic neuralgia);
- Signs and symptoms of orofacial pain disorders;
- Pacemakers;
- Obvious cognitive impairment; and
- A lack of understanding of written or spoken Japanese.

### CPT testing

The subjects sat comfortably on dental chair in a quiet room. CPTs from the left greater palatine foramen, the tip of left first finger, and left toe were measured by only one operator using the Neurometer CPT/C®.

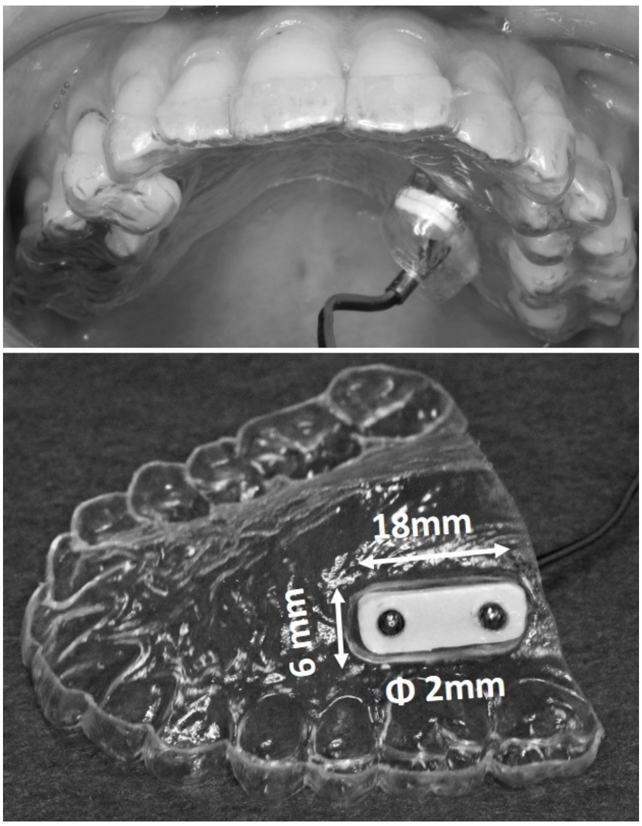


*Figure 1. Intraoral removable device with stimulating electrodes. Participants wore the measurement apparatus, containing Ø 1-mm thermoforming discs, to ensure good contact between the oral mucosa and the stimulation electrodes.*

According to the manufacturer's instructions, the electrical current slowly increased from 0.01 mA until the subjects reported a sensation. A rough perception threshold level was then set. Then, 6 to 20 cycles of randomly selected true and false stimuli above and below the preliminary perception threshold level was implemented using a microprocessor-controlled forced-choice method. The CPT measurements were performed in a double-blinded manner until the exact CPT was determined.

A measurement apparatus with φ 1 mm thermoforming discs was fabricated for each participant. Plates (18×9×6 mm) with stimulation electrodes (φ 2 mm) mounted on an intraoral removable appliance were utilized in order to ensure contact between the mucosa and stimulation electrodes *(Figure 1)*.

### Statistical analysis

Before other statistical analyses were performed, the normality of the data was tested using the Kolmogorov–Smirnov test, following which parametric statistical methods were applied.

Participants' characteristics were analyzed by a t-test and the Chi-squared test. In order to adjust for the difference in age between the DM and NDM groups, we used analysis of covariance (ANCOVA) with the Bonferroni post-hoc test to assess whether there were any differences in CPT between the DM and NDM groups; whether the CPTs obtained from the oral cavity, hand, and foot differed from each other; and whether CPTs obtained using three different current frequencies for testing (2000 Hz, 250 Hz, and 5 Hz) differed from each other. The age had possibility to work as a confounder to CPTs was set as a covariate. When a statistically significant interaction between factors was observed, a simple main effect test was conducted to analyze a between-factor interaction.

Statistical analyses were performed using SPSS® Statistics 21 (SPSS-IBM, MD, USA), with $p < 0.05$ representing significant differences.

## Results

### Participants' characteristics

The participants' characteristics are shown in *Table 1*.

*Table 1. Participants' characteristics. Proportion of male and female in DM was analyzed by Chi-squared test. Mean differences of the sex, age, body mass index, and blood sugar level between DM and NDM were analyzed by t test. DM, diabetes mellitus; NDM, non-diabetes mellitus.*

| Characteristics | DM (n=21) | NDM (n=21) | P-value |
|---|---|---|---|
| Sex (male/female) | 12-09-2018 | 17/18 | 0.589 |
| Age (years) | 72.1 ± 4.7 | 51.2 ± 23.6 | <.001 |
| Body Mass Index (Kg/m$^2$) | 23.1 ± 4.4 | 21.8 ± 3.0 | 0.21 |
| Hemoglobin A1$_c$ (%) | 6.9 ± 0.8 | 5.7 ± 0.5 | <.001 |
| Blood sugar level (mg/dL) | 153.4 ± 38.2 | 118.2 ± 22.1 | <.001 |

There were significant differences in age, HbA1c levels, and blood sugar levels between the DM and NDM groups. However, there were no significant differences in the proportion of males and females or in the body mass index between the DM and NDM groups.

## CPT values

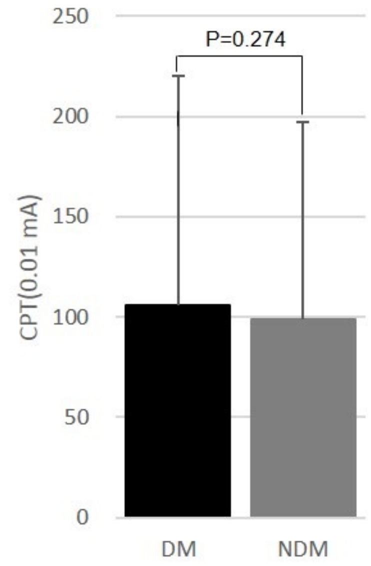


*Figure 2. CPTs of DM and NDM groups. ANCOVA revealed that individuals with DM had lower CPT values than those without DM. The mean values of DM and NDM groups in the figure represents the overall PT, which means that all CPTs obtained from foot, hand and oral cavity as well as those from 5 Hz, 250 Hz, and 2000 Hz were averaged. DM: diabetes mellitus, NDM: non-diabetes mellitus*

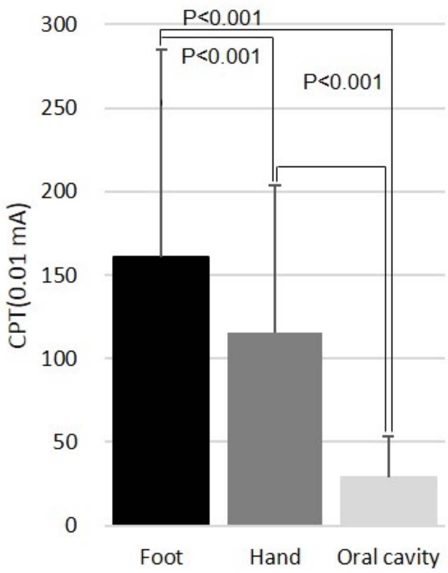


*Figure 3. CPTs of foot, hand, and the oral cavity. ANCOVA with Bonferroni post-hoc tests showed that PTs increase in the following order: oral cavity < hand < foot. The mean values of foot, hand, and the oral cavity in the figure represents the overall PT, which means that all CPTs obtained from participants with MD and NDM as well as those from 5 Hz, 250 Hz, and 2000 Hz were averaged.*

The CPT value of the DM group was 105.9 ± 114.2 × $10^{-2}$mA and that of the NDM group was 99.1 ± 98.4×$10^{-2}$mA *(Figure 2)*.

There was no significant different CPT between individuals with DM had significantly and those without DM (ANCOVA, p=0.274). The CPT values obtained from the oral cavity, hand, and foot were 28.8 ± 24.6 × $10^{-2}$mA, 115.4 ± 88.6, and 160.7 ± 124.3×$10^{-2}$mA, respectively *(Figure 3)*.

The CPT values of the oral cavity, hand, and foot differed significantly from each other (ANCOVA with Bonferroni post-hoc test, all p < 0.0001, in the order oral cavity < hand < foot). The CPT values obtained using 5 Hz, 250 Hz, and 2000 Hz were 46.8 ± 38.8×$10^{-2}$mA, 70.1 ± 52.5×$10^{-2}$mA, and 188.1 ± 130.9×$10^{-2}$mA, respectively *(Figure 4)*.

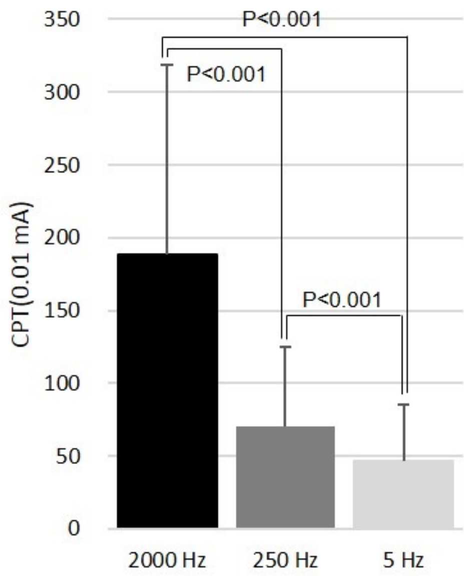


*Figure 4. CPTs of 2000 Hz, 250 Hz, and 5 Hz frequencies. ANCOVA with Bonferroni post-hoc tests showed that there was a significant difference in the PT values obtained with 5 Hz vs. 2000 Hz as well as with 250 Hz vs. 2000 Hz. The mean values of 5 Hz, 250 Hz, and 2000 Hz in the figure represents the overall PT, which means that all CPTs obtained from participants with MD and NDM as well as those from foot, hand and oral cavity were averaged.*

*Table 2. Summary results of analysis of covariance. DM- Diabetes Mellitus; ×- interaction; F- Fisher distribution.*

| Dependent variable | Mean square | F-value | P-value |
|---|---|---|---|
| Age | 262.5 | 0.097 | 0.756 |
| DM | 3255.142 | 1.2 | 0.274 |
| Frequency | 952269.992 | 351.064 | <.001 |
| Region | 698663.668 | 257.57 | <.001 |
| DM × Frequency | 10426.518 | 3.844 | 0.022 |
| DM × Region | 1091.759 | 0.402 | 0.669 |
| Frequency × Region | 171664.674 | 63.286 | 0 |
| DM × Frequency × Region | 2460.637 | 0.907 | 0.459 |

The CPT values obtained using 5 Hz and 2000 Hz differed significantly from each other (ANCOVA with Bonferroni post-hoc test, all p < 0.0001, in the order 5 Hz < 250 Hz < 2000 Hz). The *Table 2* summarized results of ANCOVA.

## Discussion

This study revealed that CPTs obtained from the oral cavity, hand, and foot differ significantly from each other; and that CPTs obtained using three different current frequencies varied; however could not show that the differences in intraoral sensation between individuals with DM and without DM.

The region-induced CPT diversity with CPT values in the order oral cavity < hand < foot suggested that regions closer to the head had smaller CPT values, corresponding to a greater sensitivity to stimulation. Several researchers reported the CPT at the foot/finger, finger, face, and face/oral cavity, [21-24]. Although they did not directly compare the face, finger, face, and oral cavity values, their findings were in line with ours. Penfield's homunculus shows the precise topography of cortical representation of particular parts of the body in discrete parts of the brain, correlating with motor and sensory phenomena in those particular regions of the body. Furthermore, Disbrow et al. examined the human somatosensory cortex in the Sylvian fissure, using functional magnetic resonance imaging to describe the number and internal organization of cortical fields present [25]. They reported that somatic stimuli applied to the lips, face, hand, trunk, and foot were registered in specific regions of the cortex. By indicating the relatively large proportion of the brain involved in sensitive and complex movement, particularly of the face and hands, the homunculus will help to illustrate a fundamental principal of sensory test modalities.

The present study also showed current frequency-induced CPT diversity, in the following order 5 Hz, 250 Hz < 2000 Hz. These results suggested the selective stimulation of nerves; large myelinated A-beta fibers, small myelinated A-delta fibers, and unmyelinated C fibers are excited selectively by 2000, 250, and 5 Hz frequencies, respectively [26]. Nerve fibers with different diameters have different characteristic refractory periods, due to the number of ion channels available per surface area of the fiber [26]. Due to these characteristics, the large-diameter fibers can respond to the rapid 2000-Hz stimulus, while small unmyelinated fibers require several milliseconds of continuous depolarization to respond, resulting in selective stimulations of the three different nerve fiber types. The CPT value at 250 Hz was similar to that at 5 Hz, while the CPT at 2000 Hz was markedly differed from that at 250 and 5 Hz. C fibers excited selectively by 5 Hz can respond to a broad range of painful stimuli, including mechanical or thermal stimulation. The A-delta fibers excited selectively by 250 Hz respond to either mechanical stimuli or temperature stimuli in the painful region and produce an acute sensation of sharp, bright pain. However, A-beta fibers excited selectively by 2000 Hz are not related to the pain sensation. The participants in our study reported electrical stimuli at 2000 Hz induced not pain but uncomfortable sensation, which may be the reason why the CPT at 2000 Hz was different than that at the other frequencies.

It is well known that diabetic peripheral neuropathy causes several symptoms, such as pain, dysesthesia, and loss of sensation, which have been evaluated by several sensory tests [9-14]. However, this study could not show the differences in intraoral sensation between individuals with DM and without DM. The limitation of this study was sample size which was too small to detect significant differences between DM and NDM groups. In the future, we will expand this study to a large sample, including patients with a wide range of DM-related conditions.

In conclusion, in this study, we demonstrated that CPT measurements were region-specific, and increased in the following order: oral cavity < hand < foot, and were higher for 2000-Hz stimulation than for 5- and 250-Hz stimulation.

## Acknowledgement

This study was conducted in accordance with the Declaration of Helsinki, and each subject received oral and written information about the study and provided informed consent. The study protocol was reviewed and approved by the Human Ethics Committee of Nihon University School of Dentistry at Matsudo (EC15-003). This research was carried out with support from the Japan Society for the Promotion of Science, Grant/Award Number: Scientific Research (C) (2) #17K11767. There are no conflicts of interests to declare.

## References

1. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1&ua=1
2. Ikeda N, Nishi N, Noda H, Noda M. Trends in prevalence and management of diabetes and related vascular risks in Japanese adults: Japan national health and nutrition surveys 2003-2012. *Diabetes Research and Clinical Practice*. 2017; **127**: 115-122.
3. Stino AM, Smith AG. Peripheral neuropathy in prediabetes and the metabolic syndrome. *Journal of Diabetes Investigation*. 2017; **8**: 646-655
4. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, et al. Diabetic foot ulcers: Part I. pathophysiology and prevention. *Journal of the American Academy of Dermatology*. 2014; **70**: 1-18.
5. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. *Diabetes Care*. 2003; **26**: 1435-1438.
6. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *Jama*. 2005; **293**: 217-228.
7. Collin HL, Niskanen L, Uusitupa M, Toyry J, Collin P, et al. Oral symptoms and signs in elderly patients with type 2 diabetes mellitus. A focus on diabetic neuropathy. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2000; **90**: 299-305.
8. Armstrong DG, Lavery LA, Quebedeaux TL, Walker SC. Surgical morbidity and the risk of amputation due to infected puncture wounds in diabetic versus nondiabetic adults. *Journal of the American Podiatric Medical Association*. 1997; **87**: 321-326.
9. Kenny GP, Sigal RJ, McGinn R. Body temperature regulation in diabetes. *Temperature (Austin, Tex)*. 2016; **3**: 119-145.
10. Feng Y, Schlosser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. *Journal Of Vascular Surgery*. 2009; **50**: 675-682.
11. Thakral G, Kim PJ, LaFontaine J, Menzies R, Najafi B, et al. Electrical stimulation as an adjunctive treatment of painful and

sensory diabetic neuropathy. *Journal of Diabetes Science and Technology*. 2013; **7**: 1202-1209.

12. Stein C, Eibel B, Sbruzzi G, Lago PD, Plentz RD. Electrical stimulation and electromagnetic field use in patients with diabetic neuropathy: systematic review and meta-analysis. *Brazilian Journal of Physical Therapy*. 2013; **17**: 93-104.

13. Thomsen NO, Cederlund R, Speidel T, Dahlin LB. Vibrotactile sense in patients with diabetes and carpal tunnel syndrome. *Diabetic Medicine : A Journal of the British Diabetic Association*. 2011; **28**: 1401-1406.

14. Donaghue VM, Giurini JM, Rosenblum BI, Weissman PN, Veves A. Variability in function measurements of three sensory foot nerves in neuropathic diabetic patients. *Diabetes Research and Clinical Practice*. 1995; **29**: 37-42.

15. Katims JJ, Naviasky EH, Rendell MS, Ng LK, Bleecker ML. Constant current sine wave transcutaneous nerve stimulation for the evaluation of peripheral neuropathy. *Archives of Physical Medicine and Rehabilitation*. 1987; **68**: 210-213.

16. Masson EA, Boulton AJ. The Neurometer: validation and comparison with conventional tests for diabetic neuropathy. *Diabetic Medicine : A Journal of the British Diabetic Association*. 1991; **8**: 63-66.

17. Pitei DL, Watkins PJ, Stevens MJ, Edmonds ME. The value of the Neurometer in assessing diabetic neuropathy by measurement of the current perception threshold. *Diabetic Medicine : A Journal of the British Diabetic Association*. 1994; **11**: 872-876.

18. Nakashima Y, Kimoto S, Ogawa T, Furuse N, Ono M, et al. Characteristics of the pain tolerance threshold induced by electrical stimulation of the alveolar ridge. *Clinical and Experimental Dental Research*. 2015; **1**: 80-86.

19. Ito N, Kimoto S, Kawai Y. Does wearing dentures change sensory nerve responses under the denture base? *Gerodontology*. 2014; **31**: 63-67.

20. Kimoto S, Ito N, Nakashima Y, Ikeguchi N, Yamaguchi H, et al. Maxillary sensory nerve responses induced by different types of dentures. *Journal of Prosthodontic Research*. 2013; **57**: 42-45.

21. Ro LS, Chen ST, Tang LM, Hsu WC, Chang HS, Huang CC. Current perception threshold testing in Fabry's disease. *Muscle Nerve*. 1999; **22**: 1531-1537.

22. Takekuma K, Ando F, Niino N, Shimokata H. Age and gender differences in skin sensory threshold assessed by current perception in community-dwelling Japanese. *Journal Of Epidemiology*. 2000; **10**: 33-38.

23. Kim HS, Kho HS, Kim YK, Lee SW, Chung SC. Reliability and characteristics of current perception thresholds in the territory of the infraorbital and inferior alveolar nerves. *Journal of Orofacial Pain*. 2000; **14**: 286-292.

24. Ogura K, Kimoto S, Yamaguchi H, Kobayashi K. Perception thresholds for electrical stimulation of the palatal mucosa. *The International Journal of Prosthodontics*. 2007; **20**: 423-431.

25. Disbrow E, Roberts T, Krubitzer L. Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. *The Journal of Comparative Neurology*. 2000; **28**: 1-21.

26. Katims JJ. Electrodiagnostic functional sensory evaluation of the patient with pain: a review of the neuroselective current perception threshold and pain tolerance threshold. *Pain Digest*. 1998; **8**: 219-230.