DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date · JUL 16 1997

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Cyberonics, Inc.; Premarket Approval of NeuroCybernetic Prosthesis (NCP®) System - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Ann Costello, Ph.D., D.M.D., CDRH, HFZ-450, July 10, 1997, 443-8517

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

Food And Drug Administration

[DOCKET NO. _____]

Cyberonics, Inc.; Premarket approval of NeuroCybernetic Prosthesis (NCP®) System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application submitted by Cyberonics, Inc., Webster, TX, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the NeuroCybernetic Prosthesis (NCP®) System which includes the Model 100 NCP Generator, the Model 200 NCP Programming Wand, the Model 250 NCP Programming Software, the Model 300 Series NCP Vagus Nerve Stimulation Lead, the Model 400 Tunneling Tool, and NCP System Accessories. After reviewing the recommendation of the Neurological Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of July 16, 1997, of the approval of the application. In addition, the NeuroCybernetic Prosthesis (NCP®) System requires tracking under section 519(e) of the act as amended by the Safe Medical Devices Act of 1990.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER); Written comments by (insert date 30 days after date of publication in the FEDERAL REGISTER).

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ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, and comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Ann H. Costello,
Center for Devices and Radiological Health (HFZ-450),
Food and Drug Administration,
9200 Corporate Blvd.,
Rockville, MD 20850,
301-443-8517.

SUPPLEMENTARY INFORMATION: On January 27, 1997, Cyberonics, Webster, TX 77598-4135, submitted to CDRH an application for premarket approval of NeuroCybernetic Prosthesis (NCP®) System. The device is a vagus nerve stimulator and is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to anti-epileptic medications.

On June 27, 1997, the Neurological Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On July 16, 1997, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch

(address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Under section 519(e) of the act as amended by the Safe Medical Devices Act of 1990, manufacturers of certain types of devices are required to adopt a method of tracking that follows the devices through the distribution chain and then identifies and follows the patients who receive them. FDA has identified the above device as a new generic type of device requiring tracking. FDA is providing a 30-day period for interested persons to submit to the Dockets Management Branch (address above) written comments regarding the agency's position that this new generic type of device requires tracking.

Opportunity For Administrative Review

Section 515(d)(3) of the Federal Food, Drug, and Cosmetic Act (the act), (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 21 CFR Part 12 of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 21 CFR 10.33(b). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and

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shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 16 1997

William H. Duffell, Jr., Ph.D.
Vice President, Clinical & Regulatory Affairs
Cyberonics, Inc.
17448 Highway 3, Suite 100
Webster, Texas 77598-4135

Re: P970003
NeuroCybernetic Prosthesis (NCP®) System
Filed: January 27, 1997
Amended: April 18, May 15, and July 16, 1997

Dear Dr. Duffell:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the NeuroCybernetic Prosthesis (NCP®) System which includes the Model 100 NCP Generator, the Model 200 NCP Programming Wand, the Model 250 NCP Programming Software, the Model 300 Series NCP Vagus Nerve Stimulation Lead, the Model 400 Tunneling Tool, and NCP System Accessories, subject to the conditions described below and in the "Conditions of Approval" (enclosed). This device is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to anti-epileptic medications. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the general conditions of approval (enclosed), you must conduct the studies outlined in the amendment dated July 16, 1997, ("Description of the Postapproval Studies - P970003"). The information to be collected for five years will include:

1. continued reporting on a cohort of E05 patients;
2. characterization of the long-term morbidity and mortality; and
3. development of an approach to identifying responders and non-responders.

If appropriate, the results of the long-term data must be reflected in the labeling (via a supplement) when the post-approval study is completed.

Expiration dating for the generator and the lead has been established and approved at one and two years, respectively. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and

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CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and

effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities, the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanently implantable device.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list examples of permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)). Pursuant to 21 CFR § 821.20(d), FDA will be adding the Vagus Nerve Stimulator/ NeuroCybernetic Prosthesis (NCP®) System to these lists by publishing a notice in the FEDERAL REGISTER announcing that FDA believes that this device is subject to tracking under section 519(e)(1). This notice will also solicit public comments on FDA's determination.

If you have questions concerning this approval order, please contact Ann H. Costello, Ph.D., D.M.D., at (301) 443-8517.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

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Issued: 5-2-95

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

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Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1)Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

> (a)unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
>
> (b)reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1)A mixup of the device or its labeling with another article.

(2)Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a)has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1)may have caused or contributed to a death or serious injury or

(2)has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, 340
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NeuroCybernetic Prosthesis (NCP®) Vagus Nerve Stimulation System
SUMMARY of SAFETY and EFFECTIVENESS DATA
Table of Contents

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SUMMARY of SAFETY and EFFECTIVENESS DATA

1. GENERAL INFORMATION

Device Generic Name:

Stimulator, Vagus Nerve

Device Trade Names:

NeuroCybernetic Prosthesis (NCP®) System

Model 100 NCP® Generator

Model 200 NCP® Programming Wand

Model 250 NCP® Programming Software

Model 300 Series NCP® Vagus Nerve Stimulation Lead

Model 400 Tunneling Tool

NCP® System Accessories

Applicant's Name and Address:

Cyberonics, Inc.

17448 Highway 3, Suite 100

Webster, TX 77598-4135 USA

PMA Number:	P970003
Date of Panel Recommendation:	June 27, 1997
Date of Notice of Approval to the Applicant:	July 16, 1997

2. INTENDED USE/INDICATIONS

The NCP® system is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications.

3. CONTRAINDICATIONS

The NCP® system cannot be used in patients after a bilateral or left cervical vagotomy.

4. WARNINGS and PRECAUTIONS

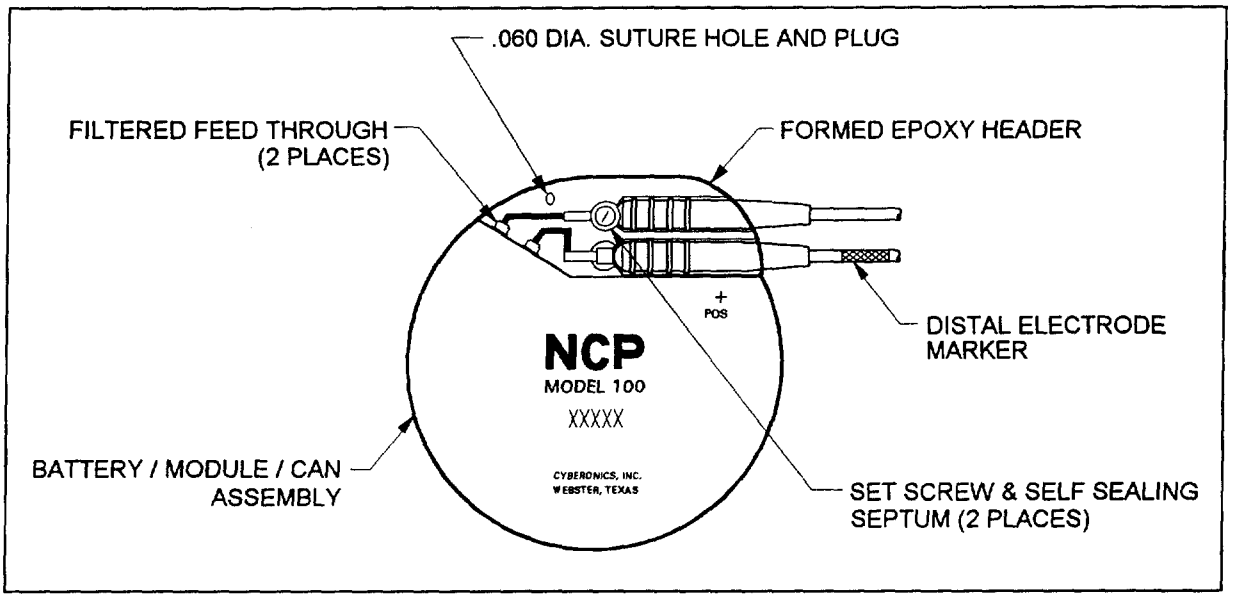
Same as final product labeling.

5. DEVICE DESCRIPTION

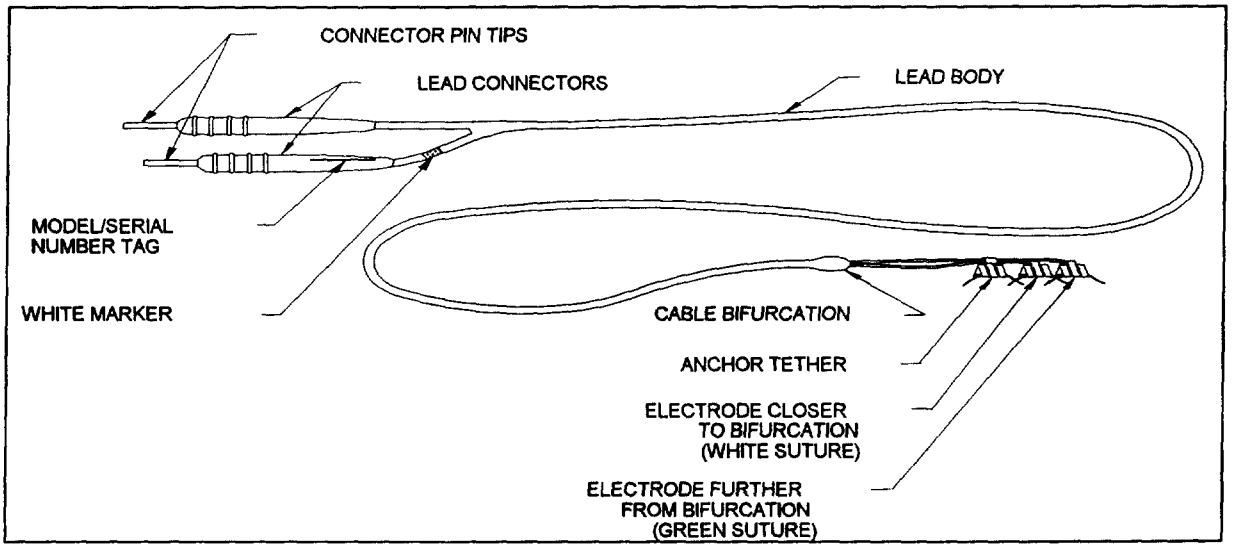
The NCP® System consists of the following components categorized into those implanted and peripheral components.

Implanted Components:

NCP® Generator (Model 100)

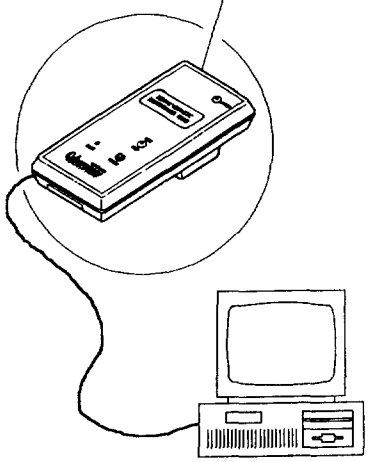


NCP® Lead (Model 300)



External Components:

NCP Programming Wand

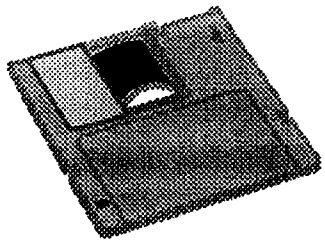


NCP Programming Wand
(Model 200)

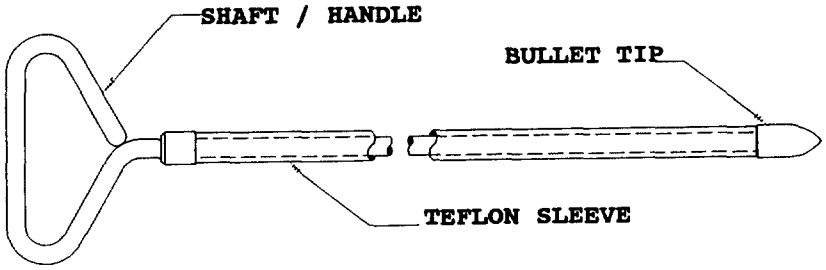
IBM Compatible Computer

NCP®

NCP Programming Software
(Model 250)



NCP Tuneling Tool
(Model 400)



Electrical signals are transmitted from the NCP® Generator to the vagus nerve via the Model 300 Series NCP® Lead. Peripheral components are used with an IBM-compatible personal computer to non-invasively activate, program, and retrieve information from the Generator. An NCP® Tunneling Tool (Model 400) is used during implantation to create a subcutaneous path for the Lead and is used in its placement as well.

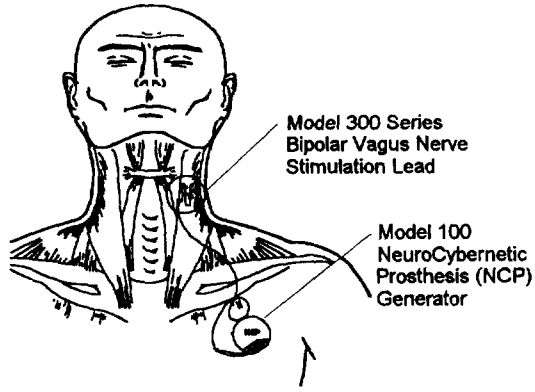


Figure 1. Placement of the Implanted Components of the NCP® System

The NCP® Generator, a device similar to a cardiac pacemaker, is surgically placed in the left chest. The NCP® Lead is connected to the Generator and attached to the left vagus nerve. Patients are provided with a hand held magnet which, by passing the magnet over the implanted NCP® Generator, can be used to manually activate the Generator to provide additional non-programmed stimulation in an effort to prevent or abort seizures and to test for battery status. Use of the magnet-activated stimulation is part of the NCP® System's prescribed treatment regimen. The magnet can also be used to deactivate (turn OFF) programmed stimulation by continuous placement of the magnet over the device. Programmed stimulation resumes when the magnet is removed.

5.1 NCP® Generator (Model 100)

The Model 100 NCP® Generator is an implantable, multiprogrammable pulse Generator that delivers electrical signals to the vagus nerve. Constant current, capacitively coupled, charge-balanced signals are transmitted from the Generator to the vagus nerve by the NCP® Lead (Model 300 Series).

The NCP® Generator is housed in a hermetically sealed titanium case. Feedthrough capacitors are used to filter electromagnetic interference from the Pulse Generator circuitry. The major components and functions of the Generator are as follows: a microprocessor, a voltage regulator, a 76.8 kHz crystal oscillator, one antenna to transmit information and another antenna to receive information, communication circuitry, DC-DC voltage generation and control circuitry, constant current control circuitry, a dual pole magnetic reed switch for manual activation of the Generator and for inhibition of the output pulses, and a lithium thionyl chloride cell to provide power for stimulation and circuit operation. The lithium thionyl chloride battery chemistry has the low impedance and high energy density characteristics required for the rapid pulsing needed in peripheral nerve stimulation, and similar batteries have been previously used in cardiac pacemakers, implantable spinal cord stimulators, and implantable drug pumps.

Therapy:

The NCP® Generator has a number of programmable settings which allow a physician to individualize the treatment for a patient. Those settings include pulse width, magnet-activated output current, normal output current, magnet-activated ON time, signal frequency, magnet-activated pulse width, signal ON time, and signal OFF time. The Applicant provides a magnet

that may be used to either manually initiate stimulation or to turn OFF the device. Device labeling instructs physicians to begin stimulation at the lowest output current settings possible (0.25 mA) and to ramp up stimulation to the desired level in 0.25 amp increments, never exceeding a level that is not tolerable to the patient.

Diagnostic and safety characteristics:

The NCP® Generator has telemetry capability which supplies information about its operating characteristics, such as parameter settings, lead impedance and history of magnet use. The Generator has a number of characteristics intended to strengthen operational reliability and safety, such as electromagnetic interference (EMI) filter capacitors, a series battery resistor to limit temperature rise in the event of short circuit, defibrillation protection diodes, direct current-blocking capacitors on both Leads that prevent direct current (DC) from being applied to the patient, a software watchdog timer to prevent continuous stimulation, and protection against voltage dips on the battery that could disrupt microprocessor memory.

5.2 NCP® Programming Wand (Model 200)

The NCP® Programming Wand (Model 200) is used with the NCP® Programming Software (Model 250) installed on a dedicated IBM-compatible personal computer to activate, program, reprogram and interrogate the NCP® Generator. The programming software is provided to the user on a 3.5-inch floppy disk. Capabilities include revision of the programmable parameters of the Generator, retrieval of telemetry data, and resetting of the Generator's microprocessor.

5.3 NCP® Programming Software (Model 250)

The NCP® Programming Software (Model 250) is a computer program which permits communication with an implanted NCP® Generator. The Programming Software is menu-driven and uses on-screen messages and prompts to assist the operator in using the system. Whenever the Programming Software is initialized, a self test is automatically run on the Software to verify checksum, file lengths, and file names. The programmed parameters and operational status can be interrogated. One or more parameters can be programmed at one time, and the programmed values are verified and displayed. The NCP® Programming System employs a strict communications protocol designed to minimize the possibility of "phantom" programming (i.e., inadvertent programming via environmental sources of electromagnetic interference or partial programming of a parameter). The Programming Software should be used on a computer dedicated only for programming the NCP® system. The Programming Software has been validated on a Compaq Contura Aero 4/25 running MS DOS 6.2 with the disk caching software disabled.

5.4 NCP® Vagus Nerve Stimulation Lead (Model 300 Series)

The Lead delivers electrical signals from the Generator to the vagus nerve. The Lead has two helical electrodes with a helical anchor tether on one end and two 5-millimeter (mm) connectors on the other end. The helix of the Lead is available in two sizes of inner diameter (2.0-mm and 3.0-mm) to allow for appropriate fit on different sized nerves. The helical design is soft, pliable, and expands or contracts with changes in nerve diameter, which may occur immediately post implant. These design features allow the 2-mm inside diameter helical electrode to fit most vagus

nerves. The Model 300 Series NCP® Lead is insulated with silicone rubber and is bifurcated at each end. The Lead wire is quadrifilar MP-35N, and the electrode is a platinum ribbon.

5.5 NCP® Tunneling Tool (Model 400)

An NCP® Tunneling Tool (Model 400) is used during implantation to create a subcutaneous path for the NCP® Lead and is used in its placement as well. The Tunneling Tool is supplied non-sterile with instruction to autoclave prior to use.

6. ALTERNATIVE PRACTICES AND PROCEDURES

A. Anti-Epileptic Drugs (AEDs)

The NCP® System clinical experience at the time of approval has been as an adjunctive treatment to anti-epileptic drug (AED) therapy. Additional anticonvulsant drugs are an alternative to treatment with vagus nerve stimulation using the NCP® System.

B. Therapeutic Resective Surgery

Epilepsy surgery may be an option for some patients. Generally less than two percent of the medically refractory patients undergo surgery each year in the U.S. The goal of resective seizure surgery is to excise a small area of brain tissue which contains a discrete seizure focus. Epilepsy surgery does have significant morbidity and mortality, including memory loss and stroke.

7. MARKETING HISTORY

On June 1, 1994, the applicant began commercial distribution of the NCP® System in Europe. The device has also been marketed in Australia, Switzerland, South Africa, Israel, China, Myanmar (Burma), Vietnam, Hungary, Hong Kong, and Canada.

The NCP® System has not been withdrawn from any country, for any reasons related to the safety or effectiveness of the device.

8. ADVERSE EVENTS

The NCP® System was implanted in 454 patients in five clinical studies involving 611 devices (some patients had Generator replacements). As of August, 1996, total NCP® exposure in these 454 patients was 901 device years. Individual patient exposure averaged 24 months with a range of 8 days to 89 months.

A total of 9 patients died during these five studies. One patient died from each: thrombotic thrombocytopenic purpura, drownings, aspiration pneumonia, pneumonia, and renal failure associated with drug and alcohol ingestion. No cause of death was apparent for the other four and they may be classified as Sudden Unexpected Death in Epilepsy (SUDEP). None of the deaths were attributed by the Investigators to the NCP® System.

8.1 Observed Adverse Events

Included among the five clinical trials were two randomized trials (Study E03 & E05) which involved 314 patients and implantation of 413 devices yielding a total NCP® System exposure

(inclusive of long term follow-up) of 591 years. These trials form the basis for the rates of observed adverse events.

Table 1 reports the adverse events from these studies during the Randomized Phase (14 week observation period) on a per patient basis. For the Extension Phase, events are reported on a per patient and per patient-year basis. The most common side effect associated with stimulation is hoarseness (voice alteration) during stimulation (hoarseness should only occur during the ON time). Most people tolerate the hoarseness well.

Table 1. Observed Adverse Events

(N=413 devices in 314 patients, 152 patients in HIGH treatment group, 591 device years)

	Randomized + Extension Phase, N= 314 patients, 591 device years				Randomized Phase, HIGH Only, N = 152 pts	
Adverse Event	**# of patients**	**% of patients**	**# of Events**	**Events per device-year**	**# of patients**	**% of patients**
Serious AEs[1]						
Surgically Related	13	4.1 %	13	0.022		
Stimulation Related	4	1.2 %	4	0.007	1	0.7 %
Non-serious AEs						
Voice Alteration	156	50%	720	1.228	91	60%
Cough Increased	129	41%	456	0.772	57	38%
Pharyngitis	84	27%	182	0.308	36	24%
Paresthesia	87	28%	377	0.638	32	21%
Dyspnea	55	18%	55	0.093	32	21%
Dyspepsia	36	12%	98	0.166	22	15%
Nausea	59	19%	154	0.261	21	14%
Laryngismus	10	3.2%	30	0.051	9	5.9%

1 - Serious AEs reported included infection, nerve paralysis, hypersthesia, facial paresis, left vocal chord paralysis, left facial paralysis, left hemidiaphragm paralysis, left recurrent laryngeal nerve injury, urinary retention, and low grade fever.

Status Epilepticus: Valid estimates of the incidence of treatment emergent status epilepticus among VNS treated patients are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 2 of 441 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Rebound after stimulation is stopped: Seizure frequency was monitored for one to four weeks after stimulation was stopped in 72 instances (68 patients) in Study E03. Seizure rate increased by greater than 1.5 standard deviations above baseline in 10% of instances (compared to 7% expected). Of these instances, 11 of 72 (15%) had a greater than 25% increase above baseline and 42 of 72 (58%) had a greater than 25% decrease in seizure rate.

8.2 Potential Adverse Events

Adverse events which may occur (including those reported in Table 1), reported in alphabetical order:

- Cough increased
- Dyspepsia, duodenal or gastric ulcer
- Dyspnea
- Facial paresis or paralysis
- Hemidiaphragm paralysis
- Hypesthesia
- Infection
- Laryngismus
- Muscle twitching during stimulation
- Nausea and vomiting
- Nerve injury
- Paresthesia
- Pharyngitis
- Voice alteration

Patients who manipulate the NCP® Pulse Generator and the Lead through the skin may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

Possible complications of NCP® System treatment include those related to implantation, those related to performance of the implanted Generator, and those related to long-term patient tolerance of the implant.

Except for Lead positioning, implantation of the NCP® Generator is similar to implantation of a cardiac pacemaker. In addition to the normal risks associated with a surgical procedure, complications associated with NCP® System implantation include, but may not be limited to, skin irritation; pain at the incision site; infection; extrusion or migration of the NCP® Generator and/or Lead; dislodgment, disconnection (Lead from Generator), breakage (Lead), or corrosion of the stimulating Lead; hematoma; fluid accumulation; cyst formation; inflammation; and histotoxic reactions. These phenomena may occur either acutely or chronically and may require device replacement to correct the complication.

Complications can include damage to the vagus nerve, either due to surgical trauma, compression by the electrode, or excessive stimulation. Hoarseness not associated with the stimulation suggests possible nerve irritation. Persistent hoarseness may be caused by nerve constriction, nerve fatigue, or Generator malfunction.

Normal stimulation of the vagus nerve and its branches may be associated with some side effects. In two randomized parallel controlled studies, a comparison between baseline rates of occurrence and treatment rates, for either HIGH or LOW, revealed the following adverse events (AEs) which had a statistically significant difference between periods in any study group: cough, dyspepsia, dyspnea, hoarseness/voice alteration, hypesthesia, infection, insomnia, laryngismus, non-specific pain, abdominal pain, paresthesia, pharyngitis, and vomiting.

The investigators reported that hoarseness, coughing, pharyngitis, and dyspnea were usually reported at the time of stimulation and were directly related to the strength of stimulation. Intolerable adverse events can generally be reduced or eliminated by a reduction in the output current, ON time, or increase in OFF time.

Most of the reported Study events were mild and well tolerated; very few clinical Study patients discontinued therapy due to side effects.

9. SUMMARY OF PRE-CLINICAL STUDIES

Pre-clinical Studies on Leads

The helical electrode component of the Leads used in the NCP® System was developed by Huntington Medical Research Institute (HMRI) and the National Institute of Neurological Disorders and Stroke (NINDS) Neural Prosthesis Program. A number of animal studies have been performed at HMRI that showed that damage associated with peripheral nerve stimulation is of two types: mechanical and electrical. Mechanical damage, manifest as connective tissue changes in the perineurium and epineurium, is apparently caused by physical trauma to the nerve, although a chemical interaction has not been ruled out. Mechanical damage can be minimized by pliable helical electrode arrays of the appropriate size which will not compress or otherwise traumatize the nerve, and by routing and stabilizing the Lead to minimize electrode movement on the nerve. Electrical damage results in changes to myelin and the axons it surrounds. Larger, more heavily myelinated axons are most susceptible. This type of damage can be minimized by lower stimulation frequencies, less total stimulation, and lower duty cycles.

9.1 Risk Analysis

The implantable portions of the NCP® System employ known implantable materials generally considered to be biocompatable and safe for permanent implant use. The Company has conducted a risk analysis which included a system hazard analysis, fault tree analysis, component reliability analysis, drift analysis and failure modes and effects analysis. The results of these and other evaluations provide evidence of the safety of the NCP® System.

9.2 Components Testing

Integrated circuits:

Each component was subjected to qualification tests by the Applicant. These tests include 1000-hour life testing, high temperature storage, temperature shock, exposure to high temperature/high humidity, for integrated circuits. All qualification tests were successfully completed.

Battery:

The Model 8602 battery has been subjected to a series of safety and qualification tests, including vibration, temperature cycling, hermeticity, low pressure, low temperature, high temperature, mechanical shock, soldering heat, high and low temperature storage, voltage reversal, incineration, impact shock, puncture at high velocity, slow dent and puncture, crush and recharge testing. No unexpected behavior of the cells was observed. Short-circuit behavior was also characterized; the cells did not explode or vent, but the cell temperature, measured at body temperature, rose from 37 to 60 °C under an extremely low impedance discharge path. The

Applicant added a 10-ohm current limit resistor to the Generator, which limited heating during a short to a negligible amount in qualification tests.

Feedthoughs:

The feedthrough utilized in the Model 100 NCP® Generator has undergone qualification testing in accordance with applicable portions of ASTM/ANSI Standard F18, ASTM F134-85, and MIL-STD 883B, which consisted of thermal shock, mechanical shock, vacuum bake, vibration, solvent resistance (ten samples), and terminal strength. All samples passed all test requirements.

9.3 Device Testing

Qualification testing was conducted to provide adequate data to support the intended use of the device system.

"Type testing" for CE Mark approval was conducted in accordance with prEN 45502-1:1993, Active Implantable Medical Devices and the requirements of Annex 1 and Annex 3 of the Commission of the European Communities Council Directive 90/385/EEC, amended by 93/42/EEC and 93/68/EEC.

Qualification tests were largely based on commonly recognized test methods and standards, such as military standards; International Standards Organization (ISO), European Standards (EN), European Committee for Standardization (CEN/CENELEC), and International Electrotechnical Commission (IEC) standards; American Society for Testing and Materials (ASTM), National Safe Transit Association (NSTA), Medical Device Standards (MDS), and United States Pharmacopeia (USP) standards; and others. More than 130 qualification tests have been performed on the devices or their components.

Model 100 Generator

The Model 100 NCP® Generator was evaluated using electrical, mechanical, electromagnetic interference, and firmware testing.

Electrical:

The electrical qualification tests consisted of

- Electrical characterization, End of Service characterization, and Communication Distance Characterization
- Direct Current leakage / Charge Balance per EN50051:1988,
- Electrosurgery Immunity - CENELEC "Standard for the Safety of Implantable Cardiac Pacemakers" (1986) and prEN45502-1 (May 1992),
- Defibrillation Immunity - prEN45502-1 (May 1992),
- Electromagnetic Interference (EMI) - EN50061:1988/prA1:1991; MDS201-0004 with modifications to testing facility and immunity levels: tested at 20V/m for frequencies from 20 MHz to 1 GHz and high field strengths at communication
- Electromagnetic Compatibility -MDS201-0004, IEC801-2 "Electromagnetic Compatibility for Industrial Process Measurement and Control Equipment, Part 2: Electrostatic Discharge (ESD) Requirements."

- Cellular phone (digital/GSM and analog) compatibility frequencies (including Cell Phone frequencies) of 450 MHz (386 V/m), 900 MHz (206 V/m), 1.45 GHz (213 V/m), and 1.9 GHz (96 V/m).
- Magnetic Resonance Imaging (MRI) compatibility -should not be done with the MR body coil. MRI should only be done using a head coil.

Mechanical

The mechanical qualification tests consisted of the following:

- Temperature Cycle - prEN45502-1 (MAY 1992), Sec. 27.1
- Shock - prEN45502-1 (MAY 1992), Sec. 24.1
- Vibration - prEN45502-1 (MAY 1992), Sec. 24.2
- Diagnostic Ultrasound - prEN45502-1 (MAY 1992), Sec. 23.1
- Gross Leak - prEN45502-1 (MAY 1992), Sec. 26.1
- Fine Leak - Helium Leak Test performed 100% in production
- Wet Rub - prEN45502-1 (MAY 1992), Sec. 14.1
- Header Adhesion - (Header sheer test, strength exceeds 50 lb.)
- Header Seal (Isolation) - prEN45502-1 (MAY 1992), Sec. 16.1
- Shipping Shock - (NSTA - 30 inch drop onto each box corner and face)
- Shipping Vibration - (NSTA - 14,200 vibratory impacts)
- Shipping Atmosphere Pressure Changes - prEN45502-1, Sec. 12.1
- Wet Wipe - prEN45502-1 (MAY 1992), Sec. 9
- Shipping Humidity - prEN45502-1 (MAY 1992), Sec. 10.1

The Model 100 Generator performed under all conditions in accordance with its design specifications.

Model 300 Series Lead

The Model 300 Series Lead was evaluated by electrical and mechanical testing.

Electrical

- Electrode electrical characterization, V_I and dV/dt pre and post sterilization
- Lead tubing leakage current - (3 month soak at +75C in saline).

Mechanical

- Lead Dielectric - prEN45502-1, Sec, 16.2 ,
- Lead Tensile (Mandrel Wrap) - prEN45502-1, Sec, 24.3,
- Flexural Fatigue - prEN45502-1, Sec, 24.4,
- Connector Integrity - prEN45502-1, Sec, 24.5,
- Connector Insertion/Extraction Force, (5 kg force)
- Repeated Insertion, (10 cycles), Lead fatigue with tether, (10^{+7} cycles), Lead fatigue without tether, (10^{+7} cycles),
- Electrode weld pull test - (Shear pull to destruction - 310 to 540 g),
- Lead connector crimp pull test - (Pull to destruction - 0.90 to 1.05 Kg),
- Tubing bond pull test - (Pull to destruction 10 assemblies - 1.0-1.5 Kg),

- Other tests: Connector leak test - 10 psi, Lead Connector Crimp Pull Test, Connector Leak Test, Tubing Bond Pull Test, Electrode Weld Pull Test, Electrode Fatigue, Electrode Helix Force, Electrode Anchor Tether Pull-Off (90°), and Electrode Pull Test (axial)
- MRI Compatibility

The Model 300 Series Lead performed under all conditions in accordance with its design specifications. However, exposure to MRI resulted in excess heating of the electrode whenever the exposed Lead length was greater than 10 cm, when it was positioned against the outer bore of the MRI instrument and when worst case scan conditions were used. No heating was observed under worst case conditions of a fully extended Lead, when the Lead was positioned in the center of the bore, or in any position for a Lead shortened to 10 cm. Final product labeling included the following PRECAUTION:

> **Magnetic Resonance Imaging** (MRI) should not be done with the MR body coil. The heat induced in the leads by a body MRI scan can cause injury. MRI should only be done using a head coil. Conditions which have been tested include:
>
> - Transmit and Receive coil type: Head Coil Only
> - Static Magnetic Field Strength: ≤ 2.0 Tesla
> - SAR: < 1.3 W/kg for 70 kg patient
> - Time varying intensity < 10 Tesla /sec

Model 200 Programming Wand

The Model 200 Programming Wand was evaluated by electrical and mechanical testing.

Electrical:

- Electrical Characterization,
- Maximum Programming Distance,
- Evoked Potential Adapter Qualification,
- Electromagnetic Interference (EMI),
- Magnetic Field Susceptibility - 30 Hz to 100 kHz per requirements of RS101 MIL-STD 461D,
- Magnetic Field Emissions - magnetic field emissions testing per requirements of RE101 MIL-STD 461D.
- Quasi Static Electric Field - sinusoidially varying electric field at 0.5 Hz with field strengths of 500 V/m to 2000 V/m per requirements of FDA Reviewer Guidance document.
- Electric Field Susceptibility - radiated electromagnetic energy field rated at 3 V/m as specified in the requirements of IEC 801-3 and the FDA Reviewer Guidance documents.
- Fast Transient Burst - transients of 0.25, 0.50, and 1 kV coupled by way of a capacitive clamp to the signal Leads per requirements of IEC 801-4 and the Reviewer Guidance documents.
- Conducted Susceptibility - conducted electromagnetic energy as specified in CS114, of MIL-STD-461D and the FDA Reviewer Guidance documents.
- Radiated Emissions - conducted and radiated emissions testing per requirements of CISPR 11.

Mechanical:

- Temperature Cycle - prEN45502-1, Sec. 27.1, (-20 °C to 55 °C, 2 cycles)

- Free Fall Test - prEN45502-1, Sec. 24.1 (3 ft drop)
- Vibration - prEN45502-1, Sec. 24.2, Wet Wipe - prEN45502-1, Sec. 11
- Shipping Shock - (NSTA - 30 inch drop), Shipping Vibration - (NSTA - 14,200 vibratory impacts)

The Model 200 Programming Wand performed under all conditions in accordance with its design specifications.

Model 250 Programming Software

The Applicant has carried out extensive development, evaluation and testing of the software in the NCP® System.

A software development procedure which governs the creation, development, review, testing, documentation, manufacturing release, discrepancy reporting and maintenance of the software products in the NCP® System was used. The Model 250 Programming Software and the Model 100 Generator software were verified and validated to perform in accordance with their requirement specifications.

Model 400 Tunneling Tool

The Model 400 Tunneling Tool was evaluated by mechanical testing.

- non-destructive shear testing - (14 lb.)
- destructive pull testing of the bullet/shaft connection (230 lb.)

The Model 400 Tunneling Tool performed under all conditions in accordance with its design specifications.

9.4 Biocompatability

The following testing has been conducted for all tissue contacting materials used in the Model 100 Generator and Model 300 Lead:

- Cytotoxicity (MEM elution method), Sensitization
- Intracutaneous reactivity, Systemic toxicity, acute (USP method)
- Pyrogenicity (USP method), Genotoxicity (Ames mutagenicity test) subcutaneous implant (USP method, rat model) for fourteen, thirty, and one hundred-five days duration, with investigation of histology and systemic effects

The results of these tests showed that the materials used in the Applicant's implantable products, as processed by and for them, are biocompatable, non-toxic, and non-pyrogenic.

9.5 Sterilization and Shelf Life Testing:

The ethylene oxide sterilization process was validated. Testing was performed to evaluate the effectiveness of the recommended steam autoclave sterilization method for the Model 400 Tunneling Tool. The shelf life of the sterile product was validated for a period of two years.

9.6 Animal Testing

Animal studies pertaining to vagus nerve stimulation can be divided into those dealing primarily with efficacy and those related to safety.

9.6.1 Animal Efficacy Studies

Animal models of epilepsy have been used to evaluate the efficacy of vagus nerve stimulation (VNS). A dog model was used to demonstrate the feasibility of vagus nerve stimulation to inhibit strychnine-induced seizures.

A second feasibility study, used the rhesus monkey to study the effects of vagus nerve stimulation on focal seizures induced by alumina gel. Long-term seizure frequency was reduced when the vagus nerve stimulation was delivered during a seizure in two of the four monkeys with alumina gel induced epilepsy. In the other two, seizures continued but became synchronous in time, i.e., they appeared at regular intervals. The protective effect observed during stimulation was found to be maintained for weeks when the therapy was discontinued, suggesting a carry over effect.

Three groups of investigators used rat models of epilepsy to investigate the effect of vagus nerve stimulation on seizures. One group used pentylenetetrazol (PTZ), 3-mercaptopropionic acid (3-MP), and maximal electroshock (MES) to induce seizures in rats. Another used a penicillin induced seizure model in rats to study the effects of vagus nerve stimulation on interictal spiking. The third group, used the kindling and PTZ models. These rat models are also used to evaluate potential AEDs.

Using the PTZ model, it was reported that vagus nerve stimulation affected two seizure phenomena: mild status epilepticus and discrete intense seizures. Muscle activity associated with status epilepticus was suppressed when enough current was delivered to recruit the vagus nerve C fibers and depress heart rate and respiration. Discrete seizures could be prevented by vagal stimulation, but not stopped once they started. Also using the PTZ model, another group reported that efficacy was proportionally dependent on the cumulative time of stimulation and that the inhibitory effect of stimulation decreases gradually after cessation of stimulation.

Using the MES model, it was reported that vagus nerve stimulation can abolish or reduce the tonic component of the convulsive response. The degree of inhibition was related to the fraction of C fibers stimulated and the frequency of stimulation (as measured by heart rate depression).

The effects of vagus nerve stimulation on seizures in rats produced by intraperitoneal injection of 3-MP appeared to be variable.

With penicillin induced seizures in the rat, VNS significantly reduced interictal spike frequency, and the spiking frequency remained lower for about three minutes after cessation of stimulation at levels which also reduced heart rate and respiration.

In the kindled rat model, VNS reduced seizure duration, and the amount of reduction was dependent on duration of stimulation prior to the seizure.

Overall, studies with a number of animal models for human seizure, which are also used to evaluate efficacy of AEDs, showed that the effect of vagus stimulation can be detected in various brain structures, that vagus nerve stimulation decreases the frequency and/or duration of seizures and that the effect is related to stimulation parameters and timing. These studies, however, did not determine whether these effects are specific to stimulation of the vagus nerve, and whether they are secondary to depressed heart rate and respiration.

9.6.2 Animal Safety Studies

Two safety studies were performed in monkeys and one was performed in sheep. In the first of these, the effect of a titanium cuff electrode on the vagus nerve of monkeys was examined. The effect of vagus nerve stimulation on cardiac and gastric function was also examined. Of the five animals implanted, two received 72 hours of stimulation without evidence of clinically significant effects on the stomach lining, and no pro-arrhythmic cardiac changes were observed.

In the second monkey safety study, spiral platinum electrodes were used. Six animals were exposed to electrodes for a minimum of 14 weeks and received at least 72 hours of 143 Hz, 50% duty cycle stimulation. Cardiovascular system effects included transient asystole and bradycardia. No stomach ulcerations were found. Histological analysis of the nerves indicated that stimulation with the spiral electrode did not result in electrical damage, and no mechanical damage to the nerve occurred in subjects in which proper electrode placement was achieved through adequate strain relief on the lead. Compression damage to large axons was found in 2 of the 4 experimental animals.

The effects of stimulation of the vagus nerve of sheep was studied in nine animals. Nerves from three of the animals which had been exposed to the system for at least ten months and which had received at least three months of stimulation were harvested. No evidence of nerve fiber degeneration, regeneration, or injury was present in any of the nerves analyzed, whether or not the nerve was stimulated. In all three animals studied for histology, epineural fibrosis and fatty infiltration of the nerve was found.

Overall, studies in animals indicate that stimulation of the vagus nerve may be conducted safely, with no damage to the axons of the vagus nerve. The spiral electrode design used in the NCP® System appears to be appropriate for chronic therapy.

10. SUMMARY OF CLINICAL STUDIES

Five acute phase studies were conducted. All patients that exited the acute phase studies were also followed in two long-term follow-up studies. The total stimulation exposure during these studies is greater than 900 patient years.

10.1 Design and Methods

10.1.1 Objective of studies

The overall objective of the clinical trial program was to collect clinical data regarding the NCP® System as an implantable vagus nerve stimulator indicated for use as adjunctive therapy in patients with medically refractory partial onset seizures.

The primary objective of the studies was to demonstrate a between group difference in mean and/or median percent change in seizure frequency between patients treated with "High" stimulation (optimal stimulation for seizure reduction) and "Low" stimulation (not expected to result in as great a seizure reduction).

Secondary objectives included the effect of VNS on within group (High *vs.* Low) changes in seizure frequency, response rates, number of seizure-free days, seizure intensity and duration, global evaluations by patients, caregivers and investigators and QOL measures.

10.1.2 Design of studies

Two of the studies (E01 and E02) were multicenter pilot studies, one (E04) was an open-label controlled longitudinal study, and two of the studies (E03 and E05) were multicenter, prospectively randomized, double blinded, parallel, active control studies. In the studies, treatment was adjunctive to AEDs; in E03 and E05, AEDs were to be held constant.

Figure 2. E01, E02, E04 Study Designs and Timelines

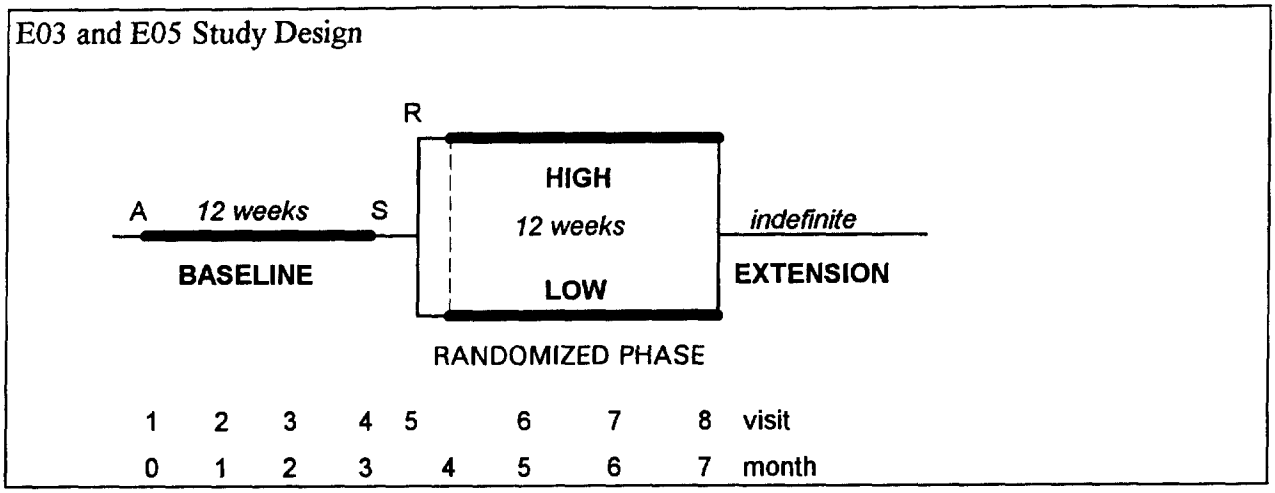
Qualification/ Historical Baseline ⇒	⇦Baseline⇨	S ⇦Rec⇨	⇦C1⇨	⇦Stim⇨ (Acute Phase)	⇦C2⇨	Long-Term Follow Up Stim⇨
	Weeks 0-4 weeks	2 Weeks	3 - 4 Weeks	12-16 Weeks	0-4 Weeks	Indef.⇨

KEY: **S** Surgery
Rec Post-surgical recovery period
C1, C2 Control periods
S1 - S4 4-week treatment periods

Analysis of the E01 and E02 acute phase mean percent seizure frequency reduction was based on the average mean percent change in seizure frequency over the Acute Phase Stimulation (16 weeks) in comparison to the first placebo stimulation control period (C1). Analysis of the E04 acute phase mean percent seizure frequency reduction was based on the average mean percent change in seizure frequency over the Acute Phase Stimulation (12 weeks) in comparison to the pre-implant Baseline Period

$$\textit{Patient's \% Change} = \frac{\textit{[seizure frequency/day]treatment} - \textit{[seizure frequency/day]Baseline} \times 100}{\textit{[seizure frequency/day]Baseline}}$$

Figure 3. E03, E05 Study Designs and Timelines



A = Admission S = Surgery R = Randomize

For E05, V6 was after two weeks of stimulation, followed by V7, V8, and V9 corresponding to V6, V7, and V8 in E03.

Analysis of the E03 and E05 acute phase seizure frequency reduction was based on the difference in the average mean and median percent change in seizure frequency for the HIGH Group vs. the LOW Group over the first three stimulation periods (12 weeks) in comparison with the 12 week baseline period.

Analysis of the Long Term Follow-up Study (for Studies E01 through E04) and XE5 Study seizure frequency was based on the difference in the average mean and median percent change in seizure frequency over the three stimulation periods ending at 6, 9 (XE5 only), 12, 18, 24, and 36 months in comparison with the control period used in the respective acute phase studies.

The following stimulation parameters were used in the Studies.

Table 2. Protocol Stimulation Parameters

Parameter	STUDY						
	E01	E02	E04	E03 HIGH (LOW)	E05 HIGH (LOW)	XE1-4	XE5 3 mo. (Longer)
CURR (mA)	1 - 6	0.5 to 5	≤ 1	0.5 - 3.0	3.5	0-12	0-3.5
FREQ (Hz)	≤ 50	20 to 50	30	20 - 50 (1 to 2)	30 (1)	1-143	20 (1-30)
PW (μsec)	250	250 to 500	500	500 (130)	500 (130)	130-1000	750 (130-1000)
ON (sec)	60	30 to 60	30	30 - 90 (30)	30 (30)	7-270	30 (7-60)
OFF (min)	60	5 to 20	10	5 (90)	5 (180)	0.2-180	1.8 (1.1-180)

The parameters used in Studies E03, E04, and E05 were similar, whereas Studies E01 and E02 used higher frequencies, longer OFF times and shorter pulse widths.

10.1.3 Statistical methods

Standard statistical tests were used in comparing changes in seizure frequency between stimulation and control or baseline periods for Studies E01, E02, and E04 between and within HIGH and LOW stimulation groups for E03 and E05. The statistical test employed most extensively in E03 was the Student's t-test with the Wilcoxon rank-sum test used as a corroborative non-parametric test. Fisher's exact test was used to compare equality of proportions between HIGH and LOW stimulation groups. All tests were two-tailed and normality assumptions were checked as required.

E05 was analyzed in essentially the same manner as E03, with the exception that different statistical tests were applied. The null hypothesis that the two treatment percent changes are equal was tested using an extended Mantel-Haenszel test with modified ridit scoring of this ordinal outcome. The ranking for the modified-ridits is done for all patients from all sites after adjustment for investigative site through the subtraction of the means for the sites.

As a supplementary parametric analysis, analysis of variance (ANOVA) techniques were carried out to analyze between-treatment group comparisons of percent change in mean seizure frequency. One ANOVA model had treatment, investigative site, and treatment-by investigative site as independent variables. A second model additionally included baseline seizure frequency as a covariate and a baseline seizure frequency-by-treatment interaction term. Treatment-by investigative site interaction was addressed in the ANOVA models even though the primary method for comparing treatments is a non-parametric extended Mantel-Haenszel test.

All hypothesis tests were two-sided with an alpha of 0.05. Statistical significance was determined by p-values less than 0.05. A p-value between 0.05 and 0.10 was considered marginally statistically significant.

10.1.4 Patient Population and Collection Criteria

The final Inclusion and exclusion criteria were similar for each study.

Table 3. Inclusion Criteria

INCLUSION CRITERIA	E01	E02	E03	E04	E05
Age	18-60	18-60	12-60	2*-60	12-65
Seizure type	SPS, CPS	SPS, CPS, 2ND	SPS, CPS, 2ND	ALL TYPES	SPS, CPS, 2ND
# AED's	1-2	1-2	0-3	Not Specified	1-3
Good physical and health	yes	yes	Not Specified	Not Specified	Yes
Mental ability	IQ>80	IQ>80	Ability to understand IC, patient or guardian	Ability to understand IC, patient or guardian	Ability to understand IC, patient or guardian
Steady state serum levels	Yes	Yes, 1 month prior to study	Yes, +/- 20% over 3 months	Not Required	Yes, +/- 20% over 3 months
Seizure rate	6/mo.	6/mo	6/mo	1/mo	6/mo with AOC
Max seizure free interval	14 days	14 days	14 days	None Specified	21 days
Women with acceptable birth control	Not Specified	Not Specified	Yes	Not Specified	Yes
Ability of patient or caregiver to accurately record seizures	Implied	Implied	Implied	Implied	Yes

Table 4. Exclusion Criteria

Exclusion Criteria	E01	E02	E03	E04	E05
Living alone	Yes	Yes	Not Specified	Not Specified	Not Specified
Ulcers	Yes	Yes	Not Specified	Not Specified	Yes, peptic
Diabetic	Yes	Yes	Not Specified	Not Specified	Not Specified
Prior cervical vagotomy	Yes	Yes	Yes	Yes	Yes
Significant heart, lung or chronic bowel	Yes (heart and lung)	Yes	Yes (heart and lung)	Not Specified	Yes (heart and lung)
Medical condition likely to deteriorate	Yes	Yes	Yes	Yes	Yes
Investigational drugs	Not Specified	Not Specified	within 2 wk. + 5X half life	Not Specified	Within 2 wk. + 5X half life
History of pseudo seizures	Implied	Implied	Implied	Not Specified	Yes

E05 patients were excluded for prior VNS treatment or any other stimulation treatment for epilepsy, as well as prior resective surgery for epilepsy. E05 patients were also excluded if they had experienced more than two episodes of status epilepticus within the last year.

* E04: Patients under 12 years old had to meet the following additional criteria:

    1. During the last five years (or over lifetime if younger) at least three anticonvulsants must have been tried (alone or in combination) to control seizures.
    2. The Investigator and family must be of the opinion (and Investigator must so document in the chart) that seizures and/or drug side effects are detrimental to the patient.
    3. Admission must first be discussed with the Applicant's staff and approval given on a case by case basis. The purpose of this condition is to provide Investigators and family with all current information, so that the best risk/benefit decision can be made for the patient.

The important differences in the inclusion/exclusion criteria are:

- E05 excluded patients with resective surgery and required patients to have at least 6 seizures/month with AOC.
- E04 included patients with all types of seizures and allowed children down to 2 years of age.

10.2 Description of Patients Studied and analyses for Gender Bias

10.2.1 Patients Studied

Overall the populations across Studies was comparable as displayed in Table 4.

Table 5. Description of Study Patients

Study No.	Group	Number of Patients	Gender	Average Age, Range	Average Years with Epilepsy, Range	Seizures/ Day	Ave. No. AEDs
E01	—	11	7 M, 4 F	31.6 (20-58)	22.2 (13-32)	2.95 mean 0.70 median	1.0
E02	—	5	3 M, 2 F	33.0 (18-42)	20.3 (5-36)	0.44 mean 0.44 median	1.0
E04	—	124	67 M, 57 F	23.9 (3.6-63)	17.4 (0.8-48)	25.2 mean 0.65 median	2.2
E03	HIGH	57	35 M, 22 F	32.9 (20-57)	22.4 (6-47)	1.45 mean, 0.7 median	2.1
	LOW	57	36 M, 21 F	33.7 (13-50)	20.5 (4-44)	1.76 mean, 0.85 median	2.1
E05	HIGH	95	49 M, 46 F	32.1 (13 - 54)	22.1 (2 - 52)	1.59 mean, 0.58 median	2.2
	LOW	103	44 M, 59 F	34.2 (15 - 60)	23.7 (2 - 48)	0.97 mean, 0.51 median	2.1

Table 6. Description of Clinical Studies

All patients enrolled in all clinical studies, N=537

Study	E01	E02	E04	E03	E05	Total
Type of Study	Pilot Longitudinal	Pilot Longitudinal	Open Longitudinal	Randomized Parallel High/Low	Randomized Parallel High/Low	-
Patients Enrolled	11	5	133	126	262	537
# Centers [a]	3	2	24	17	20	45
Reference (baseline) period	Weeks 2 through 4	Weeks 3 through 6	Weeks -4 through 0	Weeks -12 through 0	Weeks -12 through 0	-
Seizure Type	Partial	Partial	All types	Partial	Partial	-
Num. AEDs	1 to 2	1 to 2	not specified	0 to 3	1 to 3	-

a Total includes OUS centers (Canada, Holland, Germany 2, and Sweden), several US centers participated in more than one study

10.2.2 Gender Bias

Inclusion and exclusion criteria were designed and carried out to avoid gender bias in patient enrollment. Of all patients enrolled 254 of 454 (54%) were male. This proportion (254/210 =1.21) of males is consistent with the male to female incidence (1.1 to 1.7) for nonfebrile epilepsy.[1]

Separate analyses of safety and effectiveness data for males and females indicated no differences between the genders; hence, the results presented in the following analyses are representative for both men and women.

10.3 Results – Effectiveness and Safety

10.3.1 Effectiveness

The following table provides efficacy data for all studies. The mean percent reduction in seizure frequency is consistent across all studies except E04. E03, E04 and E05 studies established efficacy with statistical significance, however, two interim analyses were performed on the E03 data.

The median reduction in seizure frequency in the trials consistently improved over time. However, this data is uncontrolled and may be due to changes in drug therapy, rather than VNS.

Study E03 enrolled 115 patients, one patient dropped out prior to randomization/stimulation of the device and is not included in the efficacy tables below leaving an N=114. Study E05 enrolled 254 patients and had 55 baseline failures. In addition, 1 patient was explanted prior to randomization/stimulation of the device, 1 patient was excluded due to unreliable seizure diary counts, and 1 patient dropped from the study prior to collection of any effectiveness data leaving an N=196. All randomized/stimulated patients are included in the safety tables which follow.

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[1] page 16 in: Hauser WA, Hesdorffer DC: Epilepsy: Frequency, Causes and Consequences. Demos Publications, New York, 1990, 378 pages.

There was no statistically significant change in seizure intensity or seizure duration in either the E03 or E05 Studies.

Table 7. Seizure Rate Changes

ACUTE CHANGE IN SEIZURE FREQUENCY					EXTENSION PHASE FOLLOW-UP N, MEDIAN PERCENT SEIZURE REDUCTION				
Study	N	Mean % Seizure Reduc-tion	Median % Seizure Reduc-tion	Between Group Means p Value	6 MO	12 MO	18 MO	24 MO	36 MO
E01	10	24.3%	31.6%	N/A	10 41.90	10 43.43	10 46.19	8 58.69	4 64.84
E02	4	39.9%,	48.1%	N/A	4 3.01	4 30.04	3 67.64	2 60.32	2 31.88
E04	116	7%	21.8%	N/A	107 32.46	86 26.81	72 41.41	34 32.18	Insufficient data
E03 HIGH	57	23.6%	22.6%	0.0175	108 26.84	102 32.51	71 45.79	51 40.74	49 40.42
E03 LOW	57	6.4%	6.3%						
E05 HIGH	94	27.9%	23.4%	0.0396	89 32.5	40 34.2 (9 mo.)	N/A N/A	0	0
E05 LOW	102	15.2%	20.5%						
E01 E04 Pooled	244	11.8%	17.1%	N/A	229 29.75%	202 31.31%	156 44.25%	95 40.74%	55 40.42%
Total N for effic calcula tion	440	N/A	N/A	N/A	318	242	156	95	55

NS = Not Significant *N/A = Not Applicable*

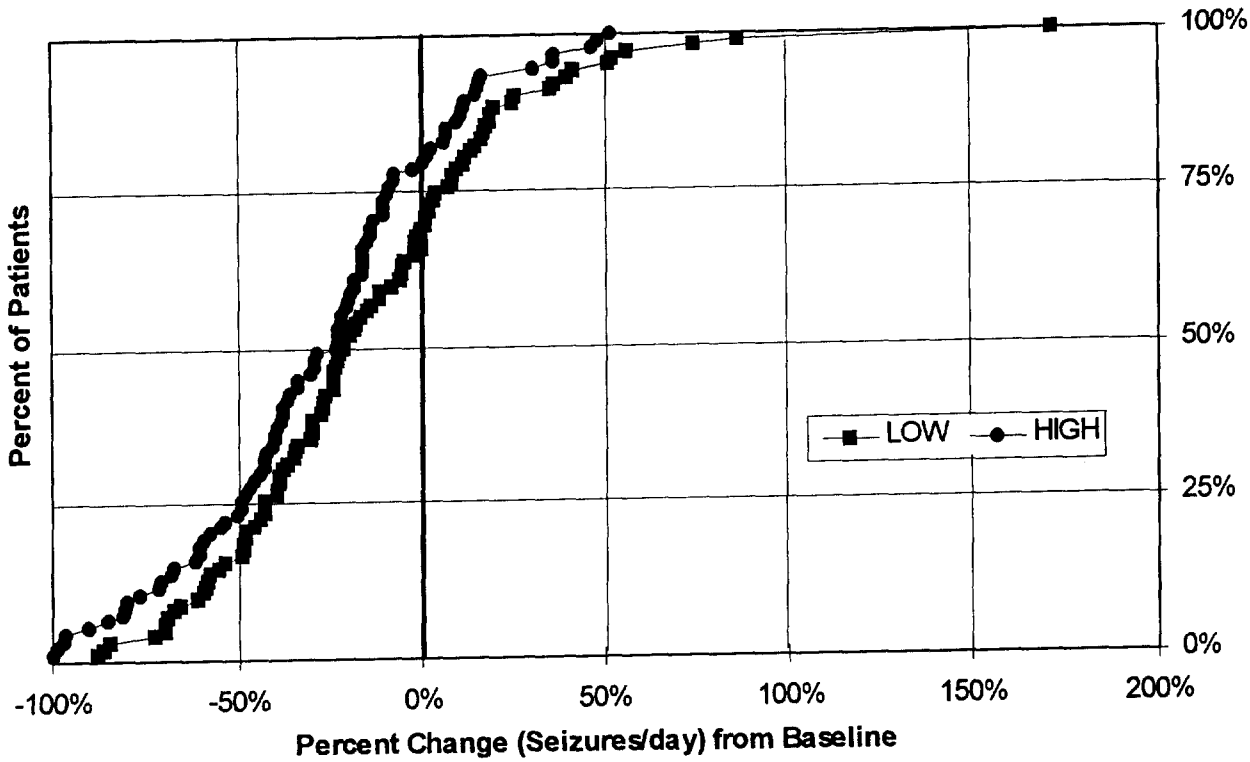
Table 8. Responder Rates

ACUTE Responder Rate (% pts >50% Reduction)				LONG TERM FOLLOWUP Responder Rate (% pts >50% Reduction)				
Study	N	Responder Rate	Betw'n Group p Value	6 MO	12 MO	18 MO	24 MO	36 MO
E01	10	30%		20% (2/10)	30% (3/10)	50% (5/10)	63% (5/8)	50% (2/4)
E02	4	50%	NA	25% (1/4)	25% (1/4)	67% (2/3)	100% (2/2)	0% (0/2)
E04	116	29.3%		37% (40/107)	31% (27/86)	39% (28/72)	35% (12/34)	na
E03HIGH	57	29.8%	0.042	26% (28/108)	31% (32/102)	45% (32/71)	39% (20/51)	39% (19/49)
E03LOW	57	14.0%		NA	NA	NA	NA	NA
E05HIGH	94	23.4%	0.171	39.3%	40%	NA	NA	NA
E05LOW	102	15.6%			(9 mo.)			
E01E04 Pooled	244	25%	NA	31.4%	31.2%	42.9%	41.1%	38.2%

N/A = Not Applicable

Figure 4. Change in Seizure Frequency, Patient Distribution

All Patients Completing Effectiveness Evaluation, N=196



	Percent Change (seizures/day) from Baseline		
	HIGH	LOW	Difference
N	94	102	196
Median	-23%	-21%	n/a
25%, 75% Quartiles	-8.9%, -49%	4.0%, -43%	n/a
95% Confidence Intervals	-35%, -21%	-23%, -7.7%	-23%, -2.3%
Range (min, max)	-100%, 52%	- 89%, 171%	-23%, -2.3%
Mean ± SD	-28% ± 34%	-15% ± 39%	-13%* ± 37%

* Difference statistically significant ($p<0.05$) by Analysis of Variance ($p=0.032$) and by Cochran-Mantel-Haenszel Aligned Ranks ($p=0.040$)

Table 9. Patient Summary Chart:
Patients Continuing Treatment as of August 22, 1996

STUDY PERIOD	E01	E02	E03	E04	Total
Patients Randomized/Stimulated (N)	10	5	114	123	253
Patients (N) Entering Extension Phase	10	5	113	123	251
Total continuing patients being treated for up to one year (N)	10/10	5/5	111/115	112/121[4]	238/251
Continuing patients being treated for up to two years (N)	9/10	4/5	71/87[1]	58[2]/70	142/173
Continuing patients being treated for up to three years (N)	7/10	3/5	57/87	21[3]/24	88/127

(1) Twenty eight (N=28) commercial European patients were excluded from follow-up after one year of treatment due to the commercial release of the NCP® system in those countries.

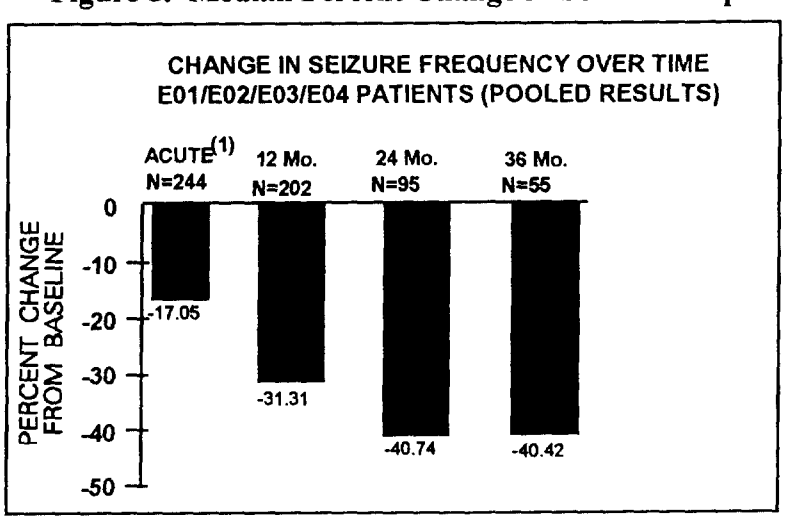
(2) As of 8/22/96. Only 70 patients had been implanted long enough to reach the 2 year treatment period; only 58 of the 70 were continuing.

(3) As of 8/22/96, Only 24 patients had been implanted long enough to reach the 3 year treatment period; only 21 of the 24 were continuing.

(4) Two of the original 123 patients entering the extension phase had been implanted for less than one year as of 8/22/96.

A total of 238 out of a possible 251 completed one year of therapy (95%); 142 out of 172 completed two years of therapy (83%); and 88 out of 126 completed three years of therapy (70%). Although these numbers of patients remained in the study, only those patients who had completed the annual follow up visits are represented in the above efficacy calculations. NCP® System treatment did not cause changes in AED plasma concentrations as measured during studies E03 and E05.

Figure 5. Median Percent Change in Seizure Frequency



(1) Note: The acute phase results include seizure frequencies of the E03 Study LOW stimulation group, which includes one-half of the E03 patients, N=57

Patients were permitted to change their AEDs during these studies and these changes may have contributed to the change in seizure frequency.

Pediatric Patients

Study E05 allowed patients as young as 12 years to enter the study. There were 20 patients in the E05 Study between 12 and 18. Their response during the Study was a 22.5% median reduction and a 26.2% mean reduction in seizures compared to baseline.

Global Rating

Global ratings by Investigators and patients support the conclusion that HIGH stimulation is associated with an improved quality of life, although improvements were seen in both groups. Patients, companions, and Investigators who were blinded to the treatment were asked to give a global rating of the patient's overall condition at each visit. A visual analog scale consisting of a 100 mm line was use. All Global scores for the Investigator, Patient and Companion are significantly improved over baseline. In the E05 study, the Investigators and Patients rated the HIGH group significantly improved over the LOW group.

Quality of Life and Cognitive Functioning

The E03 and E05 Studies used several instruments to measure QOL and cognitive functioning, with those used in the E05 Study being more comprehensive. Observed changes in the health related quality of life (HQL) and psychosocial scale scores were generally more favorable in the HIGH VNS group. There were few significant correlations between changes in cognitive tests and changes in global ratings of patient's overall well-being and seizure activity.

Other secondary endpoints

There was a statistically significant difference in mean % change in seizure frequency for within group stimulation compared to baseline. There was no statistically significant difference between groups for the number of responders (≥50% seizure reduction), number of seizure free days, seizure intensity or duration.

10.3.2 Safety

In each of the studies, the system was safe and well tolerated. The following treatment emergent signs and symptoms were observed in the Studies. Almost all were mild or moderate and anecdotally reported by Investigators to occur when the stimulator was ON and the intensity of the AE's were related to the strength (output current) of the stimulation. Symptoms that decreased or disappeared are not included in this analysis. In the E05 Study a symptom check list was used to prompt patients for adverse event reporting to ensure complete reporting of all events. Use of the checklist is likely the cause of slightly higher adverse event reporting rates in E05 Study as compared to E03.

Table 9. Observed Adverse Events

(n=413 devices in 314 patients, 152 in HIGH (optimal stimulation) treatment group, 591 device years)

	Randomized + Extension Phase, N= 314 patients, 591 device years				Randomized Phase, HIGH Only, N = 152 pts	
Adverse Event	**# of patients**	**% of patients**	**# of Events**	**Events per device-year**	**# of patients**	**% of patients**
Serious AEs1						
Surgically Related	13	4.1 %	13	0.022		
Stimulation Related	4	1.2 %	4	0.007	1	0.7 %
Non-serious AEs						
Voice Alteration	156	50%	720	1.228	91	60%
Cough Increased	129	41%	456	0.772	57	38%
Pharyngitis	84	27%	182	0.308	36	24%
Paresthesia	87	28%	377	0.638	32	21%
Dyspnea	55	18%	55	0.093	32	21%
Dyspepsia	36	12%	98	0.166	22	15%
Nausea	59	19%	154	0.261	21	14%
Laryngismus	10	3.2%	30	0.051	9	5.9%

1 - Serious AEs reported included infection, nerve paralysis, hyperesthesia, facial paresis, left vocal chord paralysis, left facial paralysis, left recurrent laryngeal nerve injury, urinary retention, and low grade fever

Table 10. Adverse Events Reported During Baseline or Stimulation

Test of Difference between Baseline (12 Weeks) and Stimulation (14 Weeks)

Adverse Event	E05					
	HIGH			LOW		
	Baseline	Treatment	p-value[C]	Baseline	Treatment	p-value[C]
Cough	28.4	52.6	<0.0001	23.3	51.5	<0.0001
Dyspepsia	5.3	21.1	0.0011	13.6	15.5	0.6171
Dyspnea	4.2	27.4	<0.0001	6.8	14.6	0.0114
Infection	4.2	14.7	0.0184	8.7	15.5	.1615
Pain, nonspecific	20.0	33.7	0.0124	19.4	37.9	0.0030
Paresthesia	1.1	24.2	<0.0001	4.9	33.0	<0.000
Throat pain[D]	15.8	42.1	<0.0001	16.5	29.1	0.0236
Voice alteration/hoarseness	6.3	72.6	<0.0001	8.7	32.0	<0.0001
Vomiting	8.4	17.9	0.0389	6.8	14.6	.0325

Adverse Event	E03					
	HIGH			LOW		
	Baseline	Treatment	p-value[C]	Baseline	Treatment	p-value[C]
Cough	0.0	12.3	0.008	3.5	10.5	.157
Dyspepsia	na	na	na	na	na	na
Dyspnea	1.8	10.5	*0.059*	0.0	0.0	na
Infection	0.0	3.5	0.157	1.8	3.5	.564
Pain, nonspecific	na	na	na	na	na	na
Paresthesia	0.0	15.8	0.003	0.0	7.0	0.046
Throat pain[D]	0.0	7.0	0.046	0.0	5.3	0.083
Voice alteration/hoarseness	0.0	38.6	<0.0001	0.0	14.0	0.005
Vomiting	1.8	1.8	ns	1.8	1.8	ns

A As reported or observed

Statistically significant <0.05

[B] As elicited using Symptoms Checklist, reported or observed

Marginally significant 0.05< p < 0.10

[C] Within group analysis

[D] Throat pain is specifically reported as an AE in E03 but not E05. For comparative purposes a separate analysis of E05 data, aggregating neck pain, Pharyngitis and Laryngismus, was done and is presented here

Table 11. Treatment Emergent Adverse Events By Severity

Adverse Event	AE's Reported During Baseline and Stimulation			Treatment Emergent AE's by Severity (% of reports)		
	E05 HIGH Group			Severity Ratings		
	Baseline [A]	Treatment [A]	pvalue [C]	Mild	Moderate	Severe
Cough	28.4%	52.6%	.0001	74%	23%	3%
Dyspepsia	5.3%	21.1%	.0011	76%	24%	0%
Dyspnea	4.2%	27.4%	<.0001	46%	54%	0%
Hypesthesia	0.0%	5.3%	.0253	100%	0%	0%
Infection	4.2%	14.7%	.0184	70%	30%	7%
Insomnia	1.1%	5.3%	.0455	75%	25%	0%
Pain, NonSpecific	20.0%	33.7%	.0124	63%	33%	4%
Paresthesia	1.1%	24.2%	<.0001	82%	18%	0%
Throat Pain & Laryngismus/Pharyngitis	15.8%	42.1%	<.0001	55%	43%	2%
Voice Alteration/Hoarseness	6.3%	72.6%	<.0001	73%	27%	0%
Vomiting	8.4%	17.9%	.0389	76%	24%	0%

AE's that are > 10% in the E05 HIGH stimulation group and were statistically significantly different from baseline are included.

Since the E03 and E05 Studies were active controlled studies as opposed to the traditional placebo controlled studies, a comparison of adverse events to baseline is required in order to obtain a more complete understanding of the differential effects of VNS therapy. A within group analysis of AEs for both HIGH and LOW groups in the E03 and E05 Studies in comparison to baseline AE rates is shown in the table above. Ninety nine percent of the side effects were rated as mild or moderate.

Table 12. Treatment Emergent Signs and Symptoms (>2%)

Study Number	E01	E02	E04	E03		E05		XE01 04		XE5
Group				HIGH[1]	LOW[2]	HIGH	LOW	1 YR	2 YR	9 MO
N	11	5	123	57	57	95	103	244	166	41
BODY AS A WHOLE										
Asthenia						7.4	1.9			12.2
Chills										2.4
Cyst						1.1	1.0			4.9
Edema Face						0.0	1.0			2.4
Fever			7.3	3.5	1.8	11.6	18.4	0.8	1.2	2.4
Flu Syndrome						1.1	3.9			2.4
Headache	60	20	8.9	5.3	7.0	24.2	23.3	4.5	1.8	17.1
Infection				3.5	3.5	11.6	11.7	2.1	1.2	4.9
Injury Accident			5.7			12.6	12.6	2.1	1.2	14.6
Malaise						1.0	0.0			4.9
Overdose						0	2.9			
Pain	30			8.8	1.8	28.4	30.1	0.4	1.2	31.7
Pain Abdominal	20		4.1	3.5	3.5	6.3	6.8	2.1	0	9.8
Pain Back				0	1.8	0	3.9	0	0	9.8
Pain Chest	20			1.8	0	9.5	12.6	0.8	0	4.9
Pain Neck	30					3.2	1.0			4.9
CARDIOVASCULAR SYSTEM										
Arrhythmia								0	0	2.4
Arrhythmia Vent										2.4
Fibrillate Atria										2.4
Hemorrhage						3.2	3.9			
Hypertension						4.2	1.0	0	0	7.3
Phlebitis						2.1	0			
Tachycardia						2.1	2.9	0.4	0	
DIGESTIVE SYSTEM										
Appetite Increase	10									
Anorexia	10					1.1	1.9	1.2	0	4.9
Constipation		20	2.4	0	0	2.1	7.8	0.4	0	2.5
Diarrhea	20		4.1	3.5	0	6.3	24.3	1.2	1.2	12.2
Dyspepsia						17.9	12.6			9.8
Dysphagia	20	60	4.9	3.5	0	2.1	6.8	2.1	1.2	2.4
Gingivitis						2.1	1.9			
Nausea	10		2.4	7.0	1.8	14.7	20.4	0.8	1.2	2.4
Vomit	10		4.9	0	1.8	17.9	13.6	1.6	1.8	4.9
HEMIC AND LYMPHATIC SYSTEM										
Anemia						0.0	1.0			2.4
Ecchymosis						3.2	3.9			7.3
METABOLIC AND NUTRITIONAL DISORDERS										
Cyanosis						0	2.9			

Table 12. Treatment Emergent Signs and Symptoms (>2%)

Study Number	E01	E02	E04	E03		E05		XE01 04		XE5
Group				HIGH[1]	LOW[2]	HIGH	LOW	1 YR	2 YR	9 MO
N	11	5	123	57	57	95	103	244	166	41
Edema						3.2	6.8			2.5
Edema Periph						0.0	1.0			2.4
Weight Decrease						1.1	2.9			2.4
MUSCULO SKELETAL SYSTEM										
Arthralgia						2.1	1.0	0.4	0	
Bone Fract Spontan						5.3	2.9			4.9
Myalgia	30		6.5			2.1	1.0	1.2	0	4.9
Myasthenia										2.4
NERVOUS SYSTEM										
Agitation				0	1.8	1.1	2.9	1.6	0	
Anxiety	10					1.1	1.0			2.4
Ataxia	10			0	0	4.2	3.9	0.4	0.6	9.8
Coordination Abnormality		20								
Convulsions						2.1	3.9			
Depression	10		0.8	1.8	1.8	3.2	0	0	0.6	12.2
Diplopia						5.3	2.9	0.4	0.6	
Dizziness				0	3.5	5.3	3.9	3.3	0.6	4.9
Dream Abnormality	10					1.1	0.0			
Emotional liability			2.4			1.1	1.9	1.2	0	
Euphoria	20									
Gait Abnorm										2.4
Hallucin								0.4	0	2.4
Hostility						1.1	1.0			2.4
Hypesthesia						2.1	0			2.4
Insomnia	10	20	2.4	5.3	1.8	4.2	4.9	0	0.6	2.4
Movement Dis						1.1	0.0			2.4
Neuralgia										2.4
Nervousness			3.3			1.1	1.9	1.6	0	2.4
Neurosis										2.4
Paresthesia			5.7	5.3	3.5	17.9	25.2	0.8	2.4	41.5
Person Disorder						1.1	0.0			2.4
Somnolence				5.3	3.5	2.1	1.9	1.2	0	2.4
Tremor			2.4	1.8	1.8	3.2	2.9	0	1.2	2.4
Twitch	50	20	3.3	1.8	0	3.2	1.0	0.8	0	9.8
Vertigo										2.4
RESPIRATORY SYSTEM										
Asthma						2.1	3.9			2.4
Cough Increased			17.1	8.8	8.8	45.3	42.7	2.9	3.0	17.1
Dyspnea	30	20	3.2	7.0	0	25.3	10.7	2.5	0	9.8

Table 12. Treatment Emergent Signs and Symptoms (>2%)

Study Number	E01	E02	E04	E03		E05		XE01 04		XE5
Group				HIGH [1]	LOW [2]	HIGH	LOW	1 YR	2 YR	9 MO
N	11	5	123	57	57	95	103	244	166	41
Hiccup	10					3.2	0			
Hyperventilate						2.1	1.0			
Laryngismus						7.4	1.0			2.4
Lung disorder						1.1	3.9			4.9
Pharyngitis	10	40	4.9	12.3	10.5	34.7	25.2	4.1	1.2	19.5
Respiratory Disorder						2.1	0			
Rhinitis			11.4	0	3.5	7.4	14.6	1.6	1.2	4.9
Sinusitis						3.2	2.9			4.9
Voice Alteration	100	80	13	36.8	10.5	66.3	30.1	7.8	5.4	75.6
SKIN AND APPENDAGES										
Application Site Reaction						1.1	2.9			2.4
Alopecia						0.0	1.0			2.4
Pruritis										4.9
Rash	10					5.3	1.9	0	0	4.9
Rash Vesis Bull						2.1	1.0			
SPECIAL SENSES										
Amblyopia						2.1	1.9	0.4	0.6	
Conjunctivitis						1.1	1.0			2.4
Glaucoma										2.4
Pain Ear		20		0	1.8	4.2	3.9	1.2	0.6	
Parosmia										2.4
Taste Pervers								0	0	2.4
Tinnitus				3.5	1.8	4.2	5.8	0	0	
UROGENITAL SYSTEM										
Dysmenorrhea						2.1	3.9			
Dysuria						0	2.9	0.4	0	
Hematuria						0.0	1.0			2.4
Incontin Urine						1.1	0.0			2.4
Infection, Urin Tract						2.1	6.8			
Menstrual Disorder				3.5	0	1.1	0	0	0	
Merorrhagia						2.1	1.9			
Urination Frequency						0.0	1.0			4.9

*1 = **HIGH** Stimulation parameters generally believed to provide maximum efficacy*

*2 = **LOW** Stimulation parameters generally believed to provide sensation of stimulation but less effective.*

Cardiac monitoring: For Study E05 all patients had 24 hour Holter monitoring twice during baseline and five times during stimulation. Data from the Holter monitoring showed no difference between either of the Treatment groups, and/or Baseline periods on cardiac endpoints. Some patients in all acute and long term studies were monitored at baseline and stimulation with EKG

or Holter recording. None of the monitoring showed any statistically significant differences between baseline and stimulation.

Pulmonary monitoring: Patients in the E05 Study were monitored once during baseline and twice during stimulation for FVC and FEV1. There was no statistical difference between the treatment groups, and/or baseline periods pulmonary endpoints. Although dyspnea was statistically significantly increased over baseline, no effect was detected with pulmonary function monitoring.

Gastric monitoring: All patients in E05 were monitored for serum gastrin levels and some patients in the other acute and long term studies were monitored for gastrin or gastric acid output. No clinically meaningful changes were observed.

DEATHS AND OTHER SERIOUS ADVERSE EVENTS

A total of 17 deaths have been reported in 950 clinical and commercial patients followed for 1650 patient-years. Nine of the deaths were judged to be possible/probable/definite Sudden Unexpected Death in Epilepsy (SUDEP). Additionally, one patient died of SUDEP during the preimplant baseline period, and two patients have died after discontinuation of treatment.

Based on the 17 deaths, there was a mortality of 10.3/1000 patient-years and a SUDEP incidence of 3.0/1000 patient-years for definite/probable and 5 for definite/probable/possible SUDEPs.

Table 13. Deaths and Other Serious Adverse Events

Study	N	No. of Deaths[1]	Other Serious AEs
E01	11	0	1 vocal cord paralysis due to surgery, resolved.
E02	5	0	0
E03	114	1 preimplant	1 vocal cord paralysis, permanent, device failure 1 infection, hospitalization complete recovery 1 MI
E04	123	0	2 Infections; 1 hospitalization for transient increase in seizures; 1 poor appetite; 1 fever; 1 coughing.
E05	198	0	Surgery & device related 3 infections which ultimately were explanted; 1 vocal cord paralysis; 1 left facial paralysis; 1 post operative fever; 1 localization of fluid around generator; and 1 left recurrent laryngeal nerve injury. Therapy related: 1 near syncope; 1 Cheyenne Stokes respiration, and 1 bleeding duodenal ulcer.
XE14	229	7	Definitely related: 1 respiratory distress; 1 obstructive bronchitis; 3 voice alteration; 1 choking Probably related: 1 Change of seizure type Possibly related: 1 Fall; 1 pulmonary congestion; 1 obstructive bronchitis.
XE5 (6 mo.)	41	2	1 probable left hemidiaphragm paralysis, 1 hospitalization for seizures, 1 institutionalized for selfabusive behavior

1 = Table does not include patients who died using a commercially available product, N = 8

10.3.3 DEVICE PERFORMANCE

DEVICE COMPLICATIONS AND OBSERVATIONS

For the purposes of this report, a device complication is an event which cannot be treated or resolved by reprogramming the device and requires intervention other than reprogramming. A device observation is an adverse event which can be corrected by reprogramming and which does not require surgical intervention

Table 14. Device Complications and Observations

Study	N	NCP® System Complications	Description
E01	11	2 Lead	1 high impedance, 1 broken wire
E02	5	None	None
E03	114	3 Lead 2 Generator	1 cut by surgeon, 1 Lead not fully inserted in Generator 1 Electrode not on nerve, but reduced seizures 1 Internal short, DC on electrode 1 Premature battery depletion, excessive drain from circuit
E04	123	0	None
E05	198	0	None
XE14		54 Lead 5 Generator	24 Lead breaks, 24 High lead impedance, 1 insulation, 1 infection, 1 patient discomfort, 1twiddler, 4Infection (explanted), 1 user error
XE5 (6 mo.)	41	1 Lead	1 Lead high impedance, Lead was twisted, no strain relief or tie down. Replaced Lead
Study	**N**	**Observations**	**NCP® System Observations**
E01	11	0	0 NCP® System
E02	5	0	0 NCP® System
E03	114	3 Generator 4 System 1 Programming Software	2 reset, 1 communication 4 infections treated with antibiotics 1 exited to DOS, program was modified
E04	123	3 Lead 3 Generator Several Programming 4 Programming Software	1 high impedance, unverified, 2 helix stuck together 1 pt discomfort, 2 erratic stim, unverified Programming difficulties Resolved by repositioning or turning off other equipment in the room 2 Operator error, 1 corrupted history file, 1 background program interfered with printing
E05	198	3 Generator 1 Lead 1 System 12 Communication	2 Pain during diagnostic tests, User error, explained in Manual 1 Programmer operator error, explained in Manual 1 "Malformed" Lead at implant, used backup Lead returned Lead within specs. 1 infection Resolved by repositioning Wand or turning off electrocautery equipment. Discovered disk caching routines on certain computers may interfere, instructed users to disable this function.

Table 14. Device Complications and Observations

Study	N	NCP® System Complications	Description
XE14 8 yr. total	229	23 Lead	11 high impedance, 4 break, 3 user error, 2 connector, 2 helix stuck together, 1 dislodged
		36 Generator	10 erratic stim (not duplicated), 8 reset, 8 user errors, 5 communication, 1 each: infection, magnet effectiveness, package anomaly, set screw, other
		8 Wand	6 communication, 2 user error
		14 Programming Software	7 communication, 3 software difficulties, 4 user error
XE5 6 mo.	89	2 Generator	2 reports of erratic stimulation; not verified
		2 Communication	2 communication difficulties resolved by repositioning

Two Generator complications have occurred related directly to device performance. One Generator malfunction caused by an internal short circuit and DC current on the ground electrode resulted in patient injury, and although the patient's nerve was believed to be permanently damaged the patient's voice fully recovered. The second was premature battery depletion due to a transient high current drain.

Over fifty Leads have been verified to have broken or developed high impedance. Design changes have been made as a result of these failures. Over 500 of the redesigned leads have reportedly been implanted, with no reported complications, other than one case where a suture was tied directly around the lead.

There have been a number of reported programming communication problems. These problems are related, in part, to a strict communication protocol which ensures reliable data transfer and programming, and in part to the use of electrocautery and other electrically noisy equipment in the vicinity of the programmer. The noise immunity of the receiver circuitry in the Programming Wand was improved, and disk caching routines in some computers was identified as a source and corrected.

11. CONCLUSIONS DRAWN FROM STUDIES

Valid scientific evidence is necessary to establish that there is reasonable assurance the NeuroCybernetic Prosthesis (NCP®) System is safe and effective for its intended use. The *in vivo* and in vitro nonclinical laboratory studies together with the clinical investigations provide reasonable assurance that the NeuroCybernetic Prosthesis (NCP®) System is safe when used as indicated in the labeling.

The results of clinical studies of the NCP® system for seizure reduction in patients with partial onset seizures support the effectiveness of the device. The mean seizure reduction experienced by the HIGH treatment groups (the group on whom labeling is based) was statistically significant as compared to the active LOW treatment control group. The HIGH group in both studies had a statistically significant mean seizure reduction as compared to baseline.

The safety of the NCP® System has been demonstrated in clinical trials with reported side effects being negligible in relationship to the severity of the disorder being treated. The most common

side effects reported are generally a function of the device's programmed stimulation setting which can be altered or adjusted to lessen the effect or discontinue it altogether.

12. PANEL RECOMMENDATIONS

On June 27, 1997, the Neurological Devices Panel recommended that the Premarket Approval Application for the NeuroCybernetic Prosthesis (NCP®) System be approved with some specific labeling recommendations. The approved labeling followed those recommendations. The panel also recommended that post approval studies will be conducted to examine the morbidity and mortality associated with the device and to develop a method to assess, prior to implant if possible, a means to determine which patients would respond to the therapy and which would not.

13. FDA DECISION

FDA and the applicant worked out conditions of approval including post-approval studies which were formally agreed to in the applicant's amendment received July 16, 1997.

In addition to the general conditions of approval, the applicant must conduct the studies outlined in the amendment dated July 16, 1997, ("Description of the Postapproval Studies - P970003"). The information to be collected for five years will include:

- continued reporting on a cohort of E05 patients;
- characterization of the long-term morbidity and mortality; and
- development of an approach to identifying responders and non-responders.

If appropriate, the results of the long-term data must be reflected in the labeling (via a supplement) when the post-approval study is completed.

FDA performed an inspection and found the applicant in compliance with the Good Manufacturing Practices (GMP) regulation (21 CFR, Part 820).

FDA concurred with the recommendations of the Neurological Devices Panel of June 27, 1997, and issued an approval order to Cyberonics on July 16, 1997

14. APPROVAL SPECIFICATIONS

- Directions for use: See the labeling.
- Hazards to health from use of the device: See indications, contraindications, warnings, precautions and adverse events in the labeling.
- Post Approval Requirements and Restrictions: See approval order.

Cyberonics®
DEVICES FOR EPILEPSY

NeuroCybernetic Prosthesis (NCP®) Pulse Generator

Model 100

Physician's Manual

(For Serial Numbers above 2000)

REF 26-0002-4600 JULY 1997

Table of Contents

1. *BRIEF DEVICE DESCRIPTION*

The Cyberonics® NeuroCybernetic Prosthesis (NCP®) System is comprised of an implantable Pulse Generator and Lead, and an external programming system used to change stimulation settings.

The Model 100 NCP[1] Pulse Generator is an implantable, multiprogrammable bipolar Pulse Generator that delivers electrical signals to the vagus nerve for the purpose of reducing the frequency of partial onset seizures. The Pulse Generator is housed in a hermetically sealed titanium case and is powered by a single lithium thionyl chloride battery.

Electrical signals are transmitted from the NCP Pulse Generator to the vagus nerve by the Model 300 Series Vagus Nerve Stimulation Lead. The Lead and the NCP Pulse Generator comprise the implantable portion of the NCP System.

The external programming system includes the Model 200 NCP Programming Wand, the Model 250 Programming Software, and an IBM compatible computer. The software, running on the computer, allows a physician to place the Wand over a Pulse Generator and read and change device settings.

2. *INTENDED USE / INDICATIONS*

The NCP System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications.

3. *CONTRAINDICATIONS*

The NCP System cannot be used in patients after a bilateral or left cervical vagotomy.

Symbols and Definitions used in this labeling include:
⚠ Notice for reader to pay special attention to following details
⊗ Not suitable for connection to a public telecommunications network or telephone equipment
SN Denotes Serial Number
⧗ Denotes Expiration Date
⊘ Denotes for Single Use Only
LOT Denotes batch code
Denotes Date of Manufacture

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1 Cyberonics and NCP are registered trademarks of Cyberonics, Inc. The NCP pulse generator is protected under U.S. Patent Nos. 4,702,254; 4,867,164; 5,025,807; 5,154,172; 5,186,170; and 5,235,980. The ROM code has also been copyrighted. The company also holds patents in foreign countries.

STERILE EO Denotes that Contents were sterilized by ethylene oxide

4. *WARNINGS*

⚠ **Avoid Excessive Stimulation**: Stimulation at a combination of high frequency (≥50 Hz) and a duty cycle exceeding 50% (ON TIME > OFF TIME) has resulted in degenerative nerve damage in laboratory animals. Excess duty cycle can be produced by frequent magnet activation (> 8 Hours of continuous magnet activation).

⚠ **Aspiration** may result from the increased swallowing difficulties reported by some patients during stimulation. **Patients who have pre-existing swallowing difficulties** are at greater risk for aspiration.

⚠ **Device Malfunction** could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated adverse effects. Patients should be instructed to use the magnet to stop stimulation if they suspect a malfunction, and then immediately contact their physician for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.

Sudden Unexplained Death in Epilepsy (SUDEP): During the pre-marketing development of the NCP System, 10 sudden and unexplained deaths (definite, probable & possible) were recorded among the 1,000 patients implanted and treated with the NCP device (2017 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 5.0 definite, probable and possible SUDEP deaths per 1,000 patient-years of experience. Although this rate exceeds that expected in a healthy (non-epileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving NCP stimulation (ranging from 1.3 for the general population of patients with epilepsy, to 3.5 for a recently studied antiepileptic drug (AED) clinical trial population similar to the NCP System clinical cohort, to 9.3 for patients with refractory partial onset epilepsy).

5. *PRECAUTIONS*

⚠ **Laryngeal irritation** may result from stimulation. **Patients who smoke** may have an increased risk of laryngeal irritation.

⚠ **Dyspnea** may result from stimulation. **Patients with chronic obstructive pulmonary disease** may have an increased risk of dyspnea.

⚠ **Resetting the NCP Pulse Generator** turns the device OFF (output current = 0 mA) and all device history information is lost. Print out device history information before resetting.

Physicain Training:

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- **Prescribing Physicians** should be experienced in the diagnosis and treatment of epilepsy and should be familiar with the use of the NCP System.
- **Implanting Physicians** should be experienced in operating in the carotid sheath and be trained for surgical implantation of the NCP system. See Section 12.2, Physician Training/Information for more information.

5.1 Sterilization, Storage and Handling

⚠ Store the device between -20°C (-4°F) to +55°C (+131°F) because temperatures outside this range can damage components.

⚠ Do not implant a device when:

⇒ It has been dropped, because this could have damaged NCP Pulse Generator components;

⇒ Its sterility indicator within the inner package is not green, because it might not be sterile;

⇒ Its storage package has been pierced or altered, because this could have rendered it non-sterile; or

⇒ Its "use before" date has expired, because this can adversely affect NCP Pulse Generator longevity or sterility.

⚠ Do not re-sterilize the NCP Pulse Generator. Return unimplanted devices to Cyberonics for re-sterilization.

⚠ Do not ultrasonically clean the NCP Pulse Generator, because this may damage Pulse Generator components.

⚠ The Pulse Generator is a single use only device. Do not reimplant a Pulse Generator explanted for any reason. Explanted generators should be returned to Cyberonics for analysis and proper disposal, along with a completed Returned Product Report form. Before returning the Pulse Generator, seal it in a pouch or other container properly labeled with a biohazard warning.

5.2 Lead Evaluation and Lead Connection

⚠ Do not use a lead other than the Model 300 Series Vagus Nerve Stimulation Lead because such use may damage the NCP Pulse Generator or injure the patient.

⚠ Exercise extreme caution if testing Leads using line powered equipment because leakage current can injure the patient.

⚠ Do not insert a Lead in the NCP Pulse Generator connector without first visually verifying that the setscrews are sufficiently retracted to allow insertion.

5.3 Environmental and Medical Therapy Hazards

Patients should exercise reasonable caution in avoidance of devices that generate a strong electric or magnetic field. If a Pulse Generator should cease operation while in the presence of ElectroMagnetic Interference (EMI), moving away from the source or turning it off may allow the Pulse Generator to return to its normal mode of operation.

5.3.1 Hospital and Medical Environments

NCP System operation should always be checked by performing device diagnostics following any of the mentioned procedures. Additional precautions for these procedures are described below.

Therapeutic radiation may damage the NCP Pulse Generator's circuitry, although no testing has been done to date and no definite information on radiation effects are available. Sources of such radiation include therapeutic X rays, cobalt machines, and linear accelerators. The effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from temporary disturbance to permanent damage and may not be detectable immediately.

External defibrillation may damage the Pulse Generator. Attempt to minimize current flowing through the Pulse Generator and Lead system by following these precautions:

⇒ Position defibrillation paddles perpendicular to the Pulse Generator / Lead system and as far from the Pulse Generator as possible.

⇒ Use the lowest clinically appropriate energy output (watt seconds).

⇒ Confirm NCP Pulse Generator function following any internal or external defibrillation.

Electrosurgical cautery may damage the Pulse Generator. Attempt to minimize current flowing through the Pulse Generator and Lead system by following these precautions:

⇒ Position electrosurgery electrodes as far from the NCP Pulse Generator and NCP Lead as possible.

⇒ Avoid electrode placement that puts the NCP Pulse Generator and NCP Lead in the direct path of current flow.

⇒ Confirm NCP Pulse Generator function following electrosurgery.

Magnetic Resonance Imaging (MRI) should not be done with MR body coil. The heat induced in the Leads by a body MRI scan can cause injury. MRI should only be done using a head coil. Conditions which have been tested include:

⇒ Transmit and Receive coil type: Head Coil Only

⇒ Static Magnetic Field Strength: ≤ 2.0 Tesla

⇒ SAR: < 1.3 W/kg for 70 kg patient

⇒ Time varying intensity < 10 Tesla /sec

⇒ Magnetic and radio-frequency (RF) fields produced by MRI may change the Pulse Generator settings (change to reset parameters), activate the device, and injure the patient.

Extracorporeal shockwave lithotripsy may damage the Pulse Generator. If therapeutic ultrasound therapy is required, avoid positioning the Pulse Generator part of the body in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the NCP Pulse Generator output to 0 mA for the treatment and retest the Pulse Generator after therapy.

Diagnostic ultrasound is not expected to affect the NCP System.

5.3.2 Home Occupational Environments

Properly operating microwave ovens, electrical ignition systems, power transmission lines, theft prevention devices, and metal detectors are not expected to affect the Pulse Generator. Similarly, most routine diagnostic procedures such as fluoroscopy and X rays are not expected to affect system operation. However because of higher energy levels, sources such as transmitting antennas may interfere with the system.

5.3.3 Cellular Phones

Based on testing to date, cellular phones have no effect on the NCP Pulse Generator operation. The NCP Pulse Generator does not have sensing Leads. These Leads contribute to the EMI sensitivity of implanted pacemakers and defibrillators.

5.3.4 Other Environmental Hazards

Strong magnets, hair clippers, vibrators, loudspeaker magnets, and other similar electrical or electromechanical devices, which may have a strong static or pulsing magnetic field, can cause inadvertent magnet activation. Patients should be cautioned to keep such devices away from the NCP Pulse Generator.

5.3.5 Programming Software

The Programming Software should be used on a computer dedicated only for programming the NCP system. The Programming Software has been validated on a Compaq® Contura Aero 4/25 running MS DOS® 6.2 with the disk caching software disabled.

(See the Model 250 Physician's Manual for more information)

5.3.6 NCP Pulse Generator and EMI Effects on Other Devices

During stimulation the NCP Pulse Generator may interfere with devices operating in the 40 kilohertz to 100 kilohertz range, such as pocket transistor radios and hearing aids. This is a theoretical possibility, and no effects on hearing aids have yet been reported, although the Pulse Generator can interfere with transistor radios when held directly over the radio. No specific testing has been done to date and no definite information on effects are available. It is suggested the Pulse Generator be moved away from equipment with which it is believed to be causing interference. Programming or interrogating the NCP Pulse Generator may momentarily interfere with other sensitive electronic equipment nearby. The NCP Pulse Generator is not expected to trigger airport metal detectors or theft protection devices.

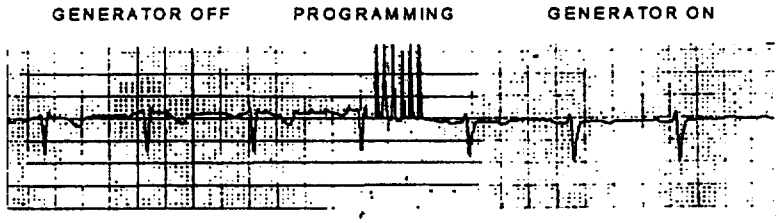
The NCP Pulse Generator may affect the operation of other implanted devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate Pulse Generator responses. If the NCP Pulse Generator patient requires concurrent implantable pacemaker and/or defibrillator therapy, careful programming of each system may be necessary to optimize the patient's benefit from each device.

⚠ The magnet provided for activation or inhibition of the NCP Pulse Generator may damage televisions, computer disks, credit cards, and other items affected by strong magnetic fields.

5.3.7 Effects on ECG Monitors

NCP Pulse Generator data communications will produce an ECG artifact. Figure 1 shows examples of this artifact in ECG tracings.

Figure 1. ECG Artifact Produced by NCP Pulse Generator communication



5.3.8 Pulse Generator Disposal

- Do not incinerate NCP Pulse Generator, because it can explode if subjected to incineration or cremation temperatures.
- Return all explanted NCP Pulse Generators to Cyberonics for analysis and safe disposal.
- Do not implant an explanted NCP Pulse Generator in another patient as sterility, functionality, and reliability cannot be ensured.

6. ADVERSE EVENTS

The NCP System was implanted in 454 patients in five clinical studies involving 611 devices (some patients had Generator replacements). As of August, 1996, total NCP exposure in these 454 patients was 901 device years. Individual patient exposure averaged 24 months with a range of 8 days to 89 months.

A total of 9 patients died during these five studies. One patient died from each: thrombotic thrombocytopenic purpura, drownings, aspiration pneumonia, pneumonia, and renal failure associated with drug and alcohol ingestion. No cause of death was apparent for the other four and they may be classified as Sudden Unexpected Death in Epilepsy (SUDEP). None of the deaths were attributed by the Investigators to the NCP System.

6.1 Observed Adverse Events

Included among the five clinical trials were two randomized trials (Study E03 & E05) which involved 314 patients and implantation of 413 devices yielding a total NCP System exposure (inclusive of long term follow-up) of 591 years. These trials form the basis for the rates of observed adverse events.

Table 1 reports the adverse events from these studies during the Randomized Phase (14 week observation period) on a per patient basis. For the Extension Phase, events are reported on a per patient and per patient-year basis. The most common side effect associated with stimulation is hoarseness (voice alteration) during stimulation (hoarseness should only occur during the ON time). Most people tolerate the hoarseness well.

Table 1. Observed Adverse Events

(N=413 devices in 314 patients, 152 patients in HIGH treatment group, 591 device years)

	Randomized + Extension Phase, N= 314 patients, 591 device years				Randomized Phase, HIGH Only, N = 152 pts	
Adverse Event	**# of patients**	**% of patients**	**# of Events**	**Events per device-year**	**# of patients**	**% of patients**
Serious AEs[1]						
Surgically Related	13	4.1 %	13	0.022		
Stimulation Related	4	1.2 %	4	0.007	1	0.7 %
Non-serious AEs						
Voice Alteration	156	50%	720	1.228	91	60%
Cough Increased	129	41%	456	0.772	57	38%
Pharyngitis	84	27%	182	0.308	36	24%
Paresthesia	87	28%	377	0.638	32	21%
Dyspnea	55	18%	55	0.093	32	21%
Dyspepsia	36	12%	98	0.166	22	15%
Nausea	59	19%	154	0.261	21	14%
Laryngismus	10	3.2%	30	0.051	9	5.9%

[1] - Serious AEs reported included infection, nerve paralysis, hypersthesia, facial paresis, left vocal chord paralysis, left facial paralysis, left hemidiaphragm paralysis, left recurrent laryngeal nerve injury, urinary retention, and low grade fever.

Status Epilepticus: Valid estimates of the incidence of treatment emergent status epilepticus among VNS treated patients are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 2 of 441 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Rebound after stimulation is stopped: Seizure frequency was monitored for one to four weeks after stimulation was stopped in 72 instances (68 patients) in Study E03. Seizure rate increased by greater than 1.5 standard deviations above baseline in 10% of instances (compared to 7% expected). Of these instances, 11 of 72 (15%) had a greater than 25% increase above baseline and 42 of 72 (58%) had a greater than 25% decrease in seizure rate.

6.2 Potential Adverse Events

Adverse events which may occur (including those reported in Table 1), reported in alphabetical order:

- Cough increased
- Dyspepsia, duodenal or gastric ulcer
- Dyspnea
- Facial paresis or paralysis
- Hemidiaphragm paralysis
- Hypesthesia
- Infection
- Laryngismus
- Muscle twitching during stimulation
- Nausea and vomiting
- Nerve injury
- Paresthesia
- Pharyngitis
- Voice alteration

Patients who manipulate the NCP Pulse Generator and the Lead through the skin may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

7. CLINICAL STUDIES

Five clinical studies have been conducted. They enrolled 537 patients, of whom 454 were implanted with the NCP System. A total of 611 devices were implanted and patient exposure totaled 901 device years with individual mean patient exposure of 24 months (range 8 days to 7.4 years). A total of 45 centers participated in these studies, 39 in the US, two in Germany and one each in Canada, Holland, and Sweden.

Table 2. Description of Clinical Studies

All patients enrolled in all clinical studies, N=537

Study	E01	E02	E04	E03	E05	Total
Type of Study	Pilot Longitudinal	Pilot Longitudinal	Open Longitudinal	Randomized Parallel High/Low	Randomized Parallel High/Low	-
Patients Enrolled	11	5	133	126	262	537
# Centers*	3	2	24	17	20	45
Reference (baseline) period	Weeks 2 through 4	Weeks 3 through 6	Weeks -4 through 0	Weeks -12 through 0	Weeks -12 through 0	-
Seizure Type	Partial	Partial	All types	Partial	Partial	-
Num. AEDs	1 to 2	1 to 2	not specified	0 to 3	1 to 3	-

* Total includes non-US centers (Canada, Holland, Germany 2, and Sweden), several US centers participated in more than one study

Purpose: To determine whether adjunctive use of optimal stimulation of the vagus nerve could reduce seizure frequency in patients with refractory partial onset seizures.

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Methods: In the two concurrent control studies (E03 and E05), patients were randomly assigned to either HIGH (optimized to the patient) or LOW (active control - longer OFF time interval) treatment groups. Patients were enrolled in the study and seen every four weeks during the baseline period (weeks -12 to 0). Patients meeting eligibility were implanted with the NCP Pulse Generator and NCP Lead. Two weeks after implantation, patients were randomized to the HIGH or LOW stimulation group and the Pulse Generator was activated. HIGH dose received a higher frequency, greater pulse width, and higher duty cycle. The randomized treatment period that followed activation of the Pulse Generator lasted 14 weeks (the last 12 weeks of which were used in the efficacy analysis -- first 2 weeks were for surgical recovery, followed by a 2 week treatment ramp up period).

Table 3. Description of Patients

All patients implanted in all clinical studies, N=454

Study	E01	E02	E04	E03	E05	Total
Patients Implanted	11	5	124	115	199	454
Patients Stimulated	10	5	123	115	198	451
Age (range)	32 (20, 58)	33 (18, 42)	24 (3, 63)	33 (13, 57)	33 (13, 60)	32 (13, 63)
Females (%)	4 (36%)	2 (40%)	57 (46%)	43 (37%)	104 (52%)	210 (46%)
Years w/ Epilepsy	22 (13-32)	20 (5-36)	17 (0.8-48)	21 (4-47)	23 (2-52)	-
Av. # AEDs	1.0	1.0	2.2	2.1	2.1	-
Median seizures per Day at Baseline	0.6	0.42	0.65	0.70 High 0.85 Low	0.58 High 0.51 Low	-

Results: The primary efficacy endpoint (percent reduction in seizure rate) was measured over 12 weeks (weeks 2 through 14). Adverse events were assessed at each visit.

Table 4. Principal Effectiveness and Safety Results

All patients in Effectiveness analyses in all clinical studies, N=441

Principal Effectiveness Results						
Study	E01	E02	E04	E03	E05	Total
Patients in Effc. Eval.	10	5	116	114	196	441
MEDIAN reduction seizures per Day	32%*	48%*	22%*	24%* High 6% Low	23%* High 21%* Low	-
MEAN reduction seizures per Day	24%*	40%*	7%	24%* High 6% Low	28%* High 15%* Low	-
Diff mean (HI-LOW)	-	-	-	17%*[3%,31%]	13%* [2%, 23%]	-
% with >50% Response	30%	50%	29%	30% High 14% Low	23% High 16% Low	-
Principal Safety Results Through Extension Phase						
Exposure (Pt-yr.)	45	20	245	456	135	901
SAEs: High/Low [a]	9% / -	0% / -	6% / -	5% / 0%	7% / 9%	-
D/C for: LOE / AE [b]	0 / 1	0 / 0	2 / 3	0 / 2	1 / 3	3 / 9
Num. Explants [c]	2	2	15	9	5	33
Death: SUDEP/Total [d]	0 / 0	0 / 0	3 / 4	0 / 3	1 / 2	4 / 9

[a] SAEs = Serious adverse events

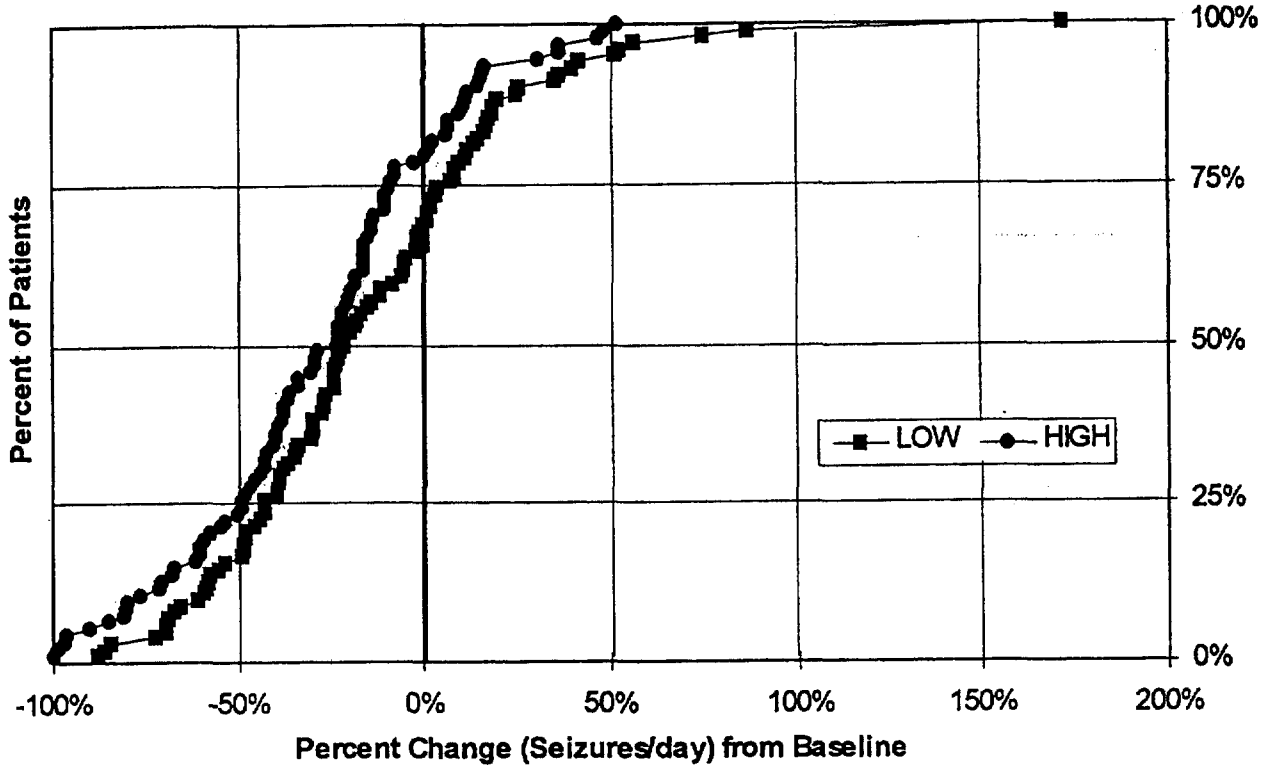
[b] D/C = Discontinued for lack of efficacy / adverse events at one year; excludes deaths

[c] Number of explants excludes deaths;

[d] All deaths occurred during the long-term follow-up, closing dates: August-Sept 1996

* Difference statistically significant, p< 0.05, by t-test or Chi square (without correction for any interim analyses)

Figure 2. Change in Seizure Frequency, Patient Distribution (with Corresponding Table)
All Patients Completing Effectiveness Evaluation, N=196



	Percent Change (seizures/day) from Baseline		
	HIGH	LOW	Difference
N	94	102	196
Median	-23%	-21%	n/a
25%, 75% Quartiles	-8.9%, -49%	4.0%, -43%	n/a
95% Confidence Intervals	-35%, -21%	-23%, -7.7%	-23%, -2.3%
Range (min, max)	-100%, 52%	- 89%, 171%	-23%, -2.3%
Mean ± SD	-28% ± 34%	-15% ± 39%	-13%* ± 37%

* Difference statistically significant ($p<0.05$) by Analysis of Variance ($p=0.032$) and by Cochran-Mantel-Haenszel Aligned Ranks ($p=0.040$)

Patient response to VNS was examined via statistical modeling (examining group characteristics) and evaluation of individual patients. No useful predictors of increase or decrease in seizure frequency were found.

Conclusions: Patients with refractory partial onset seizures treated with HIGH VNS had a statistically significant decrease in frequency of seizures when compared to baseline and when compared to patients treated with LOW (control) VNS. The most common treatment-related adverse events were voice alteration and dyspnea. Treatment was well tolerated, with 98% (306 of 324) patients implanted continuing on into the extension of this study.

7.1 Long Term Data

Long term data was collected on all available E01 through E04 Study patients. This data is uncontrolled because it comes from an open label protocol where both antiepileptic drug

medications and NCP device settings were allowed to be changed. However, all available information is presented for completeness.

Ninety-five (95%) percent of patients were continuing as of one year after their original implant, 82% were still receiving stimulation at two years, and 69% were receiving stimulation at three years. Some E04 patients had not yet had the opportunity to reach two or three years of stimulation, and were therefore not used in the calculations. Additionally, 28 E03 patients were implanted outside the U.S. in countries that later received commercial approval, and data was only available through one year of stimulation.

Table 5. Patient Summary Chart: Patients Continuing Treatment as of August 22, 1996

E0X STUDY PERIOD	E01	E02	E03	E04	Total
Patients Randomized/Stimulated (N)	10	5	115	123	253
Patients (N) Entering Extension Phase	10	5	113	123	251
Total continuing patients being treated for up to one year (N)	10/10	5/5	111/115	112[4]/121	238/251
Continuing patients being treated for up to two years (N)	9/10	4/5	71/87[1]	58[2]/70	142/172
Continuing patients being treated for up to three years (N)	7/10	3/5	57/87	21[3]/24	88/126

(1) Twenty-eight (N=28) commercial European patients were excluded from follow-up after one year of treatment due to the commercial release of the NCP System in those countries.

(2) As of 8/22/96. Only 70 patients had been implanted long enough to reach the 2 year treatment period; only 58 of the 70 were continuing.

(3) As of 8/22/96. Only 24 patients had been implanted long enough to reach the 3 year treatment period; only 21 of the 24 were continuing.

(4) Two E04 Study patients had not yet reached their one year date post implantation.

Table 6 below provides the number of patients used in the efficacy analysis. It is apparent from the table that not all continuing patients were used in the efficacy analysis. This is mostly because of missing data (some patients kept only sporadic records over the long term) although two patients were not used because they had lobectomy surgery which affected their seizure rates.

Table 6. Patients (N) Used for Efficacy Analysis

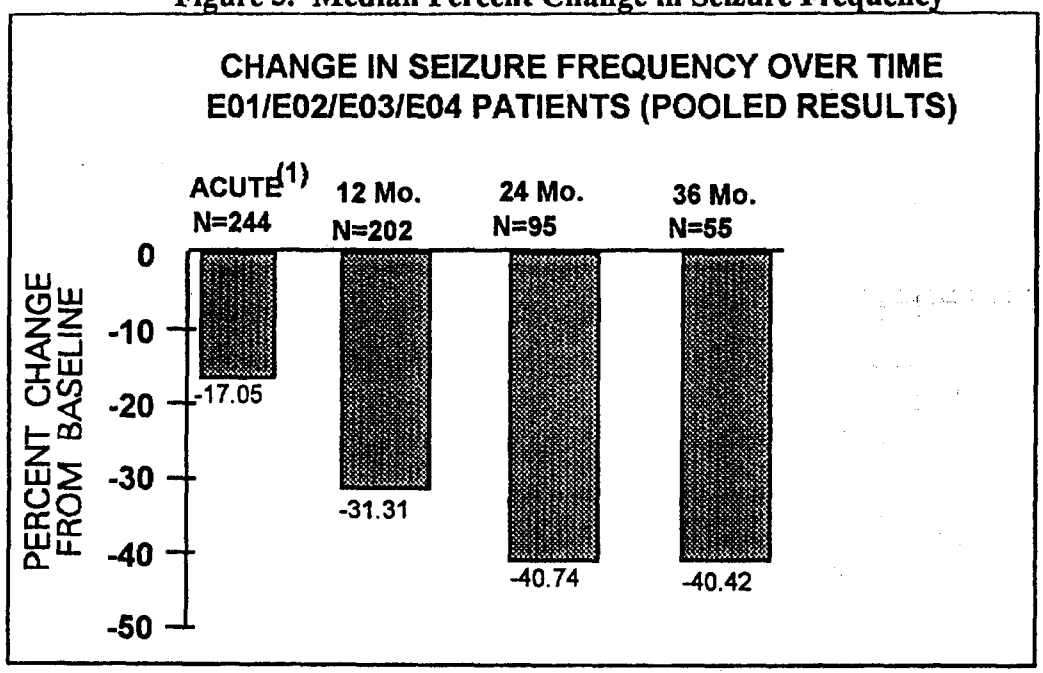
E0X STUDY PERIOD	E01	E02	E03	E04	Total
Patients Randomized/Stimulated (N)	10	5	115	123	253
Patients(N) Entering Extension Phase	10	5	113	123	251
Patients used in One Year Efficacy Analysis (N)	10/10	4/5	102/111	86/112	202/238
Patients used in Two Year Efficacy Analysis (N)	8/9	2/4	51/71[1]	34/58[2]	95/142
Patients used in Three Year Efficacy Analysis (N)	4/7	2/3	49/57	0[3]	55/67

(1) Twenty-eight (N=28) commercial European patients were excluded from follow-up after one year of treatment due to the commercial release of the NCP System in those countries.

(2) As of 8/22/96. Only 70 patients had been implanted long enough to reach the 2 year treatment period; only 58 of the 70 were continuing.

(3) No data was available at the 3 year time point for study E04.

Figure 3. Median Percent Change in Seizure Frequency



(1) Note: The acute phase results include seizure frequencies of the E03 Study LOW stimulation group, which includes one-half of the E03 patients, N=57

Patients were permitted to change their AEDs during these studies and these changes may have contributed to the change in seizure frequency.

7.2 Other Information

Although information outside the typical range gathered for Studies E03 and E05 was collected for Study E04, the information is from an open-label study and on fewer numbers of patients. Sixteen **patients under age 12** (range 3.6 to 12 years) were evaluated. These patients were found to have a 17.9% median decrease during the acute phase, with 31% experiencing a greater than 50% decrease. Additionally, 25 patients with **generalized seizures** were evaluated. These patients were found to have a 46.6% median decrease during the acute phase, with 44% experiencing a greater than 50% decrease.

8. INDIVIDUALIZATION OF TREATMENT

Patients should be started on stimulation at low current setting (0.25 mA) and the current should be gradually increased to allow accommodation to the stimulation. For patient comfort, the output current should be increased in 0.25 mA increments until comfortable tolerance is reached. Physicians should appreciate that some patients will accommodate to stimulation levels over time and therefor allow if needed further increases (in 0.25 mA steps) in output current. See Programming Software Manual.

Table 7 list the stimulation parameters used in the randomized clinical trials.

Table 7. Stimulation Parameters

Parameter	High (optimal stimulation)
Output Current	0-3.5 mA
Frequency	30 Hz
Pulse Width	500 μSec
ON Time	30 Sec
Off Time	5 Min
Magnet Parameters	
Amplitude	Same as Output Current
On Time	30 Sec
Pulse Width	500 μSec

The magnet output current should be set to a level that can be perceived by the patient to allow for testing of the Generator operation on a daily basis.

⚠ The safety and efficacy of this therapy have not been systematically established in patients with the following conditions:

- only one vagus nerve
- neurological diseases other than epilepsy
- history of ulcers (gastric, duodenal or other)
- cardiac arrhythmias or other abnormalities
- respiratory diseases or dyspnea

- under the age of 12 and over the age of 60
- primary generalized seizures
- pregnant or nursing
- pre-existing hoarseness
- history of dysautonomias
- history of vasovagal syncope

9. PATIENT COUNSELING INFORMATION

Patients should be informed to test their generator's operation daily by performing a magnet stimulation and verifying that stimulation occurs. If stimulation does not occur, their physician should be contacted.

In the unlikely event of uncomfortable adverse events, continuous stimulation or other malfunction, the patient should be advised to hold or tape the magnet directly over the implanted NCP Pulse Generator to prevent additional stimulation. If patients or caregivers find this procedure necessary they should immediately notify their physician.

10. CONFORMANCE TO STANDARDS

The NCP System conforms to the following standards:

- ANSI / AAMI NS15 Implantable peripheral nerve stimulators; and
- prEN45502-1 - Active Implantable Medical Device Directive - General Requirements.

11. HOW SUPPLIED

11.1 Sterilization

Implantable portions of the NCP System have been sterilized using ethylene oxide gas, and are supplied in a sterile package for direct introduction into the operating field. An expiration date is marked on the outer package. Storage temperatures should be within the -20°C (-4°F) to +55°C (+131°F) range. If the package has been exposed to temperatures outside this range or there is any indication of external damage, the package should be left unopened and returned to Cyberonics.

11.2 Nonpyrogenic

The implantable portions of the NCP System are nonpyrogenic.

12. *OPERATOR'S MANUAL*

12.1 Directions for Use

12.1.1 Specifications and Product Information

Table 8. Specification and Product Information

Parameter	Available Parameter Settings
Stimulation Parameters	
Output Current	0-12 mA ± 10%, in 0.25-mA steps*
Signal Frequency	1, 2, 5, 10, 15, 20, 25, 30, 40, 42, 43, 45, 47, 50, 52, 55, 59, 63, 67, 71, 77, 83, 91, 101, 112, 127, 145 Hz, ±6%
Pulse Width	130, 250, 500, 750, 1000 µsec ± 10%
Signal ON Time	7, 14, 21, 30, 60, 90, 120, 180, 210, 240, and 270 sec, ±15% (± 15%, -7 sec in MAGNET MODE)
Signal OFF Time	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, 3 min and 5 to 180 min (5 to 60 in 5-min steps; 60 to 180 in 30-min steps), +3 sec, -7 sec
Treatment Time (per day)	24 hr. (non programmable)
Treatment Start (delay time)	0 (non programmable)
Magnet Activation	Provided by magnet application (output current, pulse width, and signal ON time may be independently programmed for this purpose)
Reset Parameters	0 mA; 10 Hz; 500 µsec; ON time, 30 sec; OFF time, 60 min
Nominal	0 mA; 30 Hz; 500 µsec; ON time, 30 sec; OFF time, 10 min
Telemetry Reports	
Device History Report	Patient code, implant date, model number, serial number, total operating time, accumulated signal ON time, date and time of last 15 magnet applications
Device Diagnostic Report	Status messages for programming and telemetry, output current Lead impedance, DC-DC converter value, programmed amplitude, and device treatment status
Power Source	
Battery	One Wilson Greatbatch Ltd., Model 8602
Chemistry	Lithium thionyl chloride
Voltage	3.7 V, open circuit

* - NOTE: For output currents < 1 mA or frequencies > 100 Hz., the tolerance of the output current is ± 25%.

Rated capacity	2.8 Ampere-hours
Self-discharge rate	6.5% per year
Physical Characteristics	
Materials	
Case	Titanium, hermetically sealed
Header	Epoxy
Lead connector blocks	Stainless steel
Set screw septum	Silicone rubber
Measurements	
Lead connector receptacles	5 mm - inside diameter
Dimensions	55 mm x 13.2 mm
Weight	55 g

12.1.2 Operating Characteristics

12.1.2.1 Communicating with the NCP System

A Model 200 NCP Programming Wand connected to an IBM®-compatible personal computer running the Model 250 NCP Programming Software is needed to communicate with the NCP Pulse Generator.

⚠ Only computers which meet the requirements of IEC950 or UL1950 may be used with the programming wand.

See the Physician's Manual for the Model 200 Programming Wand for proper placement, connection of the wand to the computer, and use of the wand. See the Physician's Manual for the Model 250 Programming Software for the proper use of the software. Once the program has been initiated, software screens display prompts and messages to aid in communicating with the NCP Pulse Generator.

The NCP Pulse Generator "listens" for a communication signal for a 300-msec period every 6.8 seconds. Communication usually takes between 3 to 10 seconds but may be prolonged in the presence of EMI (electromagnetic interference). The NCP Pulse Generator listens for and implements interrogations, parameter programming instructions, requests for Device Diagnostics testing, and Device History inquiries. In response, the Pulse Generator transmits information on the stimulation parameter settings, Device Diagnostics, or Device History.

Each time the NCP Pulse Generator transmits these data, they are saved by the Model 250 Programming Software to databases on the storage disk. See the Physician's Manual for the Model 250 Programming Software for details on viewing the database information.

The NCP Pulse Generator also transmits a signal for use in Evoked Potential Monitoring.

Besides the NCP Programming Software and Wand combination, a magnet can be used to make one way communications to the NCP Pulse Generator by activating a reed switch in the electronic circuitry. The magnet can be used to initiate stimulation, inhibit stimulation temporarily, perform Magnet Mode diagnostics, and reset the NCP Pulse Generator.

12.1.2.2 Stimulation

Once the NCP Pulse Generator has been programmed, the stimulation will repeat in accordance with the programmed ON and OFF cycle until the Pulse Generator receives communication from the NCP Programming System or it is activated or inhibited with a magnet. Immediately following successful programming, it delivers a programmed stimulation which enables patient response to be evaluated. If programming is performed during stimulation, stimulation will be terminated; after programming, stimulation will begin using the revised setting.

The NCP Pulse Generator operation described in the preceding paragraph is NORMAL MODE. A MAGNET MODE stimulation is a single stimulation initiated by applying a magnet over the NCP Pulse Generator for at least one second and then immediately removing it from the area over the Pulse Generator. Stimulation will be delivered once the magnet is removed. The MAGNET MODE uses the same frequency as the NORMAL MODE, but the output current, pulse width and signal ON TIME are independently programmable.

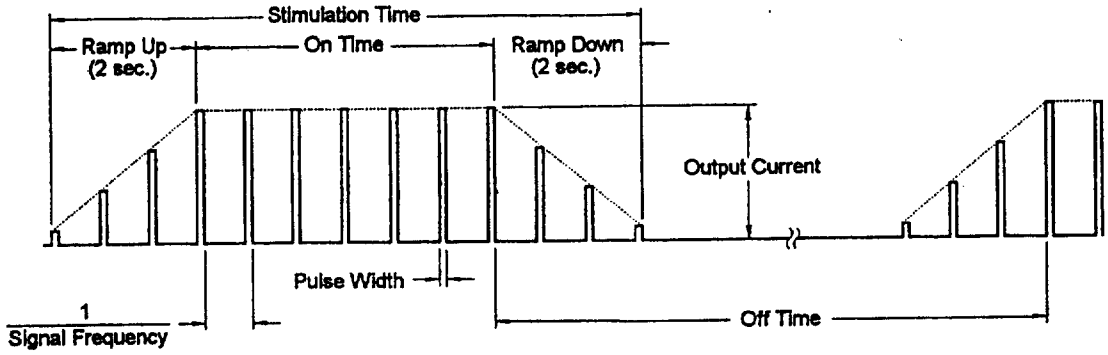
To determine the present settings of the stimulation parameters, an Interrogation is made. If Interrogation is performed during stimulation, completion of stimulation will be delayed until the Interrogation is finished.

A graphic representation of stimulation is shown in Figure 4, which depicts the relationship of the stimulation programmable parameters. The programmable parameters are independently variable, offering multiple setting combinations from which the physician may select optimal stimulation for the patient. Figure 4 shows that the output pulse can be varied both by amplitude (output current) and duration (pulse width). The number of output pulses delivered per second determines the frequency. The relation of the ON and OFF signal times is termed a "duty cycle". It is calculated by dividing the ON time (plus four seconds of Ramp-up and Ramp-down time) by the sum of the ON time and OFF time and is expressed as a percentage. The various parameter settings for stimulation are listed in "Specifications and Product Information", but certain versions of the Model 250 NCP Programming Software limit the number of available parameter settings.

While selecting a combination of parameter settings that will deliver optimal stimulation, the physician should also consider that some combinations will decrease battery life faster than others. Please see "Effects of Programmed Settings on NCP Pulse Generator Projected Lifetime".

> **Note:** Stimulation at a combination of high frequency (≥50 Hz) and ON TIME ≥ OFF TIME has resulted in degenerative nerve damage in laboratory animals. ON TIME ≥ OFF TIME can be simulated by very frequent magnet activation. Cyberonics recommends that stimulation at these combinations of ranges be avoided.

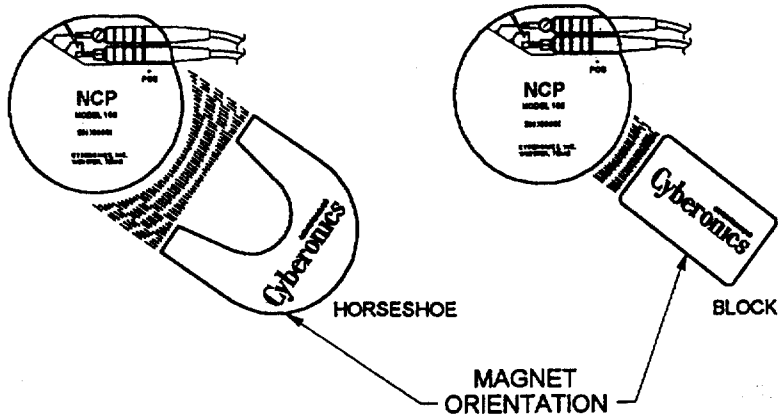
Figure 4. Stimulation (for all duty cycles except low-output settings ≤10 Hz){tc "Fig. 2 Stimulation (for all duty cycles except low-output settings ≤ 10 Hz)" \f g}



12.1.3 Uses of the Magnet

Cyberonics recommends patients be instructed to use the magnet to activate stimulation during an aura or at the start of a seizure. Magnet activation may be initiated by the patient, a companion, or the physician by placing a magnet near the NCP Pulse Generator to activate a reed switch in the Pulse Generator's electronic circuitry. This action changes the NCP Pulse Generator from NORMAL MODE to MAGNET MODE. Two differently shaped magnets, each providing a minimum of 65 Gauss at one inch, are furnished by Cyberonics. The horseshoe magnet is strongest. Proper magnet placement techniques for the magnets are shown in Figure 5.

Figure 5. Magnet Placement{tc "Fig. 3 Magnet Placement" \f g}



All magnets may lose their effectiveness over time. Avoid dropping the magnets or storing in the vicinity of other magnets.

12.1.3.1.1 Initiating Stimulation with a Magnet

To initiate stimulation, apply the magnet over the NCP Pulse Generator for at least one second and then immediately remove it from the area over the Pulse Generator. Removal of the magnet causes the NCP Pulse Generator to operate in MAGNET MODE delivering a single stimulation having the programmed magnet pulse width, magnet current and magnet signal ON time settings. The frequency will be the programmed value for NORMAL MODE operation. Any NORMAL MODE programmed stimulation will always be overridden by a MAGNET MODE, even if the

68

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MAGNET MODE output current is set to 0 mA. If MAGNET MODE stimulation is not desired, the MAGNET MODE output current may be programmed to 0 mA. Magnet use does not restart the normal OFF time. Therefore, depending on the timing of the magnet use, the patient could receive a second stimulation quickly following magnet activation. Cyberonics recommends that testing of the magnet output be performed while the patient is still in the physician's office to ensure tolerability of the magnet output. Physicians should warn patients against excessive or continuous use (> 8 hours) of magnet activated stimulation since this could result in exceeding the 50% duty cycle and may result in damage to the vagus nerve.

12.1.3.1.2 Inhibiting NCP Pulse Generator Output with a Magnet

Application of the magnet during stimulation will inhibit the output. Holding the magnet in place for at least 65 seconds will prevent the initiation of a MAGNET MODE stimulation as well as terminating any ongoing NORMAL MODE stimulation. After the magnet is removed, NORMAL MODE operation will resume with stimulation when one complete OFF time has elapsed. In the unlikely event of continuous stimulation or other malfunction, the patient should be advised to apply the magnet, secure it in place, and immediately notify his or her physician or Cyberonics.

12.1.3.1.3 Resetting the Microprocessor using a Magnet and the Programming Wand

The NCP System incorporates the ability to reset the NCP Pulse Generator microprocessor in the event of a malfunction. Resetting will be necessary only in the rare case of microprocessor memory malfunction which might be caused by conditions described in "Environmental Hazards" in this manual. Microprocessor reset is indicated when communication with the NCP Pulse Generator becomes impossible. See the "Troubleshooting" section of the Model 200 Programming Wand Physician's Manual and the "Precautions and Troubleshooting" section of the Model 250 Programming Software Physician's Manual for suggestions in solving communication difficulties. It is recommended that the physician consult a Cyberonics technical representative at (281) 332-1375, before resetting is performed. In order to effect a microprocessor reset, orient the magnet as shown in Figure 5 (the horseshoe magnet is recommended for resetting) and place the Model 200 NCP Programming Wand over the NCP Pulse Generator. While the magnet and wand are held in place, use the tip of a ball-point pen or similar object to depress the Programming Wand's RESET button for at least 30 seconds.

⚠ **All Device History information is lost and reset parameters (0 mA; 10 Hz; 500 μsec; ON time, 30 sec; OFF time, 60 min) are internally programmed in the Pulse Generator if it is reset. Resetting the NCP Pulse Generator turns the device OFF (output current = 0 mA). Reenter the NCP Pulse Generator serial number and patient code, and reprogram the Pulse Generator to desired parameters after a successful reset.**

12.1.3.2 Device History

Device History consists of the Pulse Generator serial number, the patient code, total operating time, accumulated signal ON time, total magnet activations, and the date and time of the last fifteen magnet activations (rounded to the nearest hour). Use the NCP Programming System to access and view the Device History information. Note: If a Reset is performed, the Device History data will be lost from NCP Pulse Generator memory and the stimulation parameters will

be automatically changed to the Reset Parameters shown in "Specifications and Product Information". To re-enter the patient code or Pulse Generator serial number, see the Model 250 NCP Programming Software Physician's Manual.

12.1.3.3 Device Diagnostics

Information from Pulse Generator diagnostic tests aids the physician in determining if the NCP Pulse Generator is operating properly before it is implanted, if the NCP Pulse Generator output current is being delivered at the programmed value, if Lead impedance is within an acceptable range, and in which mode the NCP Pulse Generator is operating. Details of the diagnostic tests available are found in the Model 250 Programming Software Physicians Manual.

12.1.3.3.1 Reasons for High Lead Impedance Readings

The LEAD TEST is the most appropriate of the device diagnostic tests to evaluate Lead impedance for the NCP System. The LEAD TEST is performed at 1.0 mA, 500 microsecond. Using Table 9, find the DC-DC Converter Code displayed by the LEAD TEST diagnostic screen to determine an estimate of Lead impedance in k ohms. Use of Table 7 with the DC-DC Converter Code from diagnostic screens other than LEAD and PRE-IMPLANT TESTS is not appropriate unless the NCP Pulse Generator output current is at 1.0 mA.

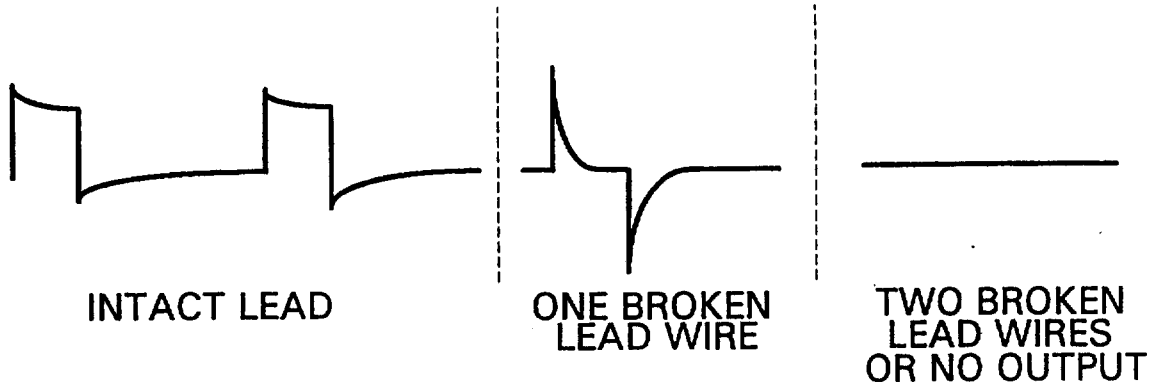
Table 9.
DC-DC Converter Codes Displayed During Lead Tests, With Corresponding Estimated Lead Impedance
{tc "Table 1. DC-DC Converter Codes Displayed During Lead Tests, With Corresponding Estimated Lead Impedance" \f t}

DC-DC CONVERTER CODE	ESTIMATED LEAD IMPEDANCE
O	<1 k ohms
1	1 to 3 k ohms
2	3 to 5 k ohms
3	5 to 8 k ohms
4	8 to 11 k ohms
5	11 to 16 k ohms
6	16 to 20 k ohms
7	> 20 k ohms

⚠ Possible causes of high Lead impedance readings are thought to include fibrosis between the nerve and the electrode, Lead fracture, Lead disconnection from Pulse Generator, and high battery impedance approaching end-of-service (EOS). High Lead impedance in combination with the patient's failure to feel even maximum output stimulus, may indicate a Lead wire fracture or another type of electrical discontinuity in the Lead. See the Model 250 Physician's Manual and the Model 300 Lead Physician's Manual for instructions on performing the Lead Test

An oscilloscope or evoked potential monitoring equipment can be used to analyze the stimulus wave form from the neck for verification of an electrical discontinuity. A differentiated wave form with narrowed pulses or no wave form at all can confirm a discontinuity. Figure 6 shows simulated waveforms expected from skin electrodes for a Lead that is intact, for a Lead that has a fracture in one wire and for a Lead that has a fracture in both wires. In addition to these approaches, Lead fractures may be identified in X-rays of the implant site.

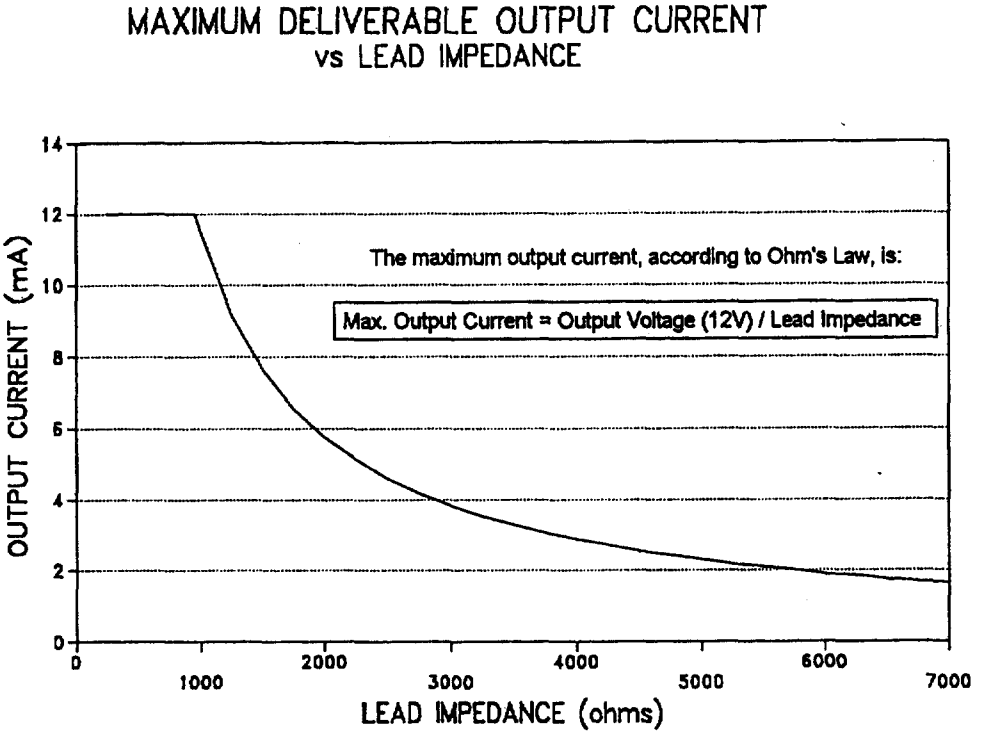
Figure 6. Typical Waveforms Obtained from Skin Electrodes



12.1.3.4 Delivery of Programmed Output Current

If the diagnostic tests indicate the OUTPUT CURRENT is LIMIT, the NCP Pulse Generator may not deliver the PROGRAMMED OUTPUT CURRENT. Reasons for failure to deliver the PROGRAMMED OUTPUT CURRENT include a high output current (output currents above 4 mA are difficult to deliver because most impedance's are above 3000 ohms - see Figure 7), high Lead impedance, or low battery voltage. Figure 7 demonstrates the relationship of Lead impedance to output current. If the NCP Pulse Generator is failing to deliver the programmed output current, the physician can reprogram to a lower output current and attempt to compensate for a decrease in delivered energy by widening the pulse width. For example, if the output current is at LIMIT for an NCP Pulse Generator programmed at 2.5 mA, 30 Hz, 500 µsec with 30 seconds ON time, then the parameters may be changed by lowering the output current to 2.0 mA and widening the pulse width to 750 µsec.

Figure 7. Relationship of Lead Impedance to Output Current

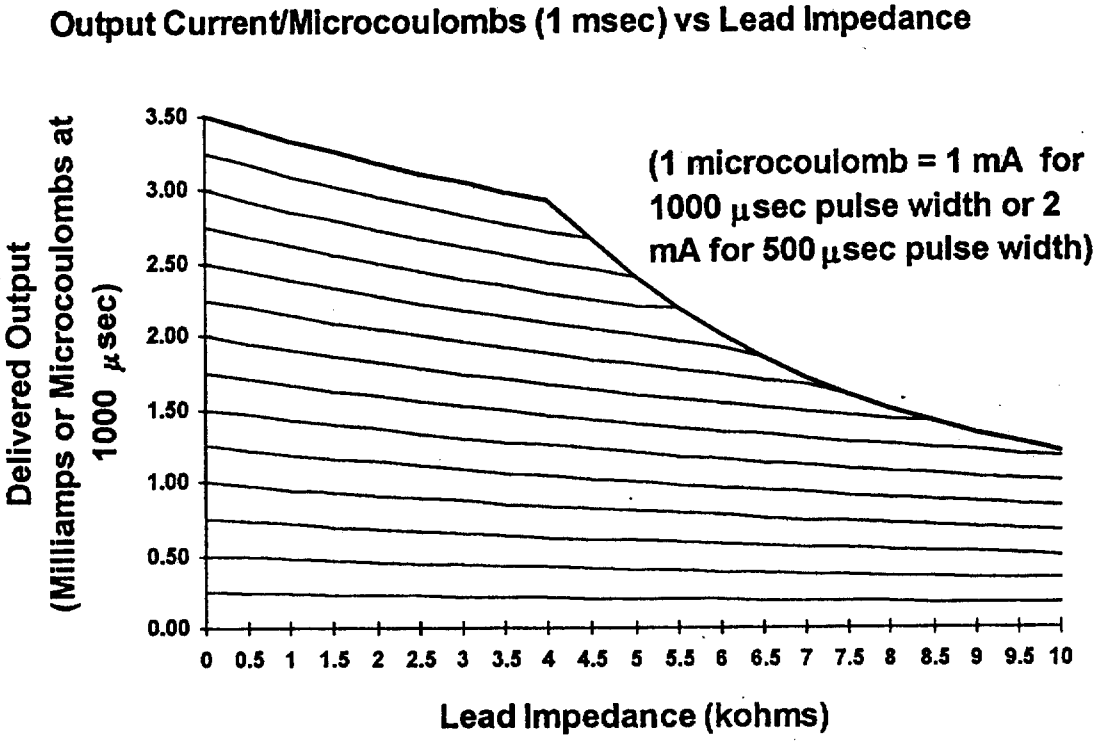


{tc "Fig. 5 Relationship of Lead Impedance to Output Current" \f g}

12.1.3.5 Charge Delivered per Pulse

The charge delivered per pulse is the parameter most important in evaluating stimulating output. It is defined as a microcoulomb, which is the product of current and time, or output current (mA) multiplied by the pulse width (msec). The graph in Figure 8 shows the relationship of programmed output current or microcoulombs vs. Lead impedance for current outputs from 0 to 3.5 mA.

Figure 8. Output Current/Microcoulombs vs. Lead Impedance{tc "Fig. 6 Output Current/Microcoulombs vs. Lead Impedance" \f g}



12.1.3.6 Evoked Potential Monitoring

In addition to the assessment methods described under "Device Diagnostics", stimulation parameters may be evaluated using evoked potential monitoring equipment. To evaluate an evoked response, program the NCP Pulse Generator to frequencies of 5 Hz and below. At these frequencies, the NCP Pulse Generator will transmit an electromagnetic trigger signal 25 ±5 msec before the stimulation pulse. The wand contains circuitry to detect this signal and can be connected to evoked potential monitoring equipment to synchronize with the output pulse. Although the stimulus artifact does not usually require blanking, this trigger can be used to activate a blanking circuit in the evoked potential monitor, if it has that capability. If the wand is to be used with an evoked potential machine, contact Cyberonics to obtain an EP Adapter Kit. See the Model 200 Programming Wand physician's manual for instructions on connecting the EP Adapter Kit.

⚠ **Do not use frequencies of 5 Hz and below for long-term stimulation. Because these frequencies generate an electromagnetic trigger signal their use results in excessive battery depletion of the implanted NCP Pulse Generator and should therefore be used for only short periods of time.**

12.1.3.7 Effect of Programmed Settings on NCP Pulse Generator Projected Lifetime

The choice of settings for output parameters affects NCP Pulse Generator battery life. Generally, a high-duty cycle will deplete the battery over a shorter period of time than a low-duty cycle. Table 10 shows duty cycles for typical ON time and OFF time settings (except for frequency settings ≤10 Hz). A two-second ramp-up time and two-second ramp-down time are present for most stimulations except those set at some low output currents and below 10 Hz. As depicted in the graphic representation of stimulation in Figure 4, neither of these two-second intervals is considered part of the stimulation ON time. However, they have been included in calculations for determining the percentage of stimulation time (duty cycle) and predicting battery life.

Table 10. Duty Cycles for various ON and OFF times (in Percentages){tc "Table 2. Duty Cycles for various ON and OFF times (in Percentages)" \f t}

	OFF TIME (Minutes)								
ON TIME SEC.	0.2	0.3	0.5	0.8	1.1	1.8	3	5	10
7	58%	44%	30%	20%	15%	10%	6%	4%	2%
14	69%	56%	41%	29%	23%	15%	9%	6%	3%
21	76%	64%	49%	36%	29%	19%	12%	8%	4%
30	81%	71%	57%	44%	35%	25%	16%	10%	5%
60	89%	82%	71%	59%	51%	38%	27%	18%	10%
90	92%	87%	78%	68%	60%	47%	35%	24%	14%
120	94%	90%	83%	74%	67%	54%	41%	30%	17%
150	95%	92%	86%	78%	71%	60%	47%	34%	21%
180	96%	93%	88%	81%	75%	64%	51%	38%	24%
210	96%	94%	89%	83%	78%	67%	55%	42%	26%
240	97%	95%	90%	85%	80%	70%	58%	45%	29%
270	97%	95%	91%	86%	82%	72%	61%	48%	31%

Battery life is expected to be approximately 56 months at programmed settings of 20 Hz, with a 500 µsec pulse width and 2 mA output, with a Lead impedance of 5 k ohms and a duty cycle of 10%. Table 11 provides battery estimated lifetimes under a variety of stimulation conditions including Lead impedance. Because of the number of possible parameter combinations, it is impractical to provide the projected life for all possible combinations. Table 11 should not be used to predict battery end of service, but it gives some indication of the effect of various parameter changes on battery life and can be used to assist in the selection of parameter settings. It also indicates that battery life can be maximized at low duty cycles and low frequencies (10 to 20 Hz) for stimulation. Not all versions of Model 250 NCP Programming Software will allow all the parameter setting combinations shown in Table 11.

Table 11. Estimated Battery Life
{tc "Table 3. Estimated Battery Life" \f t}

					PROJECTED LIFE (YEARS)		
FREQ (Hz)	PULSE WIDTH (µsec)	OUTPUT (mA)	LEAD (k ohms)	DC-DC CODE Lead Test	10% DUTY CYCLE	30% DUTY CYCLE	50% DUTY CYCLE

10	500	1	3	1-2	5.9	5.1	4.5
20	500	1	3	1-2	5.7	4.7	4.0
30	500	1	3	1-2	5.5	4.3	3.6
10	500	2	3	1-2	5.6	4.4	3.7
20	500	2	3	1-2	5.2	3.8	3.0
30	500	2	3	1-2	4.9	3.3	2.5
10	500	2	5	2-3	5.2	3.8	3.0
20	500	2	5	2-3	4.7	3.1	2.3
30	500	2	5	2-3	4.3	2.6	1.9
10	500	2	7	3	4.8	3.2	2.4
20	500	2	7	3	4.3	2.6	1.9
30	500	2	7	3	3.8	2.1	1.4
10	500	2	9	4	4.7	3.0	2.2
20	500	2	9	4	4.1	2.4	1.7
30	500	2	9	4	3.6	2.0	1.3
30	500	4	3	1-2	3.3	1.6	1.1
10	1000	1	3	1-2	5.7	4.8	4.1
20	1000	1	3	1-2	5.4	4.2	3.4
30	1000	1	3	1-2	5.1	3.7	2.9
10	1000	2	3	1-2	5.2	3.8	3.0
20	1000	2	3	1-2	4.7	3.0	2.2
30	1000	2	3	1-2	4.2	2.5	1.7
10	1000	2	5	2-3	4.8	3.3	2.5
20	1000	2	5	2-3	4.2	2.5	1.8
30	1000	2	5	2-3	3.7	2.0	1.4
10	1000	2	7	3	4.3	2.7	1.9
20	1000	2	7	3	3.6	1.9	1.3
30	1000	2	7	3	3.1	1.5	1.0
10	1000	2	9	4	4.3	2.6	1.9
20	1000	2	9	4	3.6	1.9	1.3
30	1000	2	9	4	3.1	1.5	1.0

The projected battery life is decreased as Lead impedance increases, which typically occurs with chronic implants. Although 1.5K to 3 K Ohms appears to be the typical Lead impedance at time of implant, the impedance may be expected to increase to 3K to 5 K Ohms during the life of the implant.

⚠ **Note:** Stimulation at a combination of high frequency (≥50 Hz) and ON TIME ≥ OFF TIME has resulted in degenerative nerve damage in laboratory animals. ON TIME ≥ OFF TIME can be simulated by very frequent magnet activation. Cyberonics recommends that stimulation at these combinations of ranges be avoided.

12.1.4 Implantation

12.1.4.1 Sterilization, Storage and Handling

The NCP Pulse Generator and accessories have been sterilized using ethylene oxide gas and are supplied in a sterile package to permit direct introduction into the operating field. An expiration date is marked on each package. If storage is necessary, temperatures should be within the -20°C (-4°F) to +55°C (+131°F) range. If the package has been exposed to temperatures outside this range or there is any indication of external damage, the package should be left unopened and returned to Cyberonics. In addition, the following guidelines should be observed:

⚠ The NCP Pulse Generator should not be re-sterilized by the user.

⚠ The Generator should not be ultrasonically cleaned.

⚠ The NCP Pulse Generator contains a sealed chemical battery and should not be incinerated, as an explosion could result.

⚠ A Pulse Generator explanted for any reason should not be reimplanted.

⚠ An explanted Pulse Generator should be returned to Cyberonics for analysis and proper disposal, along with a completed Returned Product Report form. Before returning the Pulse Generator, seal it in a pouch or other container properly labeled with a biohazard warning.

12.1.4.2 Package Contents

The sterile package contains:

- One Cyberonics Model 100 NCP Pulse Generator
- One vial of mineral oil
- One hex screwdriver
- One resistor assembly

Also provided along with the sterile package are the following:

- One Physician's Manual
- One Patient Identification Card, including emergency instructions
- One Returned Product Report form
- One Patient Manual

12.1.4.3 Opening the Sterile Package

Before the package is opened, it should be examined carefully for evidence of damage or compromised sterility. If the outer package has been opened or damaged, Cyberonics cannot guarantee sterility of the Pulse Generator, and it should be returned to Cyberonics. To open the package:

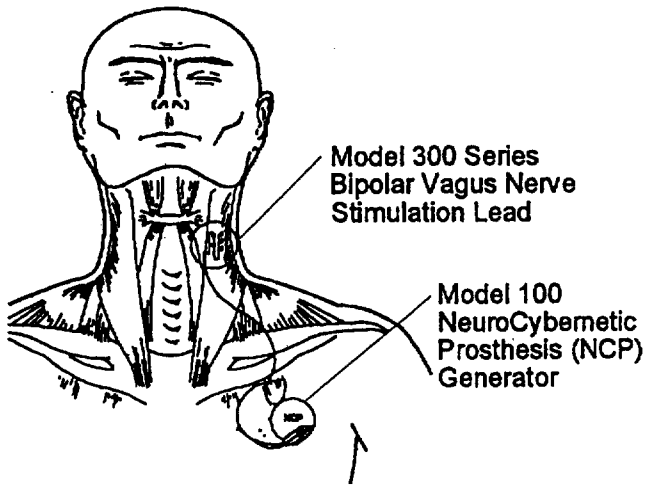
1. Grasp the tab and peel back the outer cover.
2. Observing sterile technique, lift out the sterile inner tray.
3. Grasp the tab and peel off the inner cover to expose contents. To remove an item, push down on one end and grasp the opposite (raised) end.

12.1.4.4 Lead and Pocket Location

The NCP Pulse Generator is usually implanted just below the clavicle in a pocket in the fatty tissue of the left upper chest. Suggested placement for the Model 300 Lead is the area of the left vagus nerve just above the clavicle, with the Lead subcutaneously tunneled between the stimulation site in the neck and the pocket formed in the upper chest (see Figure 9). It is recommended that both the Lead body and NCP Pulse Generator be positioned ipsilaterally with

respect to the selected stimulation site. The Cyberonics Model 400 Tunneling Tool (supplied non-sterile) is recommended for use in subcutaneously passing the Lead.

Figure 9. Placement of Generator and Lead



{tc "Fig. 7 Placement of Generator and Lead" \f g}

12.1.4.5 Recommendations for Implant

In general, implantation of the NCP Pulse Generator and Lead is similar to accepted practice for implantation of a cardiac pacemaker, with the exception of the placement of the electrodes and subcutaneous routing of the Lead body. Although the surgical approach and techniques will vary with the preference of the implanting physician, the Model 300 Lead Physician's Manual provides recommendations for implant, along with a detailed description of the order of placement of the helical electrodes and the anchor tether and other essential steps to assure correct Lead placement. Proper techniques for attachment of the electrodes and the anchor tether to the vagus nerve and for provision of adequate strain relief below and above the sternocleidomastoid muscle are critical to the long-term success of the implant.

⚠ **The Lead and its electrodes are very delicate and care should be taken not to overstretch or crush the helices.**

It is recommended that the Lead body be coiled and placed in the chest pocket to the side of the NCP Pulse Generator.

Adequate exposure of the vagus nerve (>3 cm) facilitates placement of the electrodes on the nerve. Stretching the nerve or allowing it to dry during implantation may result in temporary swelling of the nerve. Constriction of the nerve or other nerve damage may result in vocal cord dysfunction.

Cyberonics recommends that output of the NCP Pulse Generator and performance of the implanted system be tested at the time of implantation. Although an oscilloscope can be used for measurements, Cyberonics recommends use of the appropriate version of the Model 250 Programming Software and Model 200 Programming Wand (placed in a sterile drape) for routine system verification. The NCP Pulse Generator is packaged with a separate resistor assembly to be used while performing PRE-IMPLANT diagnostics. Once the electrode is placed on the nerve,

the electrode-nerve interface impedance can be tested by connecting the Lead directly to the NCP Pulse Generator and performing a Lead Test.

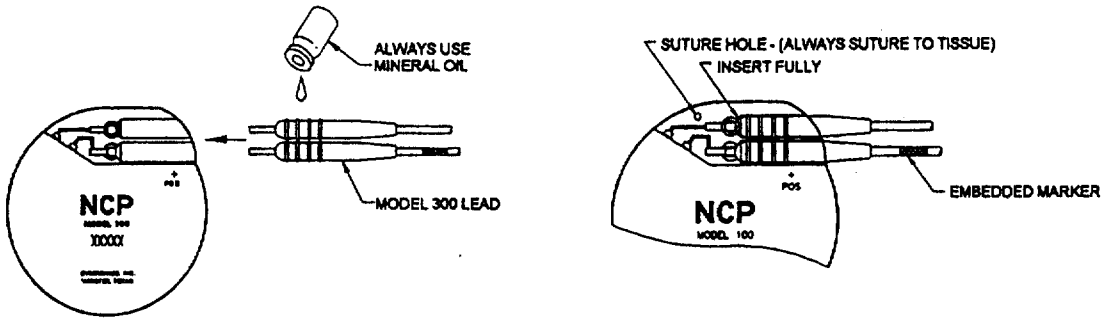
12.1.4.6 Implantation Procedure

1. After examining the exposed nerve, select an appropriately sized NCP Lead. The Model 300-20 Lead (2.0 mm electrode inner diameter) should accommodate most vagus nerves.
2. With the Cyberonics Model 400 Tunneling Tool, tunnel the connectors and Lead body subcutaneously from the neck incision to the NCP Pulse Generator pocket. See the Model 400 Tunneling Tool Directions for Use.

⚠ **Note:** In the procedures below, always push in on the hex screwdriver while turning to ensure that it is fully inserted in the set screw.

3. Attach Lead electrodes to the desired site on the vagus nerve, securing the electrode body parallel to the nerve using the integral anchor tether and tie-downs. See the NCP Lead Physician's Manual for more detailed instructions.
4. Connect the Lead directly to the NCP Pulse Generator, as follows:
   a. Verify that both set screws have been adequately loosened to allow full insertion of the connector pins.
   b. ⚠ Always apply a small amount of mineral oil (provided in the NCP Generator package) to the insulated portions of the connector pins to facilitate insertion (see Figure 10). This step is essential to minimize insertion forces and prevent possible damage to the connectors.

Figure 10. Lead Connectors Prior to Insertion and Fully Inserted



{tc "Fig. 8 Lead Connectors Prior to Insertion and Fully Inserted" \f g}

   c. Insert the Lead connector pins fully into the appropriate receptacles in the NCP Pulse Generator header. To allow escape of the back pressure created by insertion, leave the tip of the hex screw driver in the slit set screw plug of the connector being inserted. The Lead connector with a marker on the Lead and the embedded model and serial number is connected by the Lead wire to the electrode with the white suture; this connector pin is inserted into the Lead receptacle labeled "+". The remaining Lead connector is inserted into the remaining Lead receptacle.
   d. Verify that the pins are fully inserted. The ends should be visible behind the connector block. If they are not, remove the pin. To loosen a set screw, insert the hex

screwdriver through the rubber silicone plug and turn counterclockwise until the connector pin can be fully inserted.

e. After verifying that the connector pins have been fully inserted, tighten each set screw by inserting a hex screwdriver through the plug and turning clockwise until it begins ratcheting.

5. Test the impedance of the electrode-nerve interface by performing a LEAD TEST diagnostic, as described in the Model 250 Programming Software Physician's Manual.

a. Verify that the Lead Impedance status reads "OK." If status checks are not "OK", verify that the Lead connectors are properly inserted and the set screws are tightened and repeat the LEAD TEST diagnostics. If "OK" status checks cannot be obtained, perform pre-implant test on the Pulse Generator as described below. .

b. Optional physiologic monitoring of NCP System operation may be done if surgery is performed under local anesthesia. Monitor the patient's voice for signs of hoarseness while gradually increasing Pulse Generator output. After testing, reset the current to 0 mA.

6. Place the NCP Pulse Generator in the chest pocket, coiling the remaining slack of the Lead and placing it to the side or top of the NCP Pulse Generator.

⚠ **Do not place the Lead under the NCP Pulse Generator; this could result in insulation failure and system malfunction.**

7. ⚠ Secure the NCP Pulse Generator by placing a suture through the suture hole. This is important to stabilize the implant and to prevent manipulation by the patient which could damage the Lead wires.

⚠ **Do not place sutures directly around the body of the Lead; this may result in insulation failure and system malfunction.**

8. Close the surgical incisions. A neck brace can be used by the patient for the first week to help ensure proper Lead stabilization.

12.1.4.7 Pre-Implant Test

This test is to be performed in the event that the Lead Test Diagnostic status checks did not result in an "OK." This test is used to determine if the NCP Pulse Generator is functioning properly.

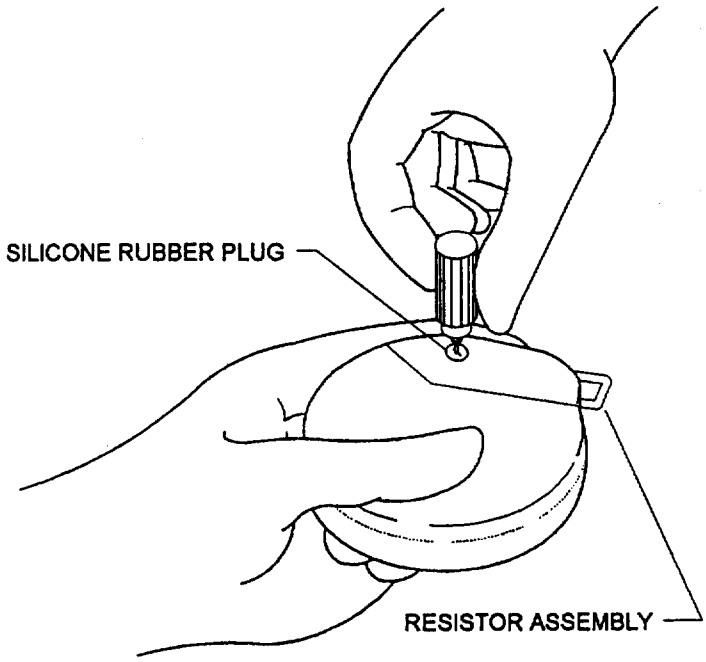
a. Remove the Lead connectors from the NCP Pulse Generator.

b. Insert the connector pins of the resistor assembly into the Lead receptacles in the NCP Pulse Generator header. (Because the resistor assembly has no polarity, either connector pin can be inserted into either Lead receptacle of the NCP Pulse Generator.) If the set screws need to be loosened for the insertion of the connector pins, avoid backing the screws out completely by using only two counterclockwise turns. Access the set screws for both Lead connector receptacles by carefully inserting the tip of the hex screwdriver through the slits in the silicone rubber plugs located on each side of the header.

Note: Fully insert the hex screwdriver into the set screws whenever you are tightening or loosening the set screws.

c. When the resistor assembly is in place tighten the set screw until the hex screwdriver begins to ratchet. See Figure 11.

Figure 11. Connecting the Resistor Assembly{tc "Fig. 9 Connecting the Resistor Assembly" \f g}



d. Perform the PRE-IMPLANT diagnostics as described in the Model 250 Programming Software Physician's Manual and verify that the Lead Impedance reads "OK". If any other status readings appear, verify that the resistor is adequately secured and repeat PRE-IMPLANT diagnostics. If repeated PRE-IMPLANT Lead Impedance diagnostic does not read "OK", do not implant the NCP Pulse Generator. Contact Cyberonics and return the NCP Pulse Generator along with a completed Returned Product Report.

e. Remove the resistor assembly by inserting the hex screwdriver through the silicone rubber plugs and turning the set screws one turn counterclockwise, again taking care not to back the set screws out completely.

12.1.5 Follow-up Information

12.1.5.1 Guidelines for Patient Follow-up

During the first few weeks following implantation, the patient should be seen to confirm wound healing and proper Pulse Generator operation. It is recommended that Pulse Generator output current be programmed to 0 mA for the first two weeks after implant.

At initial programming, Cyberonics recommends starting at nominal parameters (0 mA) and slowly increasing output current in 0.25 mA steps until the patient's voice shows signs of hoarseness. Patients who are receiving replacement generators should also be started off at

nominal parameters with 0.25 mA step increases to allow re-accommodation. Cyberonics recommends that testing of the magnet output be performed while the patient is still in the physician's office to ensure tolerability of the magnet output. The magnet output should be programmed, if necessary, at each visit to a level which produces hoarseness or tingling in the patient's neck. Some patients have reported it is easier to verify daily that stimulation is being delivered if the magnet output current is set to one step above normal stimulation settings. This slightly higher output current is intended to allow patients who have accommodated to normal stimulation to recognize or perceive the magnet stimulation thereby confirming device function.

At each visit the NCP Pulse Generator should be interrogated using the appropriate version of the Model 250 Programming Software. After reprogramming and/or diagnostics testing, data should be printed out and filed (see the Model 250 Programming Software Physician's Manual for instructions on printing out data). These data can be used for comparison with the patient's diary to evaluate NCP System therapy, to confirm proper NCP System function, and to assess the need for reprogramming.

The subsequent follow-up schedule and the nature of each examination should be determined by the physician on the basis of patient response to and tolerance of the implant. In all other respects, follow-up should be performed in accordance with standard practice for patients having seizures.

12.1.5.2 Patient Identification

Included with the NCP Pulse Generator is a Patient Identification Card which **must** be completed with the top, white copy returned to Cyberonics. This information, as required by government agencies, will become part of the Cyberonics' registry of implantees and will be used as a permanent record of implant recipient information. In addition to the form, a wallet-sized card is enclosed which contains information about the NCP Pulse Generator. The patient should carry this card at all times.

12.1.5.3 End-of-Service and Replacement Information

Cyberonics recommends that patients be instructed to manually activate the Pulse Generator with a magnet on a daily basis for the purpose of testing for the presence of stimulation. The most common reason for the absence of stimulation is battery depletion, although there may be other reasons. The Magnet Output should be programmed to a level sufficient to cause definite tingling or a voice change. Patients should be instructed to call the physician when they notice that magnet activation does not cause a sensation.

The NCP Pulse Generator battery is expected to last up to 5 years, but its lifetime is highly dependent on programmed parameters and Lead impedance (see Table 11). Immediately prior to end of service, the NCP Pulse Generator may provide unscheduled stimulation. The stimulation amplitude is at or below the programmed output amplitude. When end of service occurs, the Pulse Generator does not deliver any output, the patient will not feel the stimulus, and communication with the Pulse Generator will not be possible.

⚠ At this time seizure frequency and/or seizure intensity and/or seizure duration could increase, in some cases to levels greater than those reported before stimulation.

The NCP Pulse Generator has no distinct end-of-service warning and stimulation may stop abruptly. However, operation can be verified by either the physician or patient through magnet activation when output is programmed to a level sufficient to cause strong tingling and/or hoarseness. Failure to detect stimulation after activation with a magnet may indicate end-of-service or high Lead impedance. If this occurs, the physician should try to reset the Pulse Generator following instructions in the "Resetting the Microprocessor using a Magnet and the Programming Wand" section of this manual. If the NCP Pulse Generator cannot be reset, replacement is indicated.

Cyberonics recommends prompt replacement of the Pulse Generator at end of battery life. Prompt replacement will minimize the relapse in seizure control that would be expected when therapy has been withdrawn.

A Pulse Generator explanted for any reason should not be reimplanted. An explanted Pulse Generator should be returned to Cyberonics in a sealed pouch or container for analysis and disposal, accompanied by a completed Returned Product Report form. The pouch or container should be marked with the appropriate biohazard warning.

12.2 Physician Training/Information

Prescribing physicians are encouraged to contact Cyberonics and request a referal to a physician experienced in the operational characteristics and function of the NCP device prior to prescribing use of the device for the first time. All NCP System programming should be by or under the supervision of a physician familiar in the use of the programming software.

Initial (starting -- new or following Pulse Generator replacement) treatment output current should be set at the lowest setting (0.25 mA). Subsequent and all future device settings should be made in 0.25 mA increments up to the desired treatment level (see Individualization of Treatment section of this manual).

Implanting physicians using the NCP System should be thoroughly familiar with all associated materials including:

- Product labeling for the NCP Pulse Generator, Leads and accessories;
- Training manual & brochure;
- Electrode practice fixture - a device used to practice placement of the NCP Lead Coil around the vagus nerve; and video tapes on the proper implantation technique.

In the event intolerable adverse events are reported, physicians should always try reducing the output current (mA) as a means of eliminating or reducing the severity of a complaint. Additionally, physicians should instruct patients or caregivers on the application of the magnet to turn the NCP Pulse Generator OFF (output current 0 mA) should an adverse event become intollerable.

Cyberonics®
DEVICES FOR EPILEPSY

NeuroCybernetic Prosthesis (NCP®) Programming Software

Model 250
Version 3.8

Physician's Manual

NOTE: This manual only contains information on the use of the NCP Programming Software Version 3.8. Physician should refer to the NCP Pulse Generator Manual for important prescribing and safety information

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Description and Use

General Description

The Cyberonics® Model 250 Version 3.8 NeuroCybernetic Prosthesis (NCP®)[1] Programming Software enables interrogation and programming of the Cyberonics Model 100 NCP Pulse Generator via the Cyberonics Model 200 NCP Programming Wand. The Programming Software has been validated for use on a Compaq Contura Aero 4/25 running MS DOS 6.2 with the disk cacheing software disabled. ⚠ Cyberonics recommends that the programming software be used on a computer dedicated only for programming the NCP system.

The Programming Software can be loaded on an IBM®[2]-compatible personal computer running MS DOS versions 3.3 or 5.0 or DR DOS 6.0, which has at least 640K memory, a 3.5-inch floppy disk drive, a hard disk with 2 megabytes of free memory, and a serial communication port located at COM1. The software has not been tested for use with later versions of MS DOS, DR DOS, or with the MS WINDOWS operating system. ⚠ **Programming of the Model 100 Pulse Generator is not possible on Pentium based personal computers.** ⚠ Only computers which meet the requirements of IEC950 or UL1950 may be used with the Model 200 NCP Programming Wand. A printer is required for retrieving and printing data. Capabilities include interrogation and revision of the NCP Pulse Generator's programmed parameters, assessment of generator function, and retrieval of generator operating history. Screen displays provide prompts and messages to aid in programming and interrogating the NCP Pulse Generator.

The communications system is designed to minimize the possibility of misprogramming or "phantom" programming (inadvertent programming via environmental sources of electromagnetic interference). During a programming event each parameter is programmed and verified individually.

⚠ **Note:** The Programming Software may not be compatible with all NCP Pulse Generators. If an incompatibility message appears, contact Cyberonics, Inc.

See the Cyberonics Model 200 NCP Programming Wand Physician's Manual for a description of the Programming Wand. See the Cyberonics Model 100 NCP Pulse Generator Physician's Manual for a complete description of the NCP Pulse Generator, its indication for use, and its operation.

Symbols and Definitions

⚠ Notice for reader to pay special attention to following details

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1 Cyberonics and NCP are registered trademarks of Cyberonics, Inc. The NCP Programming Software is copyrighted.

2 IBM is a registered trademark of International Business Machines, Inc.

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⊗ Not suitable for connection to a public telecommunications network or telephone equipment

LOT Denotes batch code

In this manual, keyboard keys are indicated by symbols (for example, ENTER indicates the Enter key), text to be typed on the keyboard and entered is shown in quotation marks, and text displayed on the screen is shown in upper case letters.

Indications for Use

The Model 250 Programming Software is indicated for use only with the Model 100 NCP Pulse Generator and Model 200 NCP Programming Wand.

Preparing to Use the Programming Software

Preparing for programming operations involves connecting the hardware, loading the Programming Software, and accessing the software, which is provided on a 3.5-inch floppy disk. See the Physician's Manual for the Model 200 Programming Wand for instructions on connecting the hardware⊗.

Optional Installation of Software onto Hard Disk Drive C:

1. Insert the installation disk into drive A or B.
2. Access the disk (type "A:" or "B:").
3. Type "INSTALL C:" at the prompt A:\ or B:\.
4. Follow the on-screen directions.

Starting the Program (from any disk drive)

1. Access the disk drive containing the software. ⚠ If the Print Database feature of the software is to be used, power to the printer must be ON prior to starting the program.
2. Change to the \CYBERON.ICS subdirectory by typing "CD \CYBERON.ICS" and press ENTER.
3. Type "CYPROG" and press ENTER. This action initializes the program, which begins with a software self-test.
4. After completion of the self-test, follow the on-screen directions and enter the correct date and time, if necessary. If the date and time entry screen does not appear, see "Precautions and Troubleshooting."

After this point, operating the system is self-explanatory, with messages and prompts appearing at necessary points to instruct the user regarding the next step or to inform the user of what is occurring. Please review the menu screens throughout this manual before proceeding.

To ensure consistency and simplicity, the following conventions are used throughout the software program:

- ↑ and ↓ can be used to move the cursor around the screen to select available options. Alternatively, the number to the left of a menu item can be entered to make the selection.
- Any time a selection requires communication with the Pulse Generator, a message will appear prompting the user to place the programming wand over the Pulse Generator and press ENTER to continue.
- When a field is selected, it will appear within a highlighted block on the screen.
- To activate an operation, field, parameter, etc., press ENTER.
- Any time the F1 box appears at the bottom of a screen, the F1 key may be pressed to display a HELP message.
- An audible tone (double beep) signals successful completion of a programming operation; if this does not occur, a message will be displayed indicating a problem and/or remedial action.
- The DATA/RCVD light on the wand illuminates during successful programming or interrogation. Reposition the programming wand if the light does not blink after approximately 8 seconds.
- ESC always returns the user to the previous screen.

Checking for Programming Interference

⚠**Note**: The DATA/RCVD light on the wand can also illuminate in the presence of electromagnetic noise or interference. The Physician's Manual for the Model 200 Programming Wand describes how to detect this type of interference. If the presence of electromagnetic interference or noise is suspected, the user must be certain to verify that the programming or interrogation occurred by reviewing the Programmable Parameter Entry screen shown in Fig. 2.

Using the Software

Specific instructions for using the Model 250 NCP Programming Software Version 3.8 appear on the screen during various procedures. The following information provides an overview of each of the six functions shown on the software's Main Menu (see Fig. 1).

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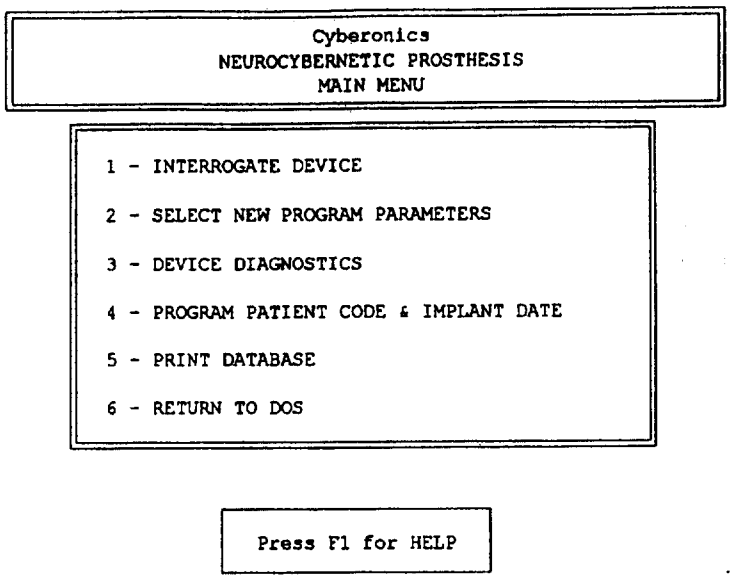

Fig. 1. Main Menu{tc "Fig. 1. Main Menu" \f g}

Interrogating the NCP Pulse Generator

Selection of INTERROGATE DEVICE is the first operation in any programming session except when PRINT DATABASE is chosen initially. Cyberonics also recommends interrogating the NCP Pulse Generator as the last step of any programming session. This allows the physician to verify correct settings for each parameter. The interrogating function provides a display of current operating parameters. To interrogate the Pulse Generator, select INTERROGATE DEVICE with the cursor. This block will be highlighted; upon successful Pulse Generator interrogation, a PROGRAMMABLE PARAMETER ENTRY SCREEN is displayed with the currently programmed parameter values displayed in the CURRENT column (see Fig. 2).

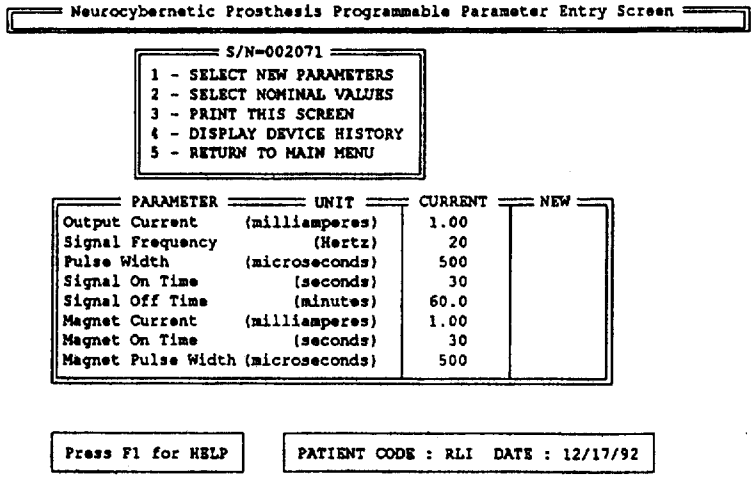

Fig. 2. Programmable Parameter Entry Screen{tc "Fig. 2. Programmable Parameter Entry Screen" \f g}

If the NCP Pulse Generator was previously programmed to a treatment time per day of less than 24 hours (using earlier versions of the Programming Software),

Pulse Generator interrogation attempts will result in the screen shown in Fig. 3. This screen provides instructions in case communication with the NCP Pulse Generator becomes impossible and provides notification that the next time the Pulse Generator is programmed, treatment time per day will automatically be set to 24 hours per day.

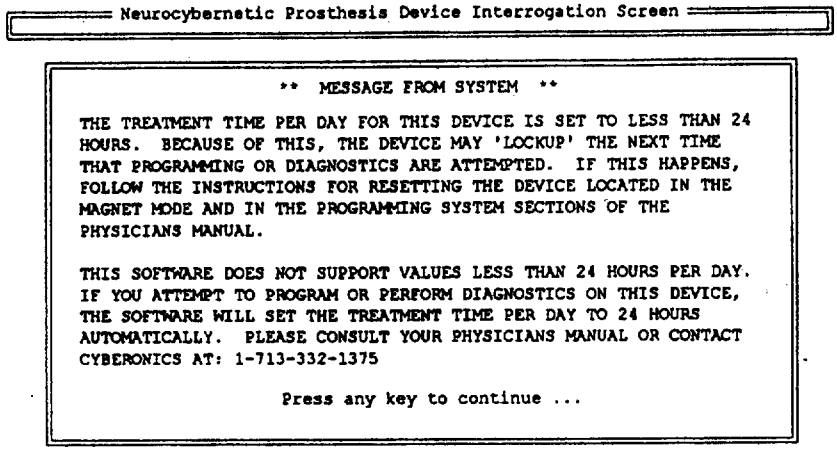

Fig. 3. Interrogation Instructions for NCP Pulse Generators Programmed to Less than 24 Hours Per Day{tc "Fig. 3. Interrogation Instructions for NCP Pulse Generators Programmed to Less than 24 Hours Per Day" \f g}

Selecting New Program Parameters

When SELECT NEW PROGRAM PARAMETERS is chosen from the Main Menu, or after an interrogation is completed, a screen will appear that is used to modify the NCP Pulse Generator's programmable parameters. Table 1 lists the settings available for each programmable parameter for this version of the Model 250 Programming Software. Treatment time per day and treatment start delay time are non-programmable.

Table 1. Programmable Parameters for the Model 100 NCP Pulse Generator{tc "Table 1. Programmable Parameters for the Model 100 NCP Pulse Generator" \f t}

Programmable Parameters	Settings
Output Current:	0.0-12 milliamperes (in 0.25-milliampere steps)
Frequency:	1, 2, 5, 10, 20, 30, 40-145 Hertz
Pulse Width:	130, 250, 500, 750, 1000 microseconds
Signal ON Time:	7, 14, 21 sec.; 30 to 270 sec. (in 30 sec. steps).
Signal OFF Time:	0.2, 0.3, 0.5, 0.8, 1.1, 1.8, and 3 min.; 5 to 180 min. (5-60 in 5 min. steps; 60-180 in 30 min. steps.)

⚠**Note: Do not use frequencies of 5 Hz and below for long-term stimulation. Because these frequencies always generate an electromagnetic trigger signal, their use results in excessive battery depletion of the implanted NCP Pulse Generator and**

should therefore be used for only short periods of time. When frequencies of 5 Hz and below are selected, the message shown in Fig. 4 will appear.

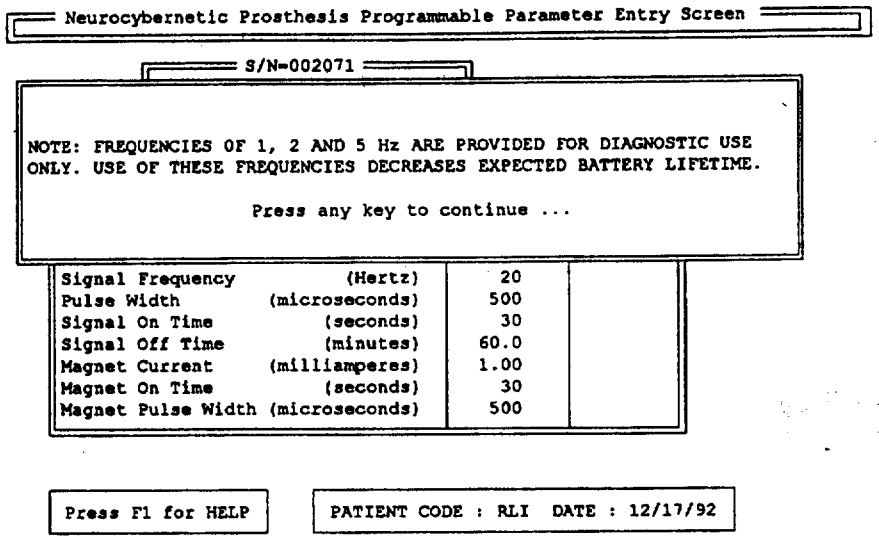

Fig. 4. Screen for Frequencies of 5 Hz or Less{tc "Fig. 4. Screen for Frequencies of 5 Hz or Less" \f g}

The PROGRAMMABLE PARAMETER ENTRY SCREEN (see Fig. 2) displays a menu permitting the user to select new or nominal values, to print the screen, to display a device history screen, or to return to the MAIN MENU. Because PRINT THIS SCREEN and RETURN TO MAIN MENU are self explanatory, only SELECT NEW PARAMETERS, SELECT NOMINAL VALUES, and DISPLAY DEVICE HISTORY are described below.

To select new parameter values:

1. Choose SELECT NEW PARAMETERS with the cursor.
2. Use ↑ or ↓ to move to the parameter to be changed. Select this parameter by pressing ENTER. A column at the right of the screen will appear showing available values. See Fig. 5. The cursor will be positioned at the present value for this parameter.

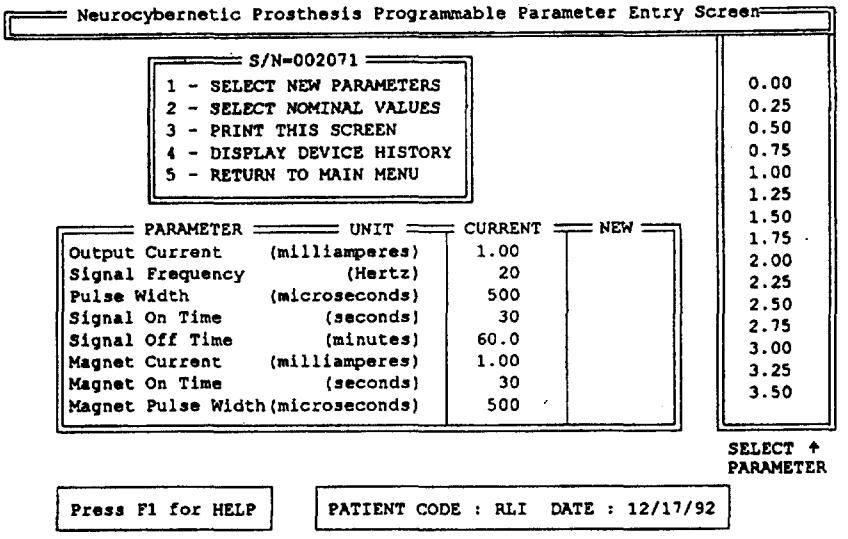

Fig. 5. Programmable Parameter Entry Screen with Parameter Value Column{tc "Fig. 5. Programmable Parameter Entry Screen with Parameter Value Column" \f g}

3. Use ↑ or ↓ to move up or down this column until a desired value is reached. Press ENTER to select the value and move it into the NEW column. ← or ESC can be used to return to the parameter list without entering any new values.
4. Repeat Steps 2 and 3 for each desired parameter value to be reprogrammed.
5. The PROGRAM/ABORT menu appears at the top right of the screen when the cursor is moved beyond the bottom of the parameter list. Highlight PROGRAM and press ENTER to indicate that the selected parameter values are to be transmitted to the NCP Pulse Generator.
6. To transmit the parameter changes to the NCP Pulse Generator, place the programming wand over the NCP Pulse Generator and program the new values by pressing ENTER.

If the NCP Pulse Generator fails to accept all programmed changes, a partial program message screen will appear providing RETRY or ABORT options. If ABORT is chosen, only existing values and those values which were programmed will be placed into the CURRENT column. Newly selected values that have not been programmed will remain in the NEW column.

Incomplete or partial programming can occur in the presence of electromagnetic interference (noise) or if proper positioning of the programming wand was interrupted during the programming sequence. See the "Precautions and Troubleshooting" section of this manual.

To select nominal values:

1. Choose SELECT NOMINAL VALUES. Nominal values will appear in the NEW column for each parameter and the PROGRAM/ ABORT menu will appear at the top right of the screen (see Fig. 6).
2. Highlight PROGRAM and press ENTER to indicate that the nominal values are to be transmitted to the NCP Pulse Generator.
3. To transmit nominal values, place the programming wand over the NCP Pulse Generator and program the nominal values by pressing ENTER.

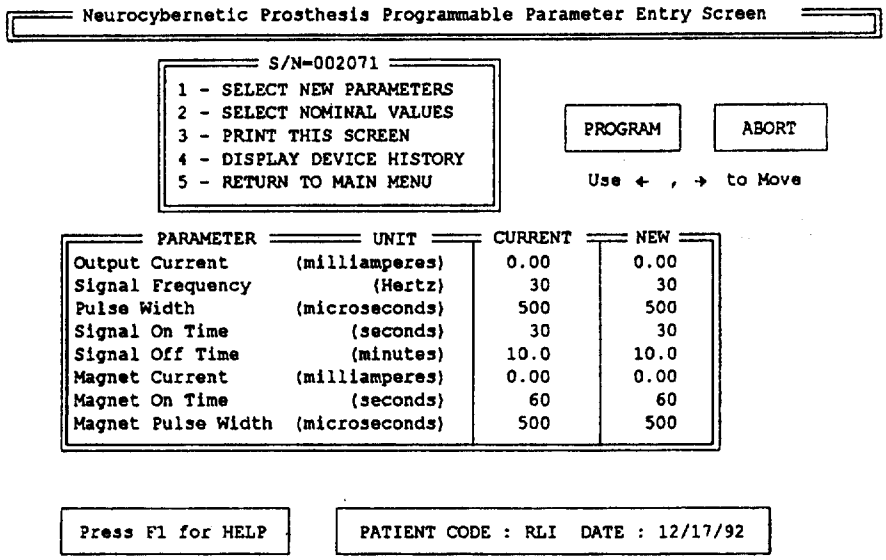

Fig. 6. Programmable Parameter Entry Screen With Nominal Values Selected{tc "Fig. 6. Programmable Parameter Entry Screen With Nominal Values Selected" \f g}

To display DEVICE HISTORY:

Select DISPLAY DEVICE HISTORY. The DEVICE HISTORY REPORT screen, PAGE 1, will appear (see Fig. 7A).

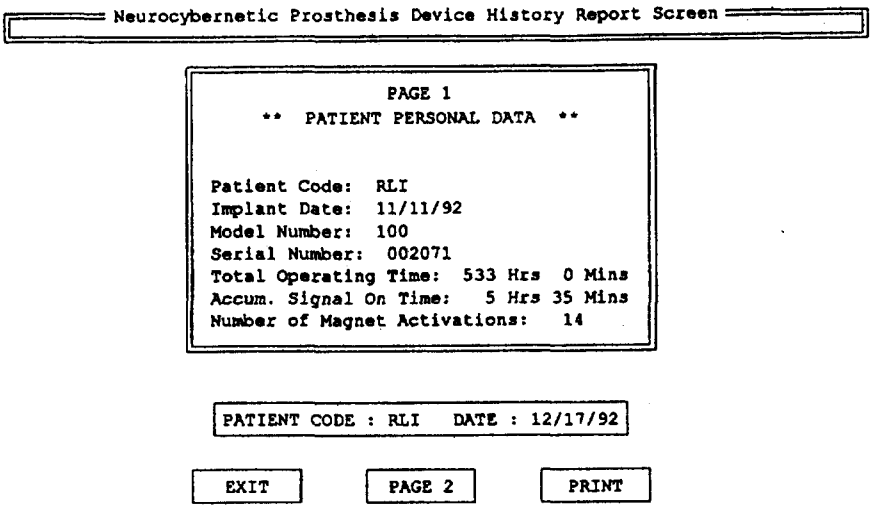

Fig. 7A. Device History Report Screen, PAGE 1{tc "Fig. 7A. Device History Report Screen, PAGE 1" \f g}

To view the date and time (to the nearest hour) of the last 15 magnet activations:

Select PAGE 2 at the bottom of the screen (Fig. 7A) to display the PAGE 2 screen on which the magnet activations will be listed (see Fig. 7B).

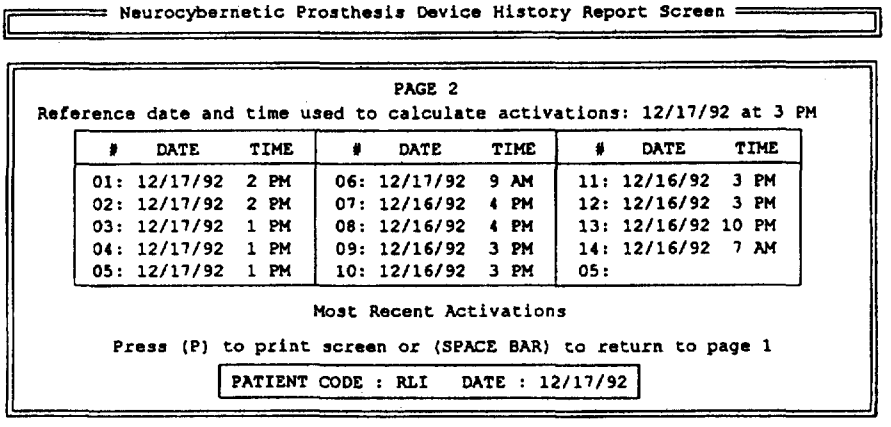

Fig. 7B. Device History Report Screen, PAGE 2{tc "Fig. 7B. Device History Report Screen, PAGE 2" \f g}

To perform other operations accessible from the PROGRAMMABLE PARAMETER ENTRY SCREEN, press the space bar to return to PAGE 1 of the DEVICE HISTORY REPORT SCREEN. Select EXIT and then press ENTER to return to the PROGRAMMABLE PARAMETER ENTRY SCREEN.

Device Diagnostics

When DEVICE DIAGNOSTICS is selected from the MAIN MENU, the DEVICE DIAGNOSTICS SCREEN will appear. This screen, which is shown in Fig. 8, enables the performance of function assessments or diagnostic tests. Several types of diagnostics are available: NORMAL MODE DIAGNOSTICS, MAGNET MODE

DIAGNOSTICS, PRE-IMPLANT TEST, and LEAD TEST. The NORMAL MODE, MAGNET MODE, and LEAD TEST diagnostics, as well as the DC-DC CONVERTER CODE, can be used at follow-up visits to ascertain lead impedance status. The PRE-IMPLANT TEST is used to verify proper Pulse Generator operation (see Fig. 9). The LEAD TEST is used during implantation and routine follow-up to assess nerve-electrode impedance.

⚠**Note**: During LEAD TEST Diagnostics, the output current is 1.0 mA and the pulse width is 500 μsec. Patients whose Pulse Generator output is normally less than these values may experience increased sensation, coughing, flushed face, or other adverse effects. See Model 100 Physician's Manual for complete description of possible adverse events.

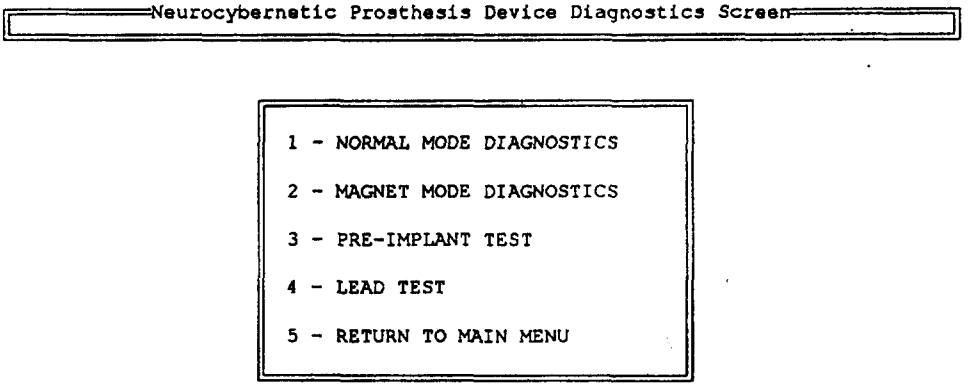

Fig. 8. Device Diagnostics Screen{tc "Fig. 8. Device Diagnostics Screen" \f g}

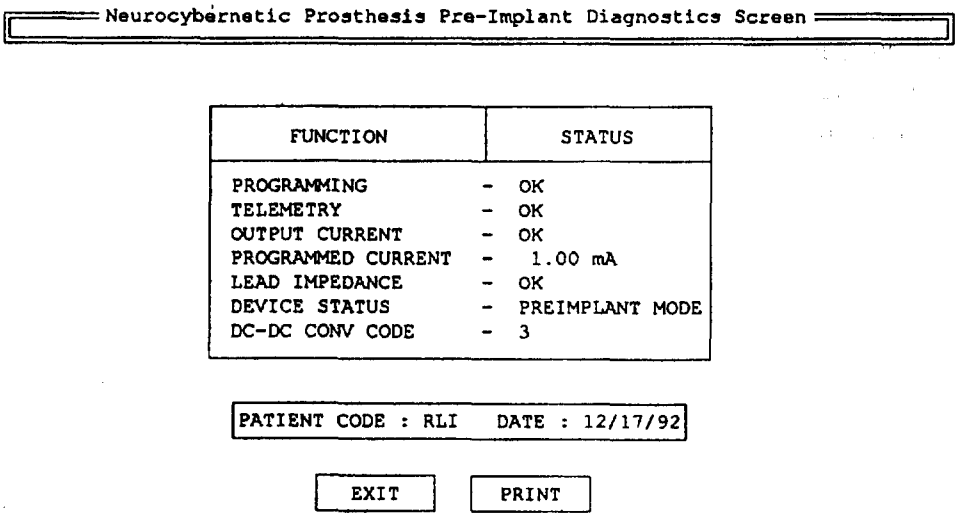

Fig. 9. Pre-Implant Diagnostics Screen{tc "Fig. 9. Pre-Implant Diagnostics Screen" \f g}

Note: To obtain accurate information from the DEVICE DIAGNOSTICS, program the NCP Pulse Generator to values in the ranges shown below for both normal and magnet modes:

OUTPUT CURRENT/ MAGNET CURRENT	>0.5 mA
FREQUENCY	>10 Hz
SIGNAL/MAGNET ON TIME	≥30 sec

The software screen for each diagnostic mode will show status readings for these functions: PROGRAMMING, TELEMETRY, OUTPUT CURRENT, PROGRAMMED CURRENT, LEAD IMPEDANCE, DEVICE STATUS, and DC-DC CONV CODE. Possible readings and significance of status readings for each of these functions are shown in Tables 2 through 8. DC-DC CONV CODE stands for DC-DC Converter code. Its use is explained in Tables 8 and 9.

Table 2. Device Diagnostic Screen STATUS readings for PROGRAMMING{tc "Table 2. Device Diagnostic Screen STATUS readings for PROGRAMMING" \f t}

PROGRAMMING Status Reading	Significance
OK	Programming operation performed successfully.
FAULT	Error occurred during programming due to improper wand positioning, electromagnetic interference, or depleted NCP Pulse Generator or wand batteries

Table 3. Device Diagnostic Screen STATUS readings for TELEMETRY{tc "Table 3. Device Diagnostic Screen STATUS readings for TELEMETRY" \f t}

TELEMETRY Status Reading	Significance
OK	Telemetry operation performed successfully.
FAULT	Error occurred during telemetry due to improper wand positioning, electromagnetic interference, or depleted NCP Pulse Generator or wand batteries

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Table 4. Device Diagnostic Screen STATUS readings for OUTPUT CURRENT{tc "Table 4. Device Diagnostic Screen STATUS readings for OUTPUT CURRENT" \f t}

OUTPUT CURRENT Status Reading	Significance
***	1. MAGNET MODE diagnostics found Pulse Generator in STANDBY MODE. Use the magnet to reactive stimulation. Retry diagnostics. 2. NORMAL MODE diagnostics found parameters are not within required ranges.
OK	Current is being output at the programmed value
LIMIT	PROGRAMMED CURRENT is possibly not being delivered at the specified level (possibly limited by battery voltage, lead impedance, or other reason). Reprogram the NCP Pulse Generator to a lower output current and a wider pulse width.

Table 5. Device Diagnostic Screen STATUS readings for PROGRAMMED CURRENT{tc "Table 5. Device Diagnostic Screen STATUS readings for PROGRAMMED CURRENT" \f t}

PROGRAMMED CURRENT Status Reading	Significance
PROGRAMMED CURRENT setting	Shows the current at which the DIAGNOSTIC TEST was run. For LEAD TEST and PRE-IMPLANT TEST, the software automatically programs the NCP Pulse Generator to 1.00 mA. After the LEAD TEST is run, the NCP Pulse Generator will be reprogrammed to the pre-test output current setting. After the PRE-IMPLANT TEST, the NCP Pulse Generator will be programmed to nominal parameter settings.
****	The Pulse Generator is in STANDBY MODE and is not delivering stimulation.

Table 6. Device Diagnostic Screen STATUS readings for LEAD IMPEDANCE{tc "Table 6. Device Diagnostic Screen STATUS readings for LEAD IMPEDANCE" \f t}

LEAD IMPEDANCE Status Reading	**Significance**
OK	Impedance is within acceptable operating range.
HIGH	Impedance is higher than expected. Indicates a possible discontinuity of the lead or fibrosis between the nerve and lead.
UNKNOWN	Impedance cannot be assessed. Reprogram NCP Pulse Generator for parameters in the ranges in NOTE under Fig. 9.
LOW	Impedance is lower than expected

Table 7. Device Diagnostic Screen STATUS readings for DEVICE STATUS{tc "Table 7. Device Diagnostic Screen STATUS readings for DEVICE STATUS" \f t}

DEVICE STATUS Status Reading	**Significance**
NORMAL MODE	NCP Pulse Generator is operating in NORMAL MODE stimulation parameters
MAGNET MODE	NCP Pulse Generator is operating in MAGNET MODE stimulation parameters
LEAD TEST MODE	NCP Pulse Generator is operating in LEAD TEST parameters.
PRE-IMPLANT MODE	NCP Pulse Generator is operating in PRE-IMPLANT TEST parameters.
STANDBY	Pulse Generator is not delivering stimulation. If shown during MAGNET MODE DIAGNOSTICS, retry the test using the magnet. If displayed during other diagnostic modes, contact Cyberonics.

Table 8. Device Diagnostic Screen STATUS readings for DC-DC CONV CODE{tc "Table 8. Device Diagnostic Screen STATUS readings for DC-DC CONV CODE" \f t}

DC-DC CONV CODE Status Reading	**Significance**
0,1,2,3,4,5,6, or 7	Although this function is displayed on all diagnostic screens, it is most useful for estimating lead impedance using the LEAD TEST. Each code represents a different lead impedance range. See Table 9.

Table 9. DC-DC Converter Codes With Corresponding Estimated Lead Impedance{tc "Table 9. DC-DC Converter Codes With Corresponding Estimated Lead Impedance" \f t}

DC-DC Converter Code	**Estimated lead impedance when DC-DC CONVERTER CODE is transmitted from NCP Pulse Generator:**
0	<1 k ohm
1	1 to 3 k ohms
2	3 to 5 k ohms
3	5 to 8 k ohms
4	8 to 11 k ohms
5	11 to 16 k ohms
6	16 to 20 k ohms
7	≥20 k ohms

On the diagnostics results screens, the PROGRAMMED CURRENT field indicates the OUTPUT CURRENT used to perform the diagnostic test. For LEAD TEST and PRE-IMPLANT TEST, the Programming Software automatically programs the NCP Pulse Generator to 1.00 mA and 500 μsec. Patients whose Pulse Generator output current is normally less than these values may experience increased sensation, coughing, flushed face, or other effects. See Model 100 Physician's Manual for complete description of possible adverse events. The OUTPUT CURRENT and LEAD IMPEDANCE are assessed and their status displayed. (See Table 9 for a listing of DC-DC CONVERTER CODES and corresponding estimated impedances). Because delivery of stimulation is required for diagnostic data collection, the Pulse Generator will automatically be programmed ON at the initiation of a diagnostic interrogation, except for MAGNET MODE DIAGNOSTICS. If the DEVICE STATUS indicates STANDBY, then the Pulse Generator was not stimulating, and the diagnostic test must be repeated. ⚠Cyberonics recommends interrogating the Pulse Generator after any diagnostics in order to verify parameter settings.

For MAGNET MODE DIAGNOSTICS, just prior to placing the Programming Wand over the Pulse Generator, apply the magnet over the NCP Pulse Generator for at least one second and then immediately remove it from the area over the Pulse Generator. This action is described in the Magnet Mode section of the Model 100 NCP Pulse Generator Physician's Manual and will ensure the effective operation of the device.

In contrast to the lead impedance, the stimulation output current should be evaluated with NORMAL MODE DIAGNOSTICS. If this test indicates the OUTPUT CURRENT is LIMIT, the NCP Pulse Generator may not deliver the PROGRAMMED OUTPUT CURRENT. Reasons for failure to deliver the PROGRAMMED OUTPUT CURRENT include a break in the Lead, high lead impedance and low battery voltage.

If the PROGRAMMING and TELEMETRY functions show the FAULT message, an error has occurred during a procedure. This may result from improper positioning of the Model 200 Programming Wand over the Model 100 NCP Pulse Generator, EMI (electromagnetic interference) or noise being sensed by the system, or a

depleted battery in the wand or NCP Pulse Generator. Information on overcoming electromagnetic interference, repositioning the Programming Wand, and wand battery problems can be found in the Model 200 Programming Wand physician's manual. The Model 100 NCP Pulse Generator Physician's Manual explains how to detect if a NCP Pulse Generator has reached end-of-service.

⚠**Note**: If a FAULT message occurs, return to the main menu and perform a device interrogation to verify that the Pulse Generator is programmed to the correct parameters. The diagnostic test was not completed, so, if desired, perform the diagnostic test again.

Programming Patient Code and Implant Date

By returning to the MAIN MENU and selecting PROGRAM PATIENT CODE & IMPLANT DATE, it is possible to choose and enter a three-character patient identification code and the implant date via the PATIENT CODE & DATE ENTRY SCREEN (see Fig. 10). These will be stored in the NCP Pulse Generator, becoming a permanent part of the Device History.

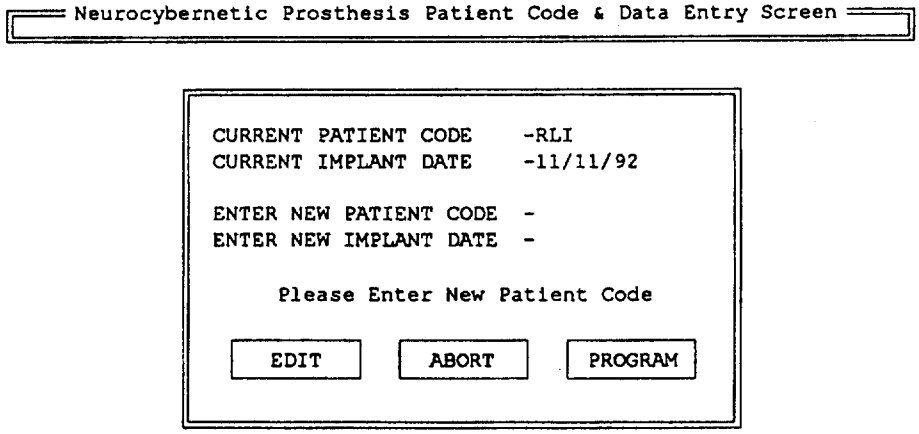

Fig. 10. Patient Code and Date Entry Screen{tc "Fig. 10. Patient Code and Date Entry Screen" \f g}

Printing Databases

Every time an interrogation or programming is successfully accomplished, the parameters are added to the existing parameter database. Another database holds Pulse Generator diagnostic information, while a third holds magnet activation times and dates. These databases are saved by the Model 250 Programming Software onto the disk and cannot be viewed from the screen. To access these databases, return to the MAIN MENU and select PRINT DATABASE. Each database may be printed in full, sorted by serial number, patient code, or by date. (All data for and after a given date are printed.) This function may be selected without first interrogating the Pulse Generator. ⚠ Power to the printer must be ON prior to starting the program or an error may occur. See Fig. 11 for the PRINT FUNCTION SCREEN. Simultaneous printing and programming should be avoided because of possible interference with communication.

Neurocybernetic Prosthesis Print Function Screen

```
1 - PRINT ALL PROGRAMMED PARAMETERS
2 - PRINT PARAMETERS BY DATE
3 - PRINT PARAMETERS BY SERIAL NUMBER OR PATIENT CODE
4 - PRINT ALL DIAGNOSTIC VALUES
5 - PRINT DIAGNOSTIC VALUES BY DATE
6 - PRINT DIAGNOSTICS BY SERIAL NUMBER OR PATIENT CODE
7 - PRINT ALL MAGNET VALUES
8 - PRINT MAGNET VALUES BY DATE
9 - PRINT MAGNET VALUES BY SERIAL NUMBER OR PATIENT CODE
0 - RETURN TO MAIN MENU
```

Fig. 11. Print Function Screen{tc "Fig. 11. Print Function Screen" \f g}

Fig. 12 provides an example of an Interrogate and Program Summary printout sorted by date.

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Interogation and Program Summary

ID	Serial Number	Stim mA	Stim mA	PW usec	On Sec	Off Min	Mag mA	Mag Sec	Time	Date	P I	Tot Hrs	Acc Hrs	Ac Mn
LI	002071	1.00	20	500	30	60	1.00	30	15:26	12/17/92	I	532	5	35
LI	002071	1.00	20	500	30	60	1.00	30	15:27	12/17/92	I	532	5	35
LI	002071	1.00	20	500	30	60	1.00	30	15:29	12/17/92	I	532	5	35
LI	002071	1.00	20	500	30	60	1.00	30	15:31	12/17/92	I	532	5	35
LI	002071	1.00	20	500	30	60	1.00	30	15:42	12/17/92	I	533	5	35
LI	002071	1.25	20	500	30	60	1.00	30	15:45	12/17/92	P	533	5	35
LI	002071	0.00	30	500	30	10	0.00	60	16:00	12/17/92	I	533	5	38
LI	002071	0.00	30	500	30	10	0.00	60	16:01	12/17/92	P	533	5	38
LI	002071	1.50	30	500	30	10	0.00	60	16:03	12/17/92	P	533	5	38
LI	002071	0.50	10	500	30	10	0.00	60	16:04	12/17/92	P	533	5	38
LI	002071	0.25	10	500	30	10	0.25	60	16:06	12/17/92	P	533	5	41
LI	002071	0.00	10	500	30	10	0.00	30	16:06	12/17/92	P	533	5	41
LI	002071	0.00	5	500	30	10	0.00	30	16:07	12/17/92	P	533	5	41
LI	002071	0.00	30	500	30	10	0.00	30	16:09	12/17/92	P	533	5	41
LI	002071	0.00	30	500	30	10	0.00	30	16:50	12/17/92	I	534	5	45
LI	002071	0.00	30	500	30	10	0.00	30	16:55	12/17/92	I	534	5	46
LI	002071	0.00	30	500	30	10	0.00	60	17:08	12/17/92	I	534	5	47
LI	002071	0.00	30	500	30	10	0.00	60	17:20	12/17/92	I	534	5	48
LI	002071	0.00	30	500	30	10	0.00	60	17:24	12/17/92	I	534	5	49
LI	002071	0.00	30	500	30	10	0.00	60	17:24	12/17/92	I	534	5	49
LI	002071	1.00	30	500	30	10	1.00	60	17:26	12/17/92	P	534	5	49
LI	002071	1.00	30	500	30	10	1.00	60	17:32	12/17/92	I	534	5	50
LI	002071	0.00	30	500	30	10	0.00	60	14:20	12/18/92	I	555	6	59
LI	002071	0.00	30	500	30	10	0.00	60	14:56	12/18/92	I	556	7	1
LI	002071	0.00	30	500	30	10	0.00	60	14:59	12/18/92	I	556	7	1
JW	000461	1.50	30	1000	90	180	2.00	60	16:24	12/18/92	I	3748	313	35
JW	000461	1.50	30	1000	90	180	2.00	60	17:32	12/18/92	I	3749	313	36
JW	000461	1.50	30	1000	90	180	2.00	60	17:34	12/18/92	I	3749	313	36
JW	000461	1.00	30	1000	90	180	2.00	60	17:35	12/18/92	P	3749	313	36
JW	000461	1.00	30	130	30	180	1.00	30	17:36	12/18/92	P	3749	313	36
JW	000461	1.00	30	130	30	180	1.00	30	17:36	12/18/92	I	3749	313	37
SS	000555	0.25	30	130	30	180	0.25	30	09:17	12/21/92	I	3813	314	5
SS	000555	0.25	30	130	30	180	0.25	30	09:21	12/21/92	I	3813	314	5
SS	000555	0.25	30	130	30	180	0.25	30	09:22	12/21/92	P	3813	314	5
LI	002071	0.00	30	500	30	10	0.00	60	09:25	12/21/92	I	622	10	38
LI	002071	0.00	30	500	30	10	0.00	60	09:41	12/21/92	I	622	10	38

Fig. 12. Interrogate and Program Summary Printout{tc "Fig. 12. Interrogate and Program Summary Printout" \f g}

Fig. 13 is an example of a Diagnostic Report, sorted by date.

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Diagnostics Report

PID	Serial Number	Time	Date	Telm	mA	DC	Impedance	Status
RLI	000461	14:43:12	12/14/92	OK	OK	0	UNKNOWN	NORMAL
RLI	000461	14:44:34	12/14/92	OK	LIMIT	7	UNKNOWN	MAGNET
		17:46:27	12/16/92	FAULT				
RLI	002071	17:47:46	12/16/92	OK	OK	3	OK	LEADTEST
RLI	002071	15:49:37	12/17/92	OK	OK	3	OK	NORMAL
RLI	002071	15:50:59	12/17/92	OK	OK	0	UNKNOWN	STANDBY
RLI	002071	15:52:59	12/17/92	OK	OK	3	OK	PREIMP
RLI	002071	15:55:02	12/17/92	OK	OK	3	OK	LEADTEST
RLI	002071	16:05:32	12/17/92	OK	OK		UNKNOWN	NORMAL
RLI	002071	16:50:56	12/17/92	OK	OK	0	UNKNOWN	NORMAL
RLI	002071	16:56:01	12/17/92	OK	OK	3	OK	PREIMP
RLI	002071	17:20:52	12/17/92	OK	OK	0	UNKNOWN	NORMAL
RLI	002071	17:25:25	12/17/92	OK	OK	0	UNKNOWN	NORMAL
RLI	002071	17:26:53	12/17/92	OK	OK	3	OK	NORMAL
RLI	002071	17:30:05	12/17/92	OK	OK	3	OK	NORMAL

Fig. 13. Device Diagnostic Report Printout{tc "Fig. 13. Device Diagnostic Report Printout" \f g}

Returning to DOS

Selecting RETURN TO DOS from the MAIN MENU returns the screen to the prompt for the disk from which the software was operating.

Maintenance, Handling, and Storage

The floppy disk should be handled and stored in the standard manner for such items. It should never be stored near a magnet. While no component of the system will withstand rough handling or abuse, no unusual handling precautions are necessary.

Precautions and Troubleshooting

This program functions on IBM®-compatible computers running MS-DOS (Version 3.3 or 5.0) or DR DOS Version 6.0, which have at least 640K memory and a serial communications port located at COM1. ⚠ Other operating systems, such as Windows, may affect the ability of the NCP Programming Software to function properly, and should not be in operation while the Model 250 software is being used. ⚠ Software that interferes with computer communication ports may affect the NCP Pulse Generator. Terminate and Stay Resident (TSR) programs, such as Sidekick, Norton Commander, and Print Spooler, should not be used with the Model 250 Software. They may interfere with communication or cause the program to fail. If an error message appears indicating communication difficulties, refer to the Troubleshooting section of the Cyberonics Model 200 Programming Wand Physician's Manual.

⚠ **Programming of the Model 100 Pulse Generator is not possible on Pentium based personal computers.**

⚠ On some computers, the use of SMARTDRV.EXE disk cacheing software has been known to interfere with diagnostic testing. SMARTDRV.EXE should be disabled if communication problems occur during diagnostic testing.

If attempts to start the program result in its termination and return to the DOS prompt, then the program self tests have found problems with the file length,

checksum, virus contamination, or have failed to find all the necessary database files. Names of the missing database files will be displayed on the screen. Attempt to re-install the program as described in "Installing the Software onto Hard Disk Drive C:".
⚠**NOTE:** Data previously added to the databases, such as interrogations, device diagnostics, and programming sessions, will be lost if the software is re-installed. Contact Cyberonics for assistance.

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Service

If any questions arise regarding use of the Model 250 NCP Programming Software, or any NCP System accessory contact Cyberonics at:

Cyberonics , Inc.
17448 Highway 3, Suite 100
Webster, TX USA 77598-4135
(281) 332-1375

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Cyberonics®
DEVICES FOR EPILEPSY

Bipolar Vagus Nerve Stimulation Lead

Model 300 Series

Physician's Manual

(for Serial Numbers above 4000)

NOTE: This manual only contains information on the use of the NCP Bipolar Vagus Nerve Stimulation Lead. Physician should refer to the NCP Pulse Generator Manual for important prescribing and safety information

REF 26-0002-4800 JULY 1997

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List of Figures

1. *BRIEF DEVICE DESCRIPTION*

The Cyberonics® Model 300 Series Bipolar Vagus Nerve Stimulation Leads are designed for use with the Cyberonics Model 100 NeuroCybernetic (NCP®)* Pulse Generator. These two devices form and comprise the implantable NCP System which delivers electrical signals to the vagus nerve for the purpose of reducing the frequency of epileptic seizures with partial onset.

The Model 300 Lead delivers the electrical signal from the NCP Pulse Generator to the vagus nerve. It is insulated with medical-grade silicone rubber and bifurcated at each end. The two helical electrodes and integral tether wrap around the vagus nerve while the connector end is tunneled subcutaneously to the NCP Pulse Generator pocket .

Fig. 1 identifies the individual parts of the Lead. The Model 300 Series Bipolar Vagus Nerve Stimulation Lead is available in two sizes of inner helical diameter to insure optimal electrode fit on different size nerves.

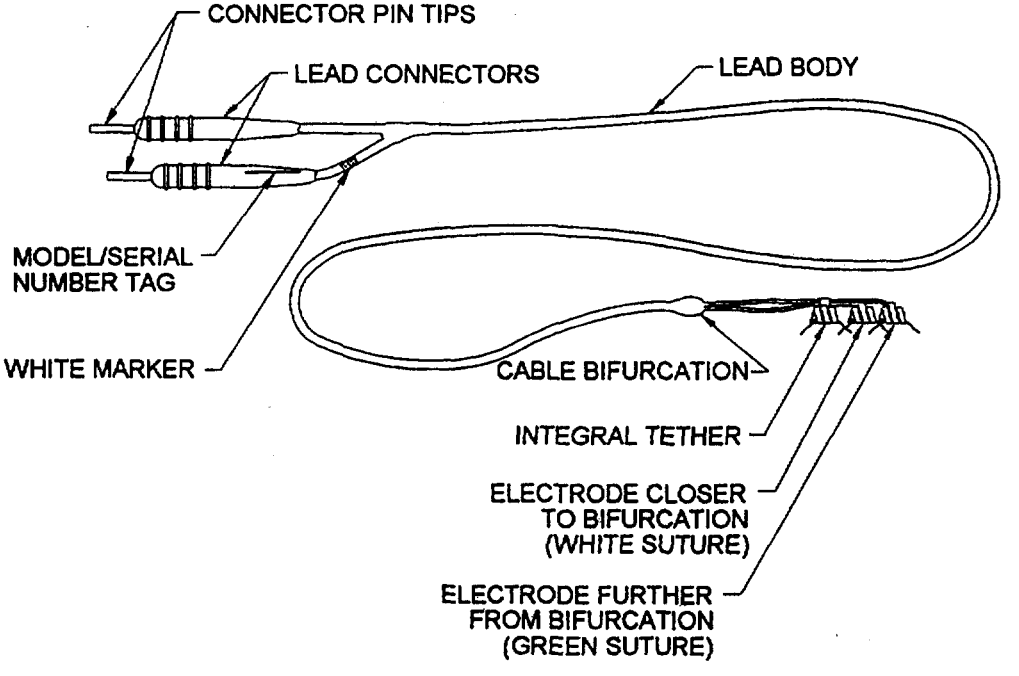

Fig. 1. Model 300 Bipolar Vagus Nerve Stimulation Lead{tc "Fig. 1. Model 300 Bipolar Vagus Nerve Stimulation Lead" \f g}

*Cyberonics and NCP are registered trademarks of Cyberonics Inc. The Leads described in this manual are protected under U.S. Patent No. 4,573,481 and 5,531,778. The integral tether is protected under U.S. Patent No. 4,979,511. The company also holds patents in foreign countries.

2. *INTENDED USE / INDICATIONS*

The NCP System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to anti-epileptic medications.

3. *CONTRAINDICATIONS*

The NCP System cannot be used in patients after a bilateral or left cervical vagotomy.

Symbols and Definitions used in this labeling include:
⚠ Notice for reader to pay special attention to following details
Not suitable for connection to a public telecommunications network or telephone equipment
SN Denotes Serial Number
Denotes Expiration Date
Denotes for Single Use Only
LOT Denotes batch code
Denotes Date of Manufacture
STERILE EO Denotes that Contents were sterilized by ethylene oxide

4. *WARNINGS*

⚠ **Avoid Excessive Stimulation**: Stimulation at a combination of high frequency (≥50 Hz) and a duty cycle exceeding 50% (ON TIME > OFF TIME) has resulted in degenerative nerve damage in laboratory animals. Excess duty cycle can be produced by frequent magnet activation (> 8 Hours of continuous magnet activation).

⚠ **Aspiration** may result from the increased swallowing difficulties reported by some patients during stimulation. **Patients who have pre-existing swallowing difficulties** are at greater risk for aspiration.

⚠ **Device Malfunction** could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated adverse effects. Patients should be instructed to use the magnet to stop stimulation if they suspect a malfunction, and then immediately contact their physician for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.

Sudden Unexplained Death in Epilepsy (SUDEP): During the pre-marketing development of the NCP System, 10 sudden and unexplained deaths (definite, probable & possible) were

recorded among the 1,000 patients implanted and treated with the NCP device (2017 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 5.0 definite, probable and possible SUDEP deaths per 1,000 patient-years of experience. Although this rate exceeds that expected in a healthy (non-epileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving NCP stimulation (ranging from 1.3 for the general population of patients with epilepsy, to 3.5 for a recently studied anti-epileptic drug (AED) clinical trial population similar to the NCP System clinical cohort, to 9.3 for patients with refractory partial onset epilepsy).

5. PRECAUTIONS

⚠ **Laryngeal irritation** may result from stimulation. **Patients who smoke** may have an increased risk of laryngeal irritation.

⚠ **Dyspnea** may result from stimulation. **Patients with chronic obstructive pulmonary disease** may have an increased risk of dyspnea.

⚠ **Resetting the NCP Pulse Generator** turns the device OFF (output current = 0 mA) and all device history information is lost. Print out device history information before resetting.

Physicain Training:

- **Prescribing Physicians** should be experienced in the diagnosis and treatment of epilepsy and should be familiar with the use of the NCP System.
- **Implanting Physicians** should be experienced in operating in the carotid sheath and be trained for surgical implantation of the NCP system. See Section 12.2, Physician Training/Information for more information.

5.1 Sterilization, Storage and Handling

⚠ Store the device between -20°C (-4°F) to +55°C (+131°F) because temperatures outside this range can damage components.

⚠ Do not implant a device when:

⇒ It has been dropped, because this could have damaged NCP Pulse Generator components;

⇒ Its sterility indicator within the inner package is not green, because it might not be sterile;

⇒ Its storage package has been pierced or altered, because this could have rendered it non-sterile; or

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⇒ Its "use before" date has expired, because this can adversely affect NCP Pulse Generator longevity or sterility.

⚠ Do not re-sterilize the Lead. Return unimplanted devices to Cyberonics for re-sterilization.

⚠ Do not ultrasonically clean the NCP Pulse Generator, because this may damage Pulse Generator components.

⚠ The Lead is a single use only device. Do not reimplant a Lead explanted for any reason. Explanted Leads should be returned to Cyberonics for analysis and proper disposal, along with a completed Returned Product Report form. Before returning the Lead, seal it in a pouch or other container properly labeled with a biohazard warning.

5.2 Lead Evaluation and Lead Connection

⚠ Do not use a Lead other than the Model 300 Series Vagus Nerve Stimulation Lead because such use may damage the NCP Pulse Generator or injure the patient.

⚠ Exercise extreme caution if testing Leads using line powered equipment because leakage current can injure the patient.

⚠ Do not insert a Lead in the NCP Pulse Generator connector without first visually verifying that the setscrews are sufficiently retracted to allow insertion.

5.3 Environmental and Medical Therapy Hazards

⇒ Patients should exercise reasonable caution in avoidance of devices that generate a strong electric or magnetic field. If a Pulse Generator should cease operation while in the presence of ElectroMagnetic Interference (EMI), moving away from the source or turning it off may allow the Pulse Generator to return to its normal mode of operation.

5.3.1 Hospital and Medical Environments

NCP System operation should always be checked by performing device diagnostics following any of the mentioned procedures. Additional precautions for these procedures are described below.

Therapeutic radiation may damage the NCP Pulse Generator's circuitry, although no testing has been done to date and no definite information on radiation effects are available. Sources of such radiation include therapeutic X rays, cobalt machines, and linear accelerators. The effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from temporary disturbance to permanent damage and may not be detectable immediately.

External defibrillation may damage the Pulse Generator. Attempt to minimize current flowing through the Pulse Generator and Lead system by following these precautions:

⇒ Position defibrillation paddles as far from the Pulse Generator and perpendicular to the implanted Pulse Generator / Lead system and as far from the Pulse Generator as possible.

⇒ Use the lowest clinically appropriate energy output (watt seconds).

⇒ Confirm NCP Pulse Generator function following any internal or external defibrillation.

Electrosurgical cautery may damage the Pulse Generator. Attempt to minimize current flowing through the Pulse Generator and Lead system by following these precautions:

⇒ Position electrosurgery electrodes as far from the NCP Pulse Generator and NCP Lead as possible.

⇒ Avoid electrode placement that puts the NCP Pulse Generator and NCP Lead in the direct path of current flow.

⇒ Confirm NCP Pulse Generator function following electrosurgery.

Magnetic Resonance Imaging (MRI) should not be done with MR body coil. The heat induced in the Leads by a body MRI scan can cause injury. MRI should only be done using a head coil. Conditions which have been tested include:

⇒ Transmit and Receive coil type: Head Coil Only

⇒ Static Magnetic Field Strength: ≤ 2.0 Tesla

⇒ SAR: < 1.3 W/kg for 70 kg patient

⇒ Time varying intensity < 10 Tesla /sec

⇒ Magnetic and radio-frequency (RF) fields produced by MRI may change the Pulse Generator settings (change to reset parameters), activate the device, and injure the patient.

Extracorporeal shockwave lithotripsy may damage the Pulse Generator. If therapeutic ultrasound therapy is required, avoid positioning the Pulse Generator part of the body in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the NCP Pulse Generator output to 0 mA for the treatment and retest the Pulse Generator after therapy.

Diagnostic ultrasound is not expected to affect the NCP System.

5.3.2 Home Occupational Environments

Properly operating microwave ovens, electrical ignition systems, power transmission lines, theft prevention devices, and metal detectors are not expected to affect the Pulse Generator. Similarly, most routine diagnostic procedures such as fluoroscopy and X rays are not expected to affect system operation. However because of higher energy levels, sources such as transmitting antennas may interfere with the system.

5.3.3 Cellular Phones

Based on testing to date, cellular phones have no effect on the NCP® Pulse Generator operation. The NCP Pulse Generator does not have sensing Leads. These Leads contribute to the EMI sensitivity of implanted pacemakers and defibrillators.

5.3.4 Other Environmental Hazards

Strong magnets, hair clippers, vibrators, loudspeaker magnets, and other similar electrical or electromechanical devices, which may have a strong static or pulsing magnetic field, can cause inadvertent magnet activation. Patients should be cautioned to keep such devices away from the NCP Pulse Generator.

5.3.5 Programming Software

The Programming Software should be used on a computer dedicated only for programming the NCP system. The Programming Software has been validated on a Compaq Contura Aero 4/25 running MS DOS 6.2 with the disk caching software disabled.

(See the Model 250 Physician's Manual for more information)

5.3.6 NCP Pulse Generator and EMI Effects on Other Devices

During stimulation the NCP Pulse Generator may interfere with devices operating in the 40 kilohertz to 100 kilohertz range, such as pocket transistor radios and hearing aids. This is a theoretical possibility, and no effects on hearing aids have yet been reported, although the Pulse Generator can interfere with transistor radios when held directly over the radio. No specific testing has been done to date and no definite information on effects is available. It is suggested the Pulse Generator be moved away from equipment with which it is believed to be causing interference. Programming or interrogating the NCP Pulse Generator may momentarily interfere with other sensitive electronic equipment nearby. The NCP Pulse Generator is not expected to trigger airport metal detectors or theft protection devices.

The NCP Pulse Generator may affect the operation of other implanted devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate Pulse Generator responses. If the NCP Pulse Generator patient requires concurrent implantable pacemaker and/or defibrillator therapy, careful programming of each system may be necessary to optimize the patient's benefit from each device.

⚠ The magnet provided for activation or inhibition of the NCP Pulse Generator may damage televisions, computer disks, credit cards, and other items affected by strong magnetic fields.

5.3.7 Effects on ECG Monitors

NCP Pulse Generator data communications will produce an ECG artifact. Figure 1 shows examples of this artifact in ECG tracings.

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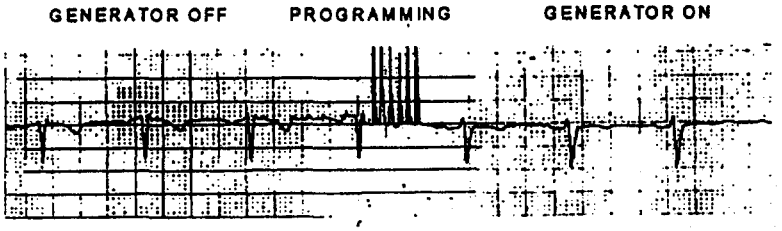
Figure 1. ECG Artifact Produced by NCP Pulse Generator Communication



5.3.8 Lead Disposal

- Do not incinerate NCP Pulse Generator because it can explode if subjected to incineration or cremation temperatures.
- Return all explanted NCP Leads to Cyberonics for analysis and safe disposal.
- Do not implant an explanted NCP Lead in another patient as sterility, functionality, and reliability cannot be ensured.

6. ADVERSE EVENTS

The NCP System was implanted in 454 patients in five clinical studies involving 611 devices (some patients had Pulse Generator replacements). As of August, 1996, total NCP exposure in these 454 patients was 901 device years. Individual patient exposure averaged 24 months with a range of 8 days to 89 months.

A total of 9 patients died during these five studies. One patient died from each: thrombotic thrombocytopenic purpura, drownings, aspiration pneumonia, pneumonia, and renal failure associated with drug and alcohol ingestion. No cause of death was apparent for the other four and they may by classified as Sudden Unexpected Death in Epilepsy (SUDEP). None of the deaths were attributed by the Investigators to the NCP System.

6.1 Observed Adverse Events

Included among the five clinical trials were two randomized trials (Study E03 & E05) which involved 314 patients and implantation of 413 devices yeilding a total NCP System exposure (inclussive of long term follow-up) of 591 years. These trials form the basis for the rates of observed adverse events.

Table 1 reports the adverse events from these studies during the Randomized Phase (14 week observation period) on a per patient basis. For the Extension Phase, events are reported on a per patient and per patient-year basis. The most common side effect associated with stimulation is hoarseness (voice alteration) during stimulation (hoarseness should only occur during the ON time). Most people tolerate the hoarseness well.

Table 1. Observed Adverse Events

(n=413 devices in 314 patients, 152 in HIGH treatment group, 591 device years)

	Randomized + Extension Phase, N= 314 patients, 591 device years				Randomized Phase, HIGH Only, N = 152 pts	
Adverse Event	**# of patients**	**% of patients**	**# of Events**	**Events per device-year**	**# of patients**	**% of patients**
Serious AEs[1]						
Surgically Related	13	4.1 %	13	0.022		
Stimulation Related	4	1.2 %	4	0.007	1	0.7 %
Non-serious AEs						
Voice Alteration	156	50%	720	1.228	91	60%
Cough Increased	129	41%	456	0.772	57	38%
Pharyngitis	84	27%	182	0.308	36	24%
Paresthesia	87	28%	377	0.638	32	21%
Dyspnea	55	18%	55	0.093	32	21%
Dyspepsia	36	12%	98	0.166	22	15%
Nausea	59	19%	154	0.261	21	14%
Laryngismus	10	3.2%	30	0.051	9	5.9%

[1] - Serious AEs reported included infection, nerve paralysis, hyperesthesia, facial paresis, left vocal chord paralysis, left facial paralysis, left hemidiaphragm paralysis, left recurrent laryngeal nerve injury, urinary retention, and low grade fever

Status Epilepticus: Valid estimates of the incidence of treatment emergent status epilepticus among VNS treated patients are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 2 of 441 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Rebound after stimulation is stopped: Seizure frequency was monitored for one to four weeks after stimulation was stopped in 72 instances (68 patients) in Study E03. Seizure rate increased by greater than 1.5 standard deviations above baseline in 10% of instances (compared to 7% expected). Of these instances, 11 of 72 (15%) had a greater than 25% increase above baseline and 42 of 72 (58%) had a greater than 25% decrease in seizure rate.

6.2 Potential Adverse Events

Adverse events which may occur (including those reported in Table 1), reported in alphabetical order:

- Cough increased
- Dyspepsia, duodenal or gastric ulcer
- Dyspnea
- Facial paresis or paralysis
- Hemidiaphragm paralysis
- Hypesthesia
- Infection

- Laryngismus
- Muscle twitching during stimulation
- Nausea and vomiting
- Nerve injury
- Paresthesia
- Pharyngitis
- Voice alteration

Patients who manipulate the NCP Pulse Generator and the Lead through the skin may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

6.3 Signs of Potential Nerve Damage

Some complications may be associated with damage to the vagus nerve. Persistent hoarseness not associated with the stimulation suggests possible nerve irritation and should be immediately investigated. Hoarseness may be caused by nerve constriction, nerve fatigue, or device malfunction.

Nerve constriction should be apparent within a few days after implant and may require explant of the Lead. Nerve fatigue usually occurs after intense stimulation parameters have been used, and may not be associated with any other adverse event. If fatigue is suspected, the NCP Pulse Generator's output should be turned OFF for several days until hoarseness subsides. Trauma to the vagus nerve at the implantation site could result in permanent vocal cord dysfunction.

7. CLINICAL STUDIES

Five clinical studies have been conducted. They enrolled 537 patients, of whom 454 were implanted with the NCP System. A total of 611 devices were implanted and patient exposure totaled 901 device years with individual mean patient exposure of 24 months (range 8 days to 7.4 years). A total of 45 centers participated in these studies, 39 in the US, two in Germany and one each in Canada, Holland, and Sweden.

Table 2. Description of Clinical Studies

All patients enrolled in all clinical studies, N=537

Study	E01	E02	E04	E03	E05	Total
Type of Study	Pilot Longitudinal	Pilot Longitudinal	Open Longitudinal	Randomized Parallel High/Low	Randomized Parallel High/Low	-
Patients Enrolled	11	5	133	126	262	537
# Centers [a]	3	2	24	17	20	45
Reference (baseline) period	Weeks 2 through 4	Weeks 3 through 6	Weeks -4 through 0	Weeks -12 through 0	Weeks -12 through 0	-
Seizure Type	Partial	Partial	All types	Partial	Partial	-
Num. AEDs	1 to 2	1 to 2	not specified	0 to 3	1 to 3	-

[a] Total includes OUS centers (Canada, Holland, Germany 2, and Sweden), several US centers participated in more than one study

Purpose: To determine whether adjunctive use of optimal stimulation of the vagus nerve could reduce seizure frequency in patients with refractory partial onset seizures.

Methods: In the two active control studies (E03 and E05), patients were randomly assigned to either HIGH (optimized to the patient) or LOW (active control - longer OFF time interval) treatment groups. Patients were enrolled in the study and seen every four weeks during the baseline period (weeks -12 to 0). Patients meeting eligibility were implanted with the NCP Pulse Generator and NCP Lead. Two weeks after implantation, patients were randomized to the HIGH or LOW stimulation group and the Pulse Generator was activated. HIGH dose received a higher frequency, greater pulse width, and higher duty cycle. The randomized treatment period that followed activation of the Pulse Generator lasted 14 weeks (the last 12 weeks of which were used in the efficacy analysis -- first 2 weeks were for surgical recovery, followed by a 2 week treatment ramp up period).

Table 3. Description of Patients

All patients implanted in all clinical studies, N=454

Study	E01	E02	E04	E03	E05	Total
Patients Implanted	11	5	124	115	199	454
Patients Stimulated	10	5	123	115	198	451
Age (range)	32 (20, 58)	33 (18, 42)	24 (3, 63)	33 (13, 57)	33 (13, 60)	32 (13, 63)
Females (%)	4 (36%)	2 (40%)	57 (46%)	43 (37%)	104 (52%)	210 (46%)
Years w/ Epilepsy	22 (13-32)	20 (5-36)	17 (0.8-48)	21 (4-47)	23 (2-52)	-
Av. # AEDrugs	1.0	1.0	2.2	2.1	2.1	-
Median seizures per Day at Baseline	0.6	0.42	0.65	0.70 High 0.85 Low	0.58 High 0.51 Low	-

Results: The primary efficacy endpoint (percent reduction in seizure rate) was measured over 12 weeks (weeks 2 through 14). Adverse events were assessed at each visit.

Table 4. Principal Effectiveness and Safety Results

All patients in Effectiveness analyses in all clinical studies, N=441

Principal Effectiveness Results						
Study	**E01**	**E02**	**E04**	**E03**	**E06**	**Total**
Patients in Effc. Eval.	10	5	116	114	196	441
MEDIAN reduction seizures per Day	32%*	48%*	22%*	24%* High 6% Low	23%* High 21%* Low	-
MEAN reduction seizures per Day	24%*	40%*	7%	24%* High 6% Low	28%* High 15%* Low	-
Diff mean (HI-LOW)	-	-	-	17%*[3%,31%]	13%* [2%, 23%]	-
% with >50% Response	30%	50%	29%	30% High 14% Low	23% High 16% Low	-
Principal Safety Results Through Extension Phase						
Exposure (Pt-yr.)	45	20	245	456	135	901
SAEs: High/Low [a]	9% / -	0% / -	6% / -	5% / 0%	7% / 9%	-
D/C for: LOE / AE [b]	0 / 1	0 / 0	2 / 3	0 / 2	1 / 3	3 / 9
Num. Explants [c]	2	2	15	9	5	33
Death: SUDEP/Total [d]	0 / 0	0 / 0	3 / 4	0 / 3	1 / 2	4 / 9

[a] SAEs = Serious adverse events

[b] D/C = Discontinued for lack of efficacy / adverse events at one year; excludes deaths

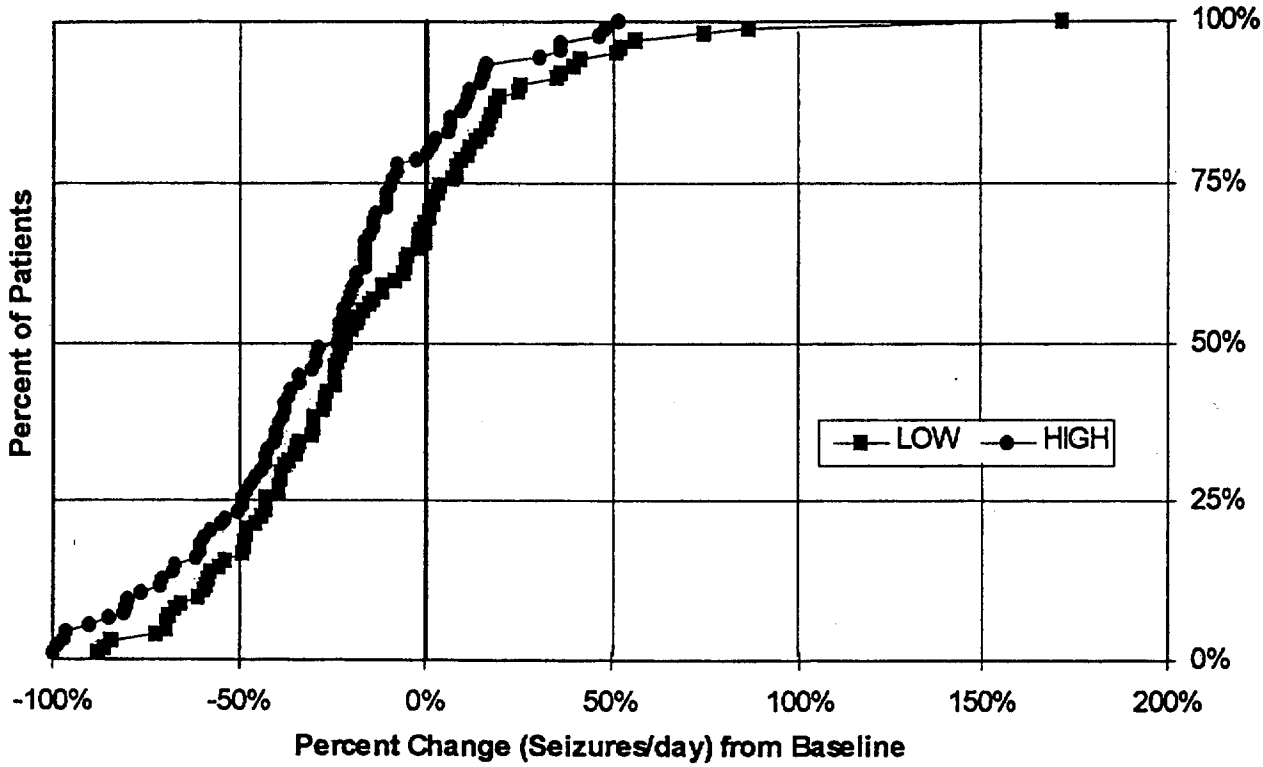
[c] Number of explants excludes deaths;

[d] All deaths occurred during the long-term follow-up, closing dates: August-Sept 1996

* Difference statistically significant, $p < 0.05$, by t-test or Chi square (without correction for any interim analyses)

Figure 2. Change in Seizure Frequency, Patient Distribution (with Corresponding Table)

All Patients Completing Effectiveness Evaluation, N=196



	Percent Change (seizures/day) from Baseline		
	HIGH	LOW	Difference
N	94	102	196
Median	-23%	-21%	n/a
25%, 75% Quartiles	-8.9%, -49%	4.0%, -43%	n/a
95% Confidence Intervals	-35%, -21%	-23%, -7.7%	-23%, -2.3%
Range (min, max)	-100%, 52%	- 89%, 171%	-23%, -2.3%
Mean ± SD	-28% ± 34%	-15% ± 39%	-13%* ± 37%

* Difference statistically significant ($p<0.05$) by Analysis of Variance ($p=0.032$) and by Cochran-Mantel-Haenszel Aligned Ranks ($p=0.040$)

Patient response to VNS was examined via statistical modeling (examining group characteristics) and evaluation of individual patients. No useful predictors of increase or decrease in seizure frequency were found.

Conclusions: Patients with refractory partial onset seizures treated with HIGH VNS had a statistically significant decrease in frequency of seizures when compared to baseline and when compared to patients treated with LOW (control) VNS. The most common treatment-related adverse events were voice alteration and dyspnea. Treatment was well tolerated, with 98% (306 of 324) patients implanted continuing on into the extension of this study.

7.1 Long Term Data

Long term data was collected on all available E01 through E04 Study patients. This data is uncontrolled because it comes from an open label protocol where both anti-epileptic drug medications and NCP device settings were allowed to be changed. However, all available information is presented for completeness.

Ninety-five (95%) percent of patients were continuing as of one year after their original implant, 82% were still receiving stimulation at two years, and 69% were receiving stimulation at three years. Some E04 patients had not yet had the opportunity to reach two or three years of stimulation, and were therefore not used in the calculations. Additionally, 28 E03 patients were implanted outside the U.S. in countries that later received commercial approval, and data was only available through one year of stimulation.

Table 5. Patient Summary Chart: Patients Continuing Treatment as of August 22, 1996

E0X STUDY PERIOD	E01	E02	E03	E04	Total
Patients Randomized/Stimulated (N)	10	5	115	123	253
Patients (N) Entering Extension Phase	10	5	113	123	251
Total continuing patients being treated for up to one year (N)	10/10	5/5	111/115	112[4] / 121	238/251
Continuing patients being treated for up to two years (N)	9/10	4/5	71/87[1]	58[2]/70	142/172
Continuing patients being treated for up to three years (N)	7/10	3/5	57/87	21[3]/24	88/126

(1) Twenty-eight (N=28) commercial European patients were excluded from follow-up after one year of treatment due to the commercial release of the NCP System in those countries.

(2) As of 8/22/96. Only 70 patients had been implanted long enough to reach the 2 year treatment period; only 58 of the 70 were continuing.

(3) As of 8/22/96. Only 24 patients had been implanted long enough to reach the 3 year treatment period; only 21 of the 24 were continuing.

(4) Two E04 Study patients had not yet reached their one year date post implantation.

Table 6 below provides the number of patients used in the efficacy analysis. It is apparent from the table that not all continuing patients were used in the efficacy analysis. This is mostly because of missing data (some patients kept only sporadic records over the long term) although two patients were not used because they had lobectomy surgery which affected their seizure rates.

Table 6. Patients (N) Used for Efficacy Analysis

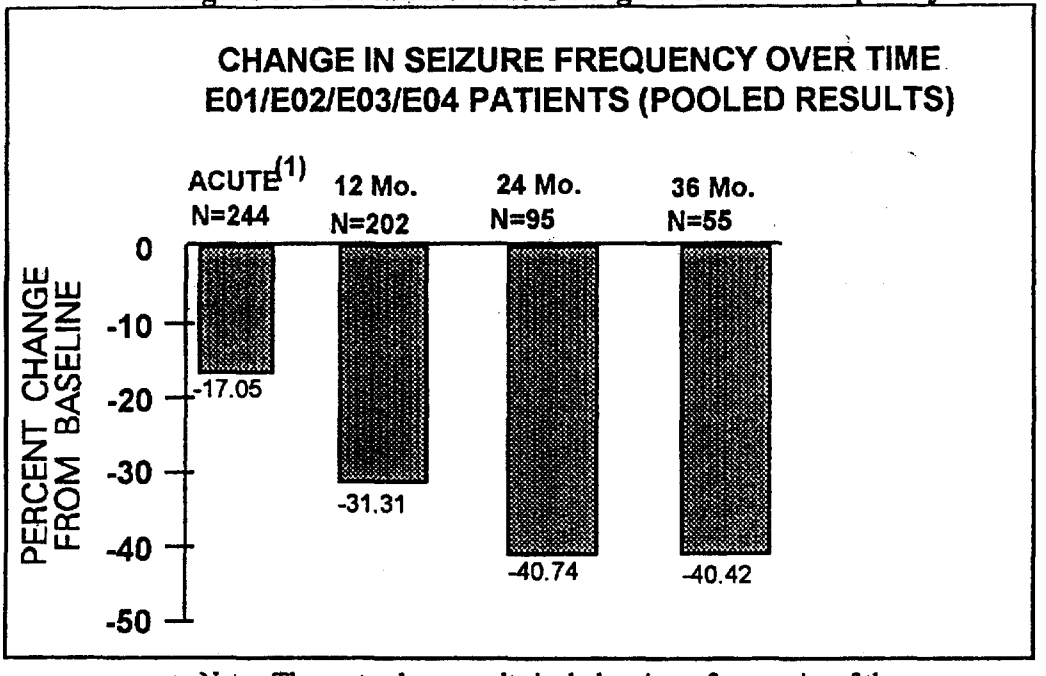
E0X STUDY PERIOD	E01	E02	E03	E04	Total
Patients Randomized/Stimulated (N)	10	5	115	123	253
Patients(N) Entering Extension Phase	10	5	113	123	251
Patients used in One Year Efficacy Analysis (N)	10/10	4/5	102/111	86/112	202/238
Patients used in Two Year Efficacy Analysis (N)	8/9	2/4	51/71[1]	34/58[2]	95/142
Patients used in Three Year Efficacy Analysis (N)	4/7	2/3	49/57	0[3]	55/67

(1) Twenty-eight (N=28) commercial European patients were excluded from follow-up after one year of treatment due to the commercial release of the NCP System in those countries.

(2) As of 8/22/96. Only 70 patients had been implanted long enough to reach the 2 year treatment period; only 58 of the 70 were continuing.

(3) No data was available at the 3 year time point for study E04.

Figure 3. Median Percent Change in Seizure Frequency



(1) Note: The acute phase results include seizure frequencies of the E03 Study LOW stimulation group, which includes one-half of the E03 patients, N=57. Patients were permitted to change their AEDs during these studies and these changes may have contributed to the change in seizure frequency.

7.2 Other Information

Although information outside the typical range gathered for Studies E03 and E05 was collected for Study E04, the information is from an open-label study and on fewer

numbers of patients. Sixteen **patients under age 12** (range 3.6 to 12 years) were evaluated. These patients were found to have a 17.9% median decrease during the acute phase, with 31% experiencing a greater than 50% decrease. Additionally, 25 patients with **generalized seizures** were evaluated. These patients were found to have a 46.6% median decrease during the acute phase, with 44% experiencing a greater than 50% decrease.

8. *INDIVIDUALIZATION OF TREATMENT*

Patients should be started on stimulation at low current setting (0.25 mA) and the current should be gradually increased to allow accommodation to the stimulation. For patient comfort, the output current should be increased in 0.25 mA increments until comfortable tolerance is reached. Physicians should appreciate that some patients will accommodate to stimulation levels over time and therefore allow if needed further increases (in 0.25 mA steps) in output current. See Programming Software Manual.

Table 7 lists the stimulation parameters used in the randomized clinical trials.

Table 7. Stimulation Parameters

Parameter	High (optimal stimulation)
Output Current	0-3.5 mA
Frequency	30 Hz
Pulse Width	500 μSec
ON Time	30 Sec
Off Time	5 Min
Magnet Parameters	
Amplitude	Same as Output Current
On Time	30 Sec
Pulse Width	500 μSec

The magnet output current should be set to a level that can be perceived by the patient to allow for testing of the Pulse Generator operation on a daily basis.

⚠ The safety and efficacy of this therapy have not been systematically established in patients with the following conditions:

- only one vagus nerve
- neurological diseases other than epilepsy
- history of ulcers (gastric, duodenal or other)
- cardiac arrhythmias or other abnormalities
- respiratory diseases or dyspnea
- under the age of 12 and over the age of 60
- primary generalized seizures

- pregnant or nursing
- pre-existing hoarseness
- history of dysautonomias
- history of vasovagal syncope

9. PATIENT COUNSELING INFORMATION

Patients should be informed to test their Pulse Generator's operation daily by performing a magnet stimulation and verifying that stimulation occurs. If stimulation does not occur, their physician should be contacted.

In the unlikely event of uncomfortable adverse events, continuous stimulation or other malfunction, the patient should be advised to hold or tape the magnet directly over the implanted NCP Pulse Generator to prevent additional stimulation. If patients or caregivers find this procedure necessary, they should immediately notify their physician.

10. CONFORMANCE TO STANDARDS

The NCP System conforms to the following standards:

- ANSI / AAMI NS15 Implantable peripheral nerve stimulators; and
- prEN45502-1 - Active Implantable Medical Device Directive - General Requirements.

11. HOW SUPPLIED

11.1 Sterilization

Implantable portions of the NCP System have been sterilized using ethylene oxide gas, and are supplied in a sterile package for direct introduction into the operating field. An expiration date is marked on the outer package. Storage temperatures should be within the -20°C (-4°F) to +55°C (+131°F) range. If the package has been exposed to temperatures outside this range or there is any indication of external damage, the package should be left unopened and returned to Cyberonics.

11.2 Nonpyrogenic

The implantable portions of the NCP System are nonpyrogenic.

12. Operator's Manual

12.1 Directions for Use

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12.1.1 Specifications and Product Information

Table 8. Specification and Product Information

(All Dimensions Nominal)

Connector Assembly	
Connector Body	
Diameter	5 mm
Material	Silicone rubber
Connector Pins	
Diameter	1.6 mm
Material	300 series stainless steel
Lead Body	
Diameter	2.0 mm (6 French)
Insulation	Silicone rubber
Conductor Coil Construction	Helical, quadfilar
Conductor Material	MP-35N alloy
Overall Length	43 cm
Lead Resistance	120 to 180 ohms (connector pin to common electrode)
Electrodes and Integral Tether	
Helical Material	Silicone elastomer
Conductor Material	Platinum
Separation	8 mm (center to center)
Suture Material	Polyester

Inner Diameter of Helix

Model Number	Inner Diameter (mm)
300-20	2.0
300-30	3.0

Tie-downs	
Dimensions	5.7 mm X 7.7 mm
Material	Radiopaque Silicone Rubber

12.1.2 Implantation

12.1.2.1 Package Contents

The sterile package contains:

- One Model 300 Series Bipolar Vagus Nerve Stimulation Lead with integral tether
- Four silicone rubber tie-downs

Also provided are the following:

- One Physician's Manual
- One Returned Product Form
- One Patient Identification Card

12.1.2.2 Opening the Sterile Package

Before the package is opened, it should be examined carefully for evidence of damage or compromised sterility. If the outer package has been opened or damaged, Cyberonics cannot guarantee sterility of the Pulse Generator, and it should be returned to Cyberonics. To open the package:

1. Grasp the tab and peel back the outer cover.
2. Observing sterile technique, lift out the sterile inner tray.
3. Grasp the tab and peel off the inner cover to expose contents. To remove an item, push down on one end and grasp the opposite (raised) end.

12.1.2.3 Lead and Pocket Location

Implantation of the NCP System is similar to accepted practice for implantation of a cardiac pacemaker, with the exception of the placement of the electrodes and the subcutaneous routing of the Lead body (see Fig. 2 for general placement of the Pulse Pulse Generator and Lead). Information concerning implantation of the NCP Pulse Pulse Generator is provided in the Model 100 NCP Pulse Pulse Generator Physician's Manual and a detailed explanation of the Lead electrode and Lead body placements is provided later in this manual. The following overview summarizes the recommended sequence for implantation of the NCP System:

1. Using the Model 400 Tunneling Tool, tunnel the connector end of the Model 300 Lead subcutaneously from the neck incision site to the NCP Pulse Pulse Generator pocket. It is recommended that both the Lead body and NCP Pulse Pulse Generator be positioned ipsilaterally with respect to the selected stimulation site.
2. Attach the helical electrodes and integral tether to the desired site on the vagus nerve, securing the Lead body parallel to the nerve using the integral tether and tie-downs.
3. After loosening the set screws in the NCP Pulse Generator, lubricate the insulated portions of the Lead connector pins and plug them into the NCP Pulse Generator. Verify the pins are fully inserted, and tighten the set screws.
4. Coil the Lead body excess and place it and the NCP Pulse Generator in the chest pocket. Place the coiled Lead excess to the side of the NCP Pulse Generator.

⚠Do not place the Lead under the NCP Pulse Generator; this may result in insulation failure and system malfunction.

5. See the Model 100 NCP Pulse Generator Physician's Manual for more detailed information concerning the implantation procedure for the Pulse Generator.

⚠ Cyberonics recommends that careful attention be directed to electrode placement and Lead routing in order to maximize system performance and minimize possible mechanical damage to the nerve or Lead. Lead integrity information can be obtained by using the Cyberonics Model 200 Programming Wand, Model 250 Programming Software, and an IBM®-compatible personal computer. The software includes a Lead test diagnostics feature which can be used to assess Lead impedance.

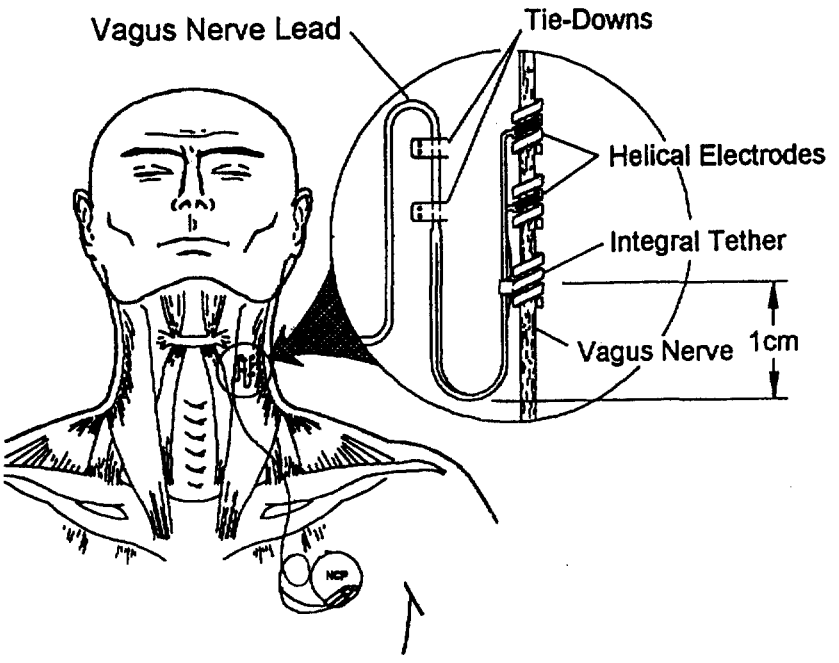

Fig. 2 Electrode Placement Technique{tc "Fig. 2. Electrode Placement Technique" \f g}

⚠**Note**: The Model 300 Lead (especially the helical electrodes) can be damaged if stretched, pinched, or crushed. Avoid subjecting the electrodes to such stresses. The silicone rubber insulation can attract particulate matter; do not expose it to dust or other similar particulates.

While the specific surgical approach and techniques will vary with the implanting physician, the following instructions provide guidance for implantation of the Lead:

⚠**Note**: It is very important to follow infection control precautions. Infections related to any implanted device are difficult to treat and explantation of the device may be required to eliminate the infection. Cyberonics recommends that the patient be given antibiotics pre-operatively. The surgeon should ensure that all instruments, including the tunneling tool, are sterile prior to the operation.

1. After administering appropriate anesthesia, expose the left carotid sheath as it extends along the superior-medial border of the sternocleidomastoid muscle.
2. Locate and expose **at least 3 cm** of the left vagus nerve. The recommended stimulation site is a 3-cm section of the vagus, just above the clavicle, where it is clear of branches. This usually lies in a posterior groove between the carotid and internal jugular vein.
3. Create a subcutaneous pocket in the chest below the clavicle for the NCP Pulse Generator.
4. If the electrode diameter appears to be a suitable size for the exposed section of the vagus nerve, remove the Lead from its sterile package.

⚠**NOTE:** Care should be taken when choosing the appropriate model electrode. The correct size model should be chosen and the package opened only after the vagus nerve has been exposed to allow selection of the size that will best fit the nerve. The Model 300-20 Lead (2.0 mm, inner diameter) should accommodate most nerves. If the Model 300-20 Lead electrode appears to be inappropriate, choose an electrode which will fit snugly without constricting the nerve.

5. Tunnel the Lead connector and Lead body through subcutaneous tissue from the neck to the chest. The Cyberonics Model 400 Tunneling Tool (supplied non-sterile) is recommended for this purpose. A more detailed description of the tunneling process can be found in the Cyberonics Model 400 Tunneling Tool Package Insert.

⚠**CAUTION: The electrodes are very delicate and care should be taken not to crush them when using forceps. Do not over straighten or stretch the helices when wrapping them around the nerve.**

⚠ **CAUTION: Do not soak the NCP Lead in saline or like solution prior to implantation as it may cause the connector pin boots to swell in size and become difficult to insert into the NCP Pulse Generator.**

⚠**Avoid stretching the nerve with forceps. Use soft rubber vessel loops to raise the nerve, if necessary.**

⚠**Avoid letting the nerve become dry during the surgical procedure. Dehydration can result in nerve damage and swelling.**

6. Wrap the helical electrodes and integral tether around the nerve trunk, beginning with the electrode further from the Lead bifurcation (marked with a green suture embedded in the helical material). This electrode should be proximal to the patient's head; the connector pin associated with it (identified by a green marker) is to be inserted into the negative terminal of the Model 100 NCP Pulse Generator.

   a. With forceps, gently pull each end of the electrode, using the attached sutures to spread the electrode (see Fig. 3).

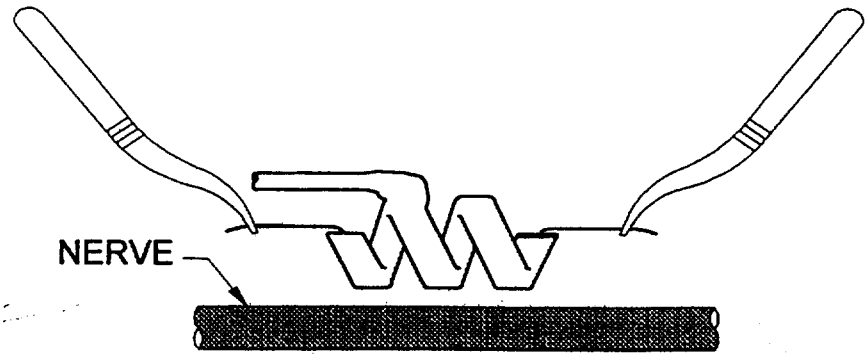

Fig. 3. Spreading the Electrode{tc "Fig. 3. Spreading the Electrode" \f g}

b. Starting with the opened electrode spread directly above and parallel to the exposed nerve, turn the electrode in a clockwise manner at a 45 degree angle to the nerve (see Fig. 4). Place the turn of the electrode where the Lead wire connects to the electrode (the section with the metal ribbon) onto the nerve (see Fig. 5).

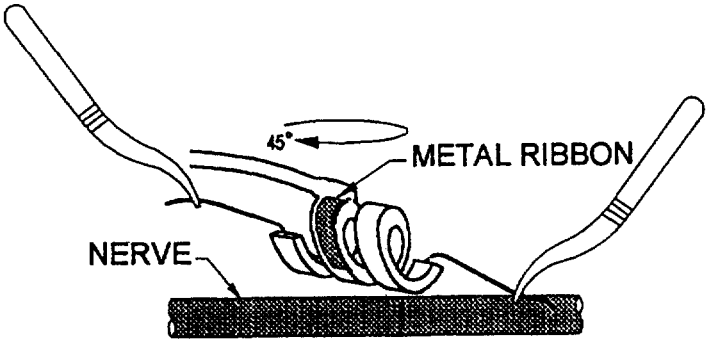

Fig. 4. Turning the Electrode{tc "Fig. 4. Turning the Electrode" \f g}

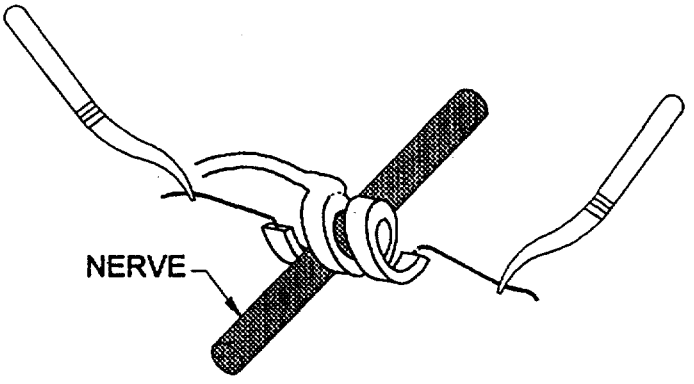

Fig. 5. Placement of the Turn{tc "Fig. 5. Placement of the Turn" \f g}

c. Push the distal portion of the electrode under the nerve and back around so it encircles the nerve (see Figs. 6A and 6B).

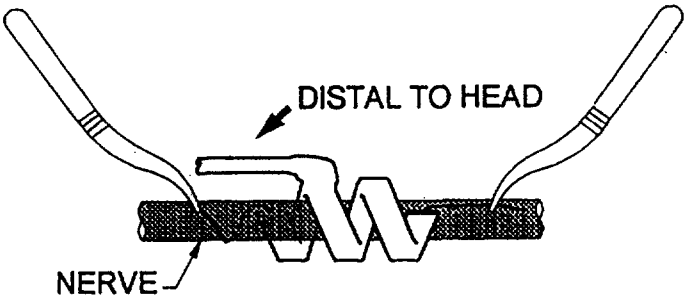

Fig. 6A. Initial Placement of the Distal Portion of the Electrode{tc "Fig. 6A. Initial Placement of the Distal Portion of the Electrode" \f g}

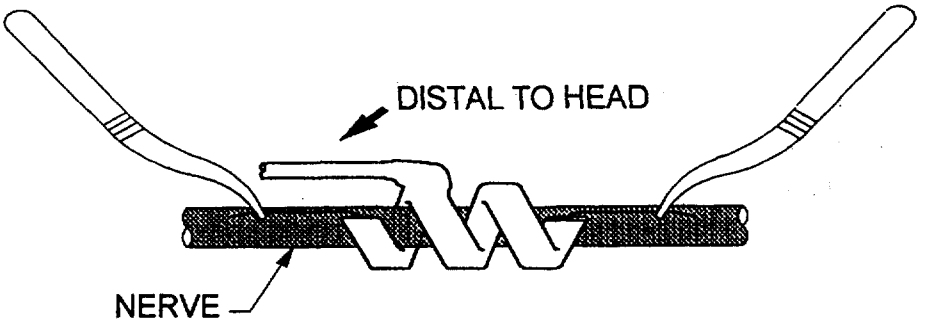

Fig. 6B. Electrode Placement After Distal Portion Encircles the Nerve{tc "Fig. 6B. Electrode Placement After Distal Portion Encircles the Nerve" \f g}

d. Push the proximal portion of the electrode under the nerve and back around so that it encircles the nerve (see Fig. 7).

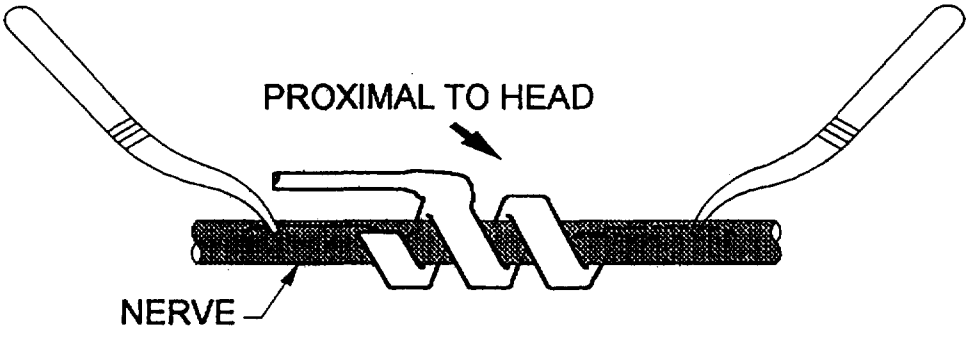

Fig. 7. Placement of the Proximal Portion of Electrode{tc "Fig. 7. Placement of the Proximal Portion of Electrode" \f g}

e. Repeat Steps 5a through 5d for the electrode with the white suture (which should be the electrode further from the patient's head but nearer to the Lead bifurcation) and for the integral tether. The electrode with the white suture embedded in the helix corresponds to the connector that has the white marker at the connector end; this connector is inserted into the positive terminal of the NCP Pulse Generator. See Fig. 10 below. The integral tether has a green suture embedded in its helix, and is the helix closest to the Lead bifurcation. After the white suture electrode and the integral tether have been placed, verify that the Lead body exits each helix in the same direction and that the bodies are aligned parallel to one another and the nerve. The correct placement of the electrodes and integral tether is shown in Fig. 8.

⚠**NOTE**: Depending on the surgeon's preference, the electrodes may alternatively be placed by putting the anchor tether on first (distal to head), then placing the electrode closer to the Lead bifurcation, then placing the electrode further from the Lead bifurcation. The polarity of stimulation does not change.

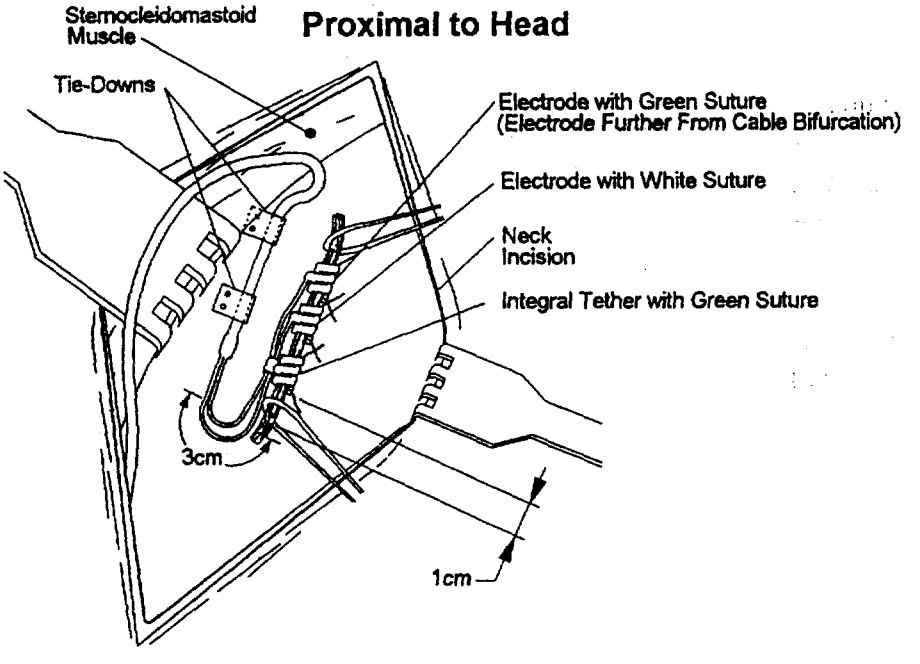

Fig. 8. Placement of Electrodes and Integral Tether{tc "Fig. 8. Placement of Electrodes and Integral Tether" \f g}

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⚠**CAUTION: The sutures embedded in the helices of the electrodes and integral tether must not be tied together or to adjacent fascia. The sutures should be used only to manipulate the helices and then should be trimmed when the electrodes are in place.**

7. The Lead body should be formed into a 3-cm strain relief bend with at least 1 cm of Lead routed parallel to the nerve. This parallel portion can be placed in a pocket formed adjacent to the integral tether, as shown in Fig. 8. The 3-cm strain relief bend should be attached loosely with tie-downs to the adjacent fascia before it is routed over the muscle (see Fig. 8). Four tie-downs are provided in the Lead package.

⚠**CAUTION: The Lead wire has a potential for fracture if the recommended 3- cm strain relief bend is not provided as described.**

8. Additionally, a large subcutaneous strain relief loop must be formed in the neck and loosely attached to fascia with a tie-down before the Lead is routed over the clavicle to provide for neck movement. This strain relief loop should be large enough to provide several centimeters of Lead extension when the neck is turned to its maximum stretched positions (see Fig. 9). Provide adequate slack on both sides of the clavicle to prevent tension over the clavicle from damaging the Lead.

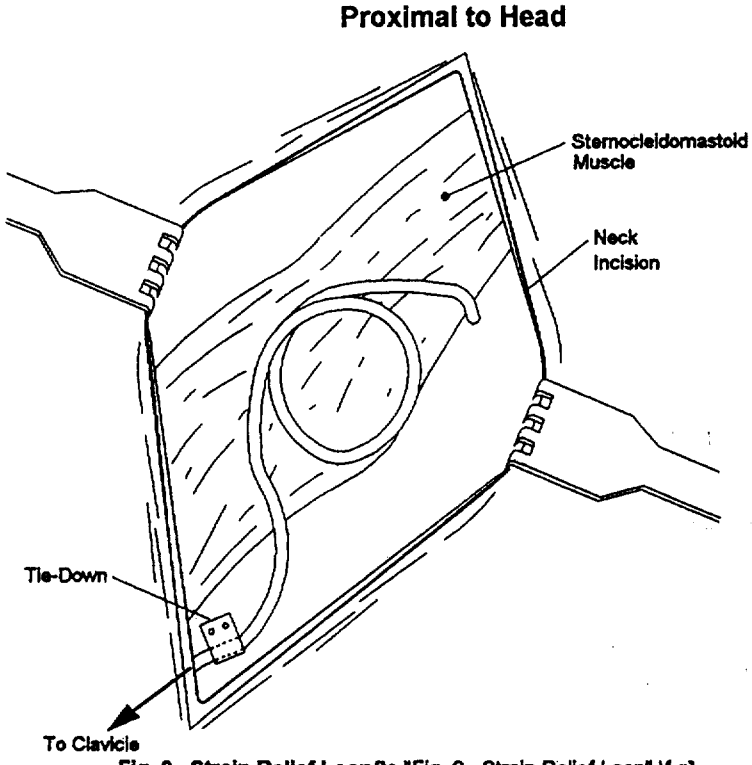
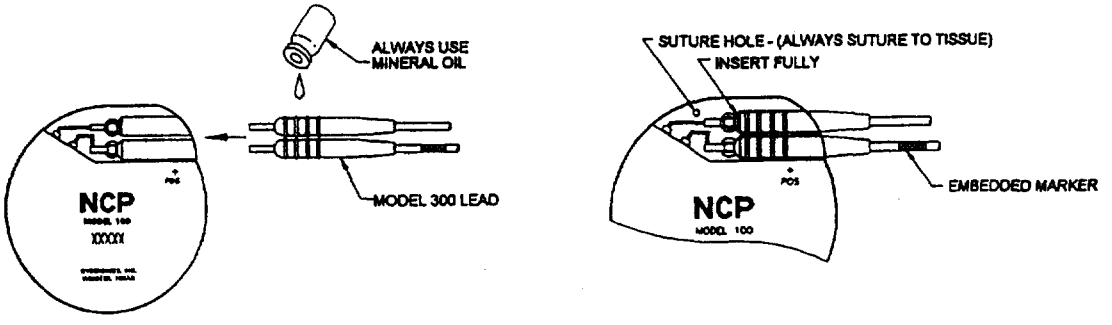


Fig. 9. Strain Relief Loop{tc "Fig. 9. Strain Relief Loop" \f g}

⚠**CAUTION: Routing and stabilization of the Lead is critical in minimizing dynamic forces on the Lead and nerves.**

- ⚠Never route the Lead through muscle.
- ⚠Never suture the Lead or Lead body to muscle tissue.
- ⚠Always use the tie-downs. Placing the sutures directly on the Lead body may result in insulation damage or wire failure.

9. Connect the Lead directly to the NCP Pulse Generator, as follows:
   a. Verify that both set screws have been adequately loosened to allow full insertion of the connector pins.
   b. ⚠Always apply a small amount of mineral oil (provided in the NCP Pulse Generator package) to the insulated portions of the connector pins to facilitate insertion (see Figure 10). This step is essential to minimize insertion forces and prevent possible damage to the connectors.



{tc "Fig. 10 Lead Connectors Prior to Insertion and Fully Inserted" \f g}
Figure 10. Lead Connectors Prior to Insertion and Fully Inserted

   c. Insert the Lead connector pins fully into the appropriate receptacles in the NCP Pulse Generator header. To allow escape of the back pressure created by insertion, leave the tip of the hex screwdriver in the slit set screw plug of the connector being inserted. The Lead connector with a white marker on the Lead and the embedded model and serial number is connected by the Lead wire to the electrode with the white suture; this connector pin is inserted into the Lead receptacle labeled "+". The remaining Lead connector is inserted into the remaining Lead receptacle.
   d. Verify that the pins are fully inserted. The ends should be visible behind the connector block. If they are not, remove the pin. To loosen a set screw, insert the hex screwdriver through the rubber silicone plug and turn counterclockwise until the connector pin can be fully inserted.

e. After verifying that the connector pins have been fully inserted, tighten each set screw by inserting a hex screwdriver through the plug and turning clockwise until it begins ratcheting.

⚠**Note:** Always push in on the hex screwdriver while turning to ensure that it is fully inserted in the set screw.

10. Test the impedance of the electrode-nerve interface by performing a LEAD TEST diagnostic, as described in the Model 250 Programming Software Physician's Manual.

    a. Verify that the Lead Impedance status reads "OK." If status checks are not "OK", verify that the Lead connectors are properly inserted and the set screws are tightened and repeat the LEAD TEST diagnostics. If "OK" status checks cannot be obtained, perform pre-implant test on the Pulse Generator as described below.

    b. Optional physiologic monitoring of NCP System operation may be done if surgery is performed under local anesthesia. Monitor the patient's voice for signs of hoarseness while gradually increasing Pulse Generator output. After testing, reset the current to 0 mA.

11. Place the NCP Pulse Generator in the chest pocket, coiling the remaining slack of the Lead and placing it to the side or top of the NCP Pulse Generator.

⚠ **Do not place the Lead under the NCP Pulse Generator; this could result in insulation failure and system malfunction.**

12. ⚠Secure the NCP Pulse Generator by placing a suture through the suture hole. This is important to stabilize the implant and to prevent manipulation by the patient which could damage the Lead wires.

⚠ **Do not place sutures directly around the body of the Lead; this may result in insulation failure and system malfunction.**

13. Close the surgical incisions. Cyberonics recommends irrigation of both incision sites with copious amounts of bacitracin solution or equivalent solution prior to closure. Cyberonics also recommends the neck incision be closed with cosmetic closure techniques to minimize scarring. Additionally, Cyberonics recommends that antibiotics be administered post-operatively at the discretion of the physician. A neck brace can be used by the patient for the first week to help ensure proper Lead stabilization.

12.1.2.4 Pre-Implant Test

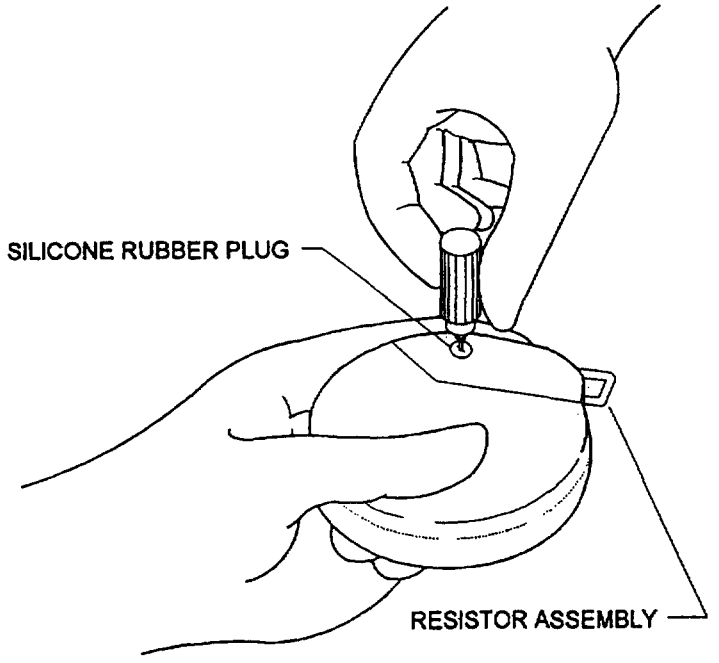
This test is to be performed in the event that the Lead Test Diagnostic status checks did not result in an "OK." This test is used to determine if the NCP Pulse Generator is functioning properly.

a. Remove the Lead connectors from the NCP Pulse Generator.

b. Insert the connector pins of the resistor assembly into the Lead receptacles in the NCP Pulse Generator header. (Because the resistor assembly has no polarity, either connector pin can be inserted into either Lead receptacle of the NCP Pulse Generator.) If the set screws need to be loosened for the insertion of the connector pins, avoid backing the screws out completely by using only two counterclockwise turns. Access the set screws for both Lead connector receptacles by carefully inserting the tip of the hex screwdriver through the slits in the silicone rubber plugs located on each side of the header.

Note: Fully insert the hex screwdriver into the set screws whenever you are tightening or loosening the set screws.

c. When the resistor assembly is in place, tighten the set screw until the hex screwdriver begins to ratchet. See Figure 11.



{tc "Fig.11 Connecting the Resistor Assembly" \f g}

Figure 11. Connecting the Resistor Assembly

d. Perform the PRE-IMPLANT diagnostics as described in the Model 250 Programming Software Physician's Manual and verify that the Lead Impedance reads "OK". If any other status readings appear, verify that the resistor is adequately secured and repeat PRE-IMPLANT diagnostics. If repeated PRE-IMPLANT Lead Impedance diagnostic does not read "OK", do not implant the NCP Pulse Generator. Contact Cyberonics and return the NCP Pulse Generator along with a completed Returned Product Report.

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e. Remove the resistor assembly by inserting the hex screwdriver through the silicone rubber plugs and turning the set screws one turn counterclockwise, again taking care not to back the set screws out completely.

12.1.2.5 Patient Identification

⚠ Included with each Model 300 Lead is a Patient Identification Card which **must** be filled out with the top white copy returned to Cyberonics. The information will become part of the Cyberonics registry of implantees, and it will be used as a permanent record of implant recipient information. In addition to the form, a wallet-sized card is enclosed which contains emergency information about the NCP System. The patient should carry this card at all times.

12.2 Physician Training/Information

Prescribing physicians are encouraged to contact Cyberonics and request a referal to a physician experienced in the operational characteristics and function of the NCP device prior to prescribing use of the device for the first time. All NCP System programming should be by or under the supervision of a physician familiar in the use of the programming software.

Initial (starting -- new or following Pulse Generator replacement) treatment output current should be set at the lowest setting (0.25 mA). Subsequent and all future device should be made in 0.25 mA increments up to the desired treatment level (see Individualization of Treatment section of this manual).

Implanting physicians using the NCP System should be thoroughly familiar with all associated materials including:

- Product labeling for the NCP Pulse Generator, Leads and accessories;
- Training manual & brochure;
- Electrode practice fixture - a device used to practice placement of the NCP Lead Coil around the Vagus nerve; and Video tapes on the proper implantation technique.

In the event intolerable adverse events are reported, physicians should always try reducing the output current (mA) as a means of eliminating or reducing the severity of a complaint. Additionally, physicians should instruct patients or caregivers on the application of the magnet to turn the NCP Pulse Generator OFF (output current 0 mA) should a adverse event become intollerable.

12.3 Mechanism of Action

The precise mechanism(s) by which the NCP System exerts its anticonvulsant action are unknown. In animal experiments designed to model anticonvulsant activity, vagus nerve stimulation affected seizures and or seizure spread in the maximum electroshock (MES), pentylenetetrazol (PTZ) tests, 3-mercaptopropionic acid (3-MP), alumina gel, potassium penicillin, strychnine, and kindling in altering seizures activity. With the exception of the alumina gel model, vagus nerve stimulation did effect the heart and respiratory rate, which may have contributed to the alteration in seizure activity. Localization of vagus initiated activity in the brain has been observed through animal studies of *FOS* immunoreactivity and regional brain glucose metabolism and PET imaging in human patients. The [^{15}O] H_2O PET Study demonstrated that VNS by the NCP System does increase blood flow in rostral medulla and right thalmus, right anterior parietal cortex and bilaterally in the hypothalamus, anterior insula, and inferior cerebellum. Decreases in blood flow were detected bilaterally in hippocampus, amygdala, and posterior cingulate gyrus.

12.4 Service

If there are questions regarding use of the NCP System or any of its accessories, contact Cyberonics at:

Cyberonics, Inc.
17448 Highway 3, Suite 100
Webster, TX USA 77598-4135
(281) 332-1375

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Cyberonics®
DEVICES FOR EPILEPSY

MODEL 400
TUNNELING TOOL

For Use With Cyberonics
Model 300 Series
Bipolar Vagus Nerve Stimulation Leads

Directions for Use

CE 0344

Authorized by KEMA in 1994 for the Active Implantable Medical Device Directive 90/385/EEC; amended by 93/42/EEC and 93/68/EEC.

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Description and Use

General Description

The Cyberonics®[1] Model 400 Tunneling Tool is designed for use during implantation of the Cyberonics Model 300 Bipolar Vagus Nerve Stimulation Lead and is recommended for subcutaneous tunneling of the lead connectors from the neck to the chest. Dimensions have been optimized to minimize the risk of damage to the lead electrodes which may occur with the use of general-purpose tunnelers.

The Model 400 Tunneling Tool consists of a stainless-steel shaft, fluorocarbon polymer sleeve (28 cm length X 6.4 mm inside diameter X 7.9 mm outside diameter) and acetal bullet (7.9 mm outside diameter). The overall length of the tool is 34 cm. A diagram of the assembled device is shown in Fig. 1.

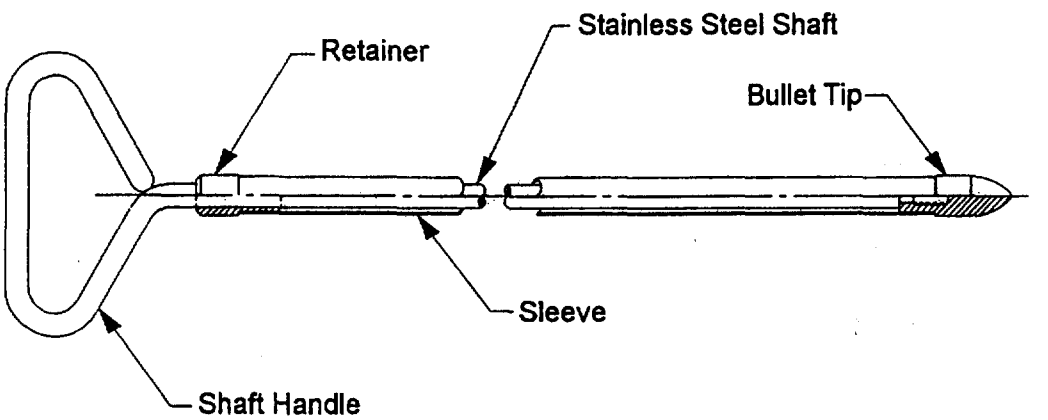

Fig. 1. Assembled Model 400 Tunneling Tool

Indications

The Model 400 Tunneling Tool is an integral component of the NeuroCybernetic Prosthesis (NCP®)[2] System and is indicated for use only to aid in placement of a Cyberonics Model 300 Series Bipolar Vagus Nerve Stimulation Lead.

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[1] Cyberonics is a registered trademark of Cyberonics, Inc.
[2] NCP is a registered trademark of Cyberonics, Inc.

Symbols and Definitions

⚠ Notice for reader to pay special attention to following details

Denotes for Single Use Only

LOT Denotes batch code

Denotes Date of Manufacture

Precautions

- The Model 400 Tunneling Tool is supplied **NON-STERILE** and must be sterilized before use.
- The tool should not be reused.
- Care should be taken not to injure any arteries, veins, or nerves during the tunneling procedure.

Directions for Use

The following directions cover the use of the Tunneling Tool. Placement of the lead electrodes onto the nerve is explained in the Physician's Manual for the Model 300 Series Bipolar Vagus Nerve Stimulation Lead. Implantation of the Model 100 NCP Generator is explained in the Physician's Manual for the Model 100 NCP Generator.

The Tunneling Tool is supplied **non-sterile** in an assembled configuration in a sealed pouch.

1. Remove the Tunneling Tool assembly from the pouch in a clean work area. Unscrew the bullet tip from the end of the shaft and disassemble the tool into its three components (shaft, sleeve, and bullet tip). Place these parts in an appropriate container and sterilize before use, using a 10-minute flash sterilization procedure. ⚠Recommended parameters are 132°C (270°F) and a 10-minute cycle.

2. At the time of surgery, place the components of the Tunneling Tool onto the sterile field and reassemble prior to use. This is done by placing one end of the sleeve over the shaft until it seats onto the retainer at the handle end of the shaft. Carefully screw the bullet tip onto the shaft. The sleeve should be centered over the neck of the bullet and should be lightly compressed between the shaft retainer and bullet (see Fig. 1). ⚠**DO NOT OVER-TIGHTEN THE BULLET.**

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3. The Tunneling Tool can now be manually shaped as required, and is inserted by exerting force on the handle end and directing the tool through the subcutaneous tissue as needed.

⚠ **Note:** Excessive bending or overforming of the sleeve may cause the sleeve to kink.

4. Once the chest and neck incisions are made, the Tunneling Tool and the lead are ready to be passed. Cyberonics recommends that the bullet-tip end first be placed through the neck incision and tunneled subcutaneously toward the chest incision. Once the bullet tip has passed from one incision site to the other, it should be unscrewed and the shaft withdrawn from the sleeve, leaving the sleeve extending through both incisions (see Fig. 2).

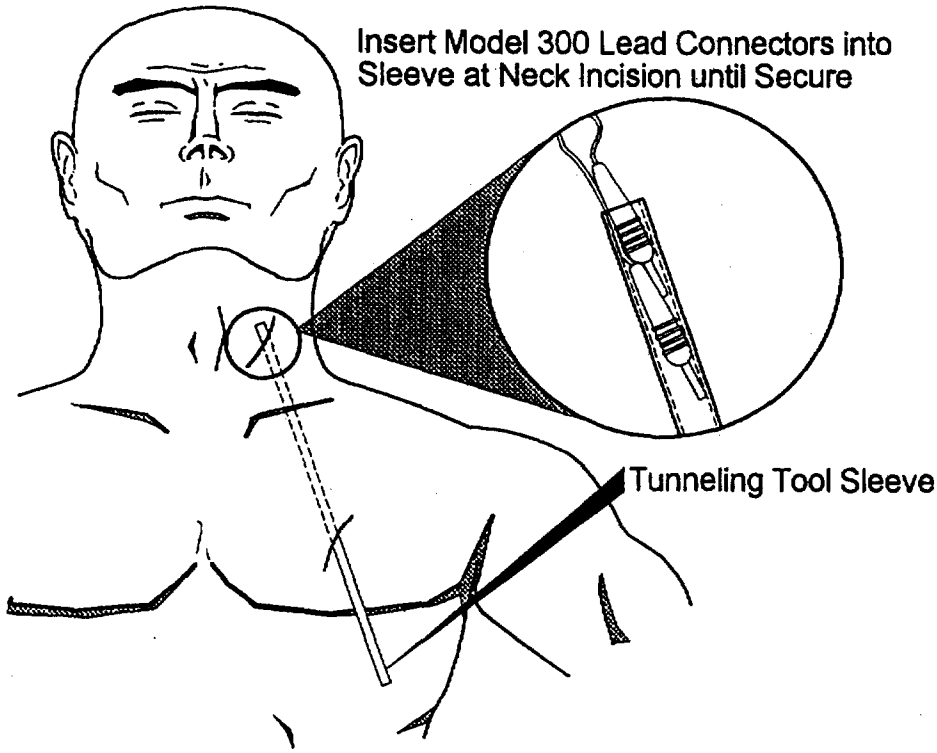

Fig. 2. Position of Sleeve and Lead Connectors

5. With the sleeve in place between the two incisions, carefully insert both lead connectors, one behind the other, inside the end of the sleeve at the neck incision (see Fig. 2). The second connector will form a slight compression fit between the first lead connector tubing and the inside of the sleeve, which will allow use of the sleeve to pull the lead connectors from the neck incision to the chest incision. After the sleeve and connectors have been carefully pulled through to the chest incision, remove the connectors from the sleeve, leaving the electrode array at the neck incision site.

6. ⚠The Model 400 Tunneling Tool should be discarded after use.

Service

Cyberonics, Inc.
17448 Highway 3, Suite 100
Webster, TX USA 77598-4135
or
Cyberonics Europe, S.A.
Belgicastraat 2
1930 Zaventem
Belgium

Cyberonics®
DEVICES FOR EPILEPSY

PATIENT'S MANUAL

FOR

VAGUS NERVE STIMULATION

with Cyberonics' NeuroCybernetic
Prosthesis (NCP®) System

NOTE: Throughout this manual you will notice the ⚠ alert symbol. Please pay special attention to the sentences directly after this symbol.

REF 26-0002-4400 JULY 1997

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INTRODUCTION

Many people have epilepsy. Although doctors and scientists have learned a lot about epilepsy over the years and developed different drugs and other treatments, some people still continue to have seizures.

Because drugs have failed to adequately control your seizures, or because their side effects are too intolerable, your doctor has suggested trying the NCP® System. The NCP System automatically sends a mild electrical stimulation to a nerve that carries information to your brain. This nerve is called the vagus nerve, and this form of therapy is called Vagus Nerve Stimulation (VNS™).

The NCP System is implanted inside your body by a surgeon, and includes the stimulation device implanted in your chest, and the lead that attaches to the vagus nerve in your neck. The implant surgery generally lasts from one to three hours.

After the NCP System is implanted, your doctor will program the device to deliver stimulation automatically, 24 hours a day. During routine office visits, your doctor can use a special wand connected to a computer with software to change your treatment for optimal results. The NCP System is expected to last from 3 to 5 years, depending on the settings you need. The NCP device can be replaced in a simple operation generally lasting from 30 minutes to one hour.

You will also be given a magnet that you can use to activate stimulation when you want. This is in addition to the automatic stimulation. All you do is hold the magent to your body where the NCP device is implanted, and then remove the magnet. This starts stimulation. However, stimulation is stopped for as long as you hold the magnet directly over the NCP device. Your doctor and his staff will help you practice using the magnet so that you can use it properly.

The following is a quick reference guide that you can use to look up some of the most important information to remember about the NCP System. It will be most useful after you have read the whole manual.

A list of frequently asked questions is included at the end of this manual.

QUICK REFERENCE GUIDE

YOUR RESPONSIBILITIES:

- CHECK the NCP Pulse Generator daily by starting stimulation with the magnet (see **Daily Stimulation Check** section)
- USE the magnet to stop stimulation if stimulation becomes painful or irregular (see **Stopping Stimulation with a Magnet** section)
- NOTIFY your doctor immediately if: (see **Safety, Complications & Side Effects** section)
    - Your voice is constantly hoarse

- ♦ The stimulation becomes painful or irregular
- ♦ The stimulation causes any choking or difficulty breathing or difficulty swallowing
- ♦ You suspect the NCP Pulse Generator may not be stimulating properly
- ♦ You notice anything new or unusual that you associate with stimulation

- ALSO notify your doctor immediately if you stop feeling normal stimulation (see **Possible Complications Associated with Loss of Stimulation** section)
  - ♦ Your seizure frequency and/or seizure intensity and/or seizure length may increase after normal stimulation stops
  - ♦ Your seizures may increase to levels greater than those before stimulation started if normal stimulation stops
- CONTACT your doctor before having any medical tests performed (see **Environmental Hazards** section)
- CONTACT your doctor before having any other medical devices implanted (see **Environmental Hazards** section)

MY DOCTOR'S PHONE NUMBER IS _____

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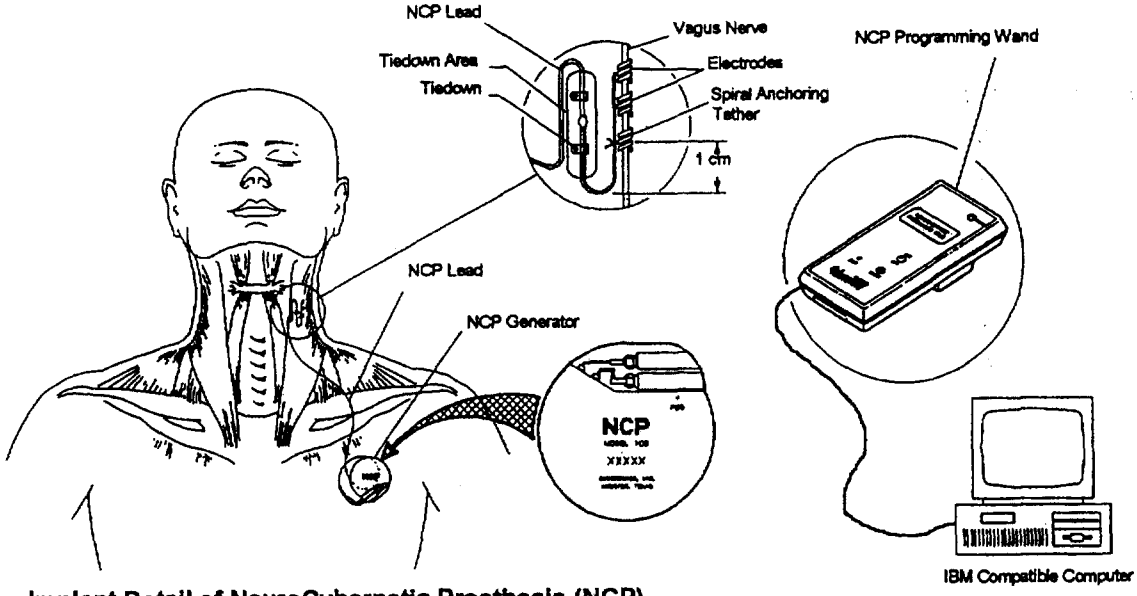
GENERAL DESCRIPTION

The Cyberonics® NeuroCybernetic Prosthesis (NCP®)[1] Pulse Generator is an implantable Pulse Generator that sends signals to the vagus nerve in order to reduce the frequency of epileptic seizures. Your doctor will determine whether the NCP Pulse Generator is the correct treatment for your type of epilepsy.

Signals are sent from the NCP Pulse Generator to the vagus nerve through the NCP Lead. The NCP Pulse Generator and NCP Lead are surgically implanted in an operation lasting approximately two hours. General anesthesia is typically used. The NCP Pulse Generator is placed in a surgically made pocket under the skin in the upper chest. The NCP Lead is attached to the left vagus nerve in the lower left side of the neck. The surgeon then connects the lead to the Pulse Generator. See Figure 1 for an illustration of NCP Pulse Generator and NCP Lead placement.

Fig. 1. Placement of Pulse Generator and Lead{tc "Fig. 1. Placement of Pulse Generator and Lead" \f g}



Implant Detail of NeuroCybernetic Prosthesis (NCP)

The NCP Pulse Generator and NCP Lead are made from materials which have a long history in medical implants. The NCP Lead is about the size and shape of a 40-cm (about 1.5 feet) piece of spaghetti. The NCP Pulse Generator is about the size and shape of a large pocket watch. It is battery powered and expected to last from three to five years depending on the settings your doctor uses.

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[1] Cyberonics and NCP are registered trademarks of Cyberonics, Inc.

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The NCP Pulse Generator stimulates in two ways. First, your physician sets the Pulse Generator to automatically stimulate. Typically, settings are 30 seconds ON and 5 minutes OFF 24-hours a day. Second, you are given a magnet which can be placed over the NCP Pulse Generator and then immediately removed to start stimulation (see **Starting Stimulation with a Magnet** section). Also, the magnet may be used to stop stimulation by holding the magnet over the NCP Pulse Generator (see **Stopping Stimulation with a Magnet** section). The Pulse Generator will not stimulate while a magnet is over it.

The NCP Pulse Generator has a variety of settings for your doctor to choose from. He or she can change the NCP Pulse Generator settings during an office visit by using an NCP Programming Wand and computer with software (see Figure 1). The wand is placed over your chest and sends the setting changes from the computer into your NCP Pulse Generator. It is a simple procedure that takes only a few minutes. You will feel nothing during device programming.

Symbols and Definitions

⚠ Pay special attention to items marked with this symbol.

Indications

The NCP System is indicated for use as an add-on or additional therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures (seizure that starts in one part of the brain), which haven't responded to available treatments.

Types of People Using Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS) has been found safe and effective in people who have "complex partial seizures" (seizure that starts in a defined location in the brain and adversely affects thought process or awareness) that are not controlled by other types of therapies. However, people with other seizure types have used the NCP System as part of clinical studies. Your doctor should determine whether your epilepsy is the correct type to treat with VNS and whether you have any other medical conditions which warrant extra consideration. People who use VNS generally keep taking their antiepileptic medications even while receiving stimulation.

Over 450 people have been involved in clinical trials testing VNS. Most of these patients had over six seizures per month in spite of taking epilepsy medication, and all of them had at least one seizure per month. The typical trial patient was approximately 33 years old (range 3 to 63) and had epilepsy for over 20 years before trying VNS. Most of these patients took two antiepileptic drugs while they received stimulation. Both men and women were tested with VNS. Some patients have received VNS for almost 8 years. Over 1,000 people have been implanted with the NCP System throughout the world.

Contraindications

The NCP System cannot be used in people after either both vagus nerves are cut or after the left vagus nerve is cut.

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⚠ WARNINGS

⚠ **Avoid Excessive Stimulation**: Excessive stimulation can be produced by frequent magnet activation (> 8 Hours of continuous magnet activation).

⚠ **Aspiration** (fluid in the lungs) may result from the increased swallowing difficulties reported by some people during stimulation. **People who have pre-existing swallowing difficulties** are at greater risk for aspiration.

⚠ **Use the magnet** to stop stimulation if you suspect the device is not operating properly or is causing painful stimulation. If this occurs, you should immediately contact your physician for further evaluation. Surgery may be required if a malfunction occurs.

You should also review the above warnings with your doctor, or any other warnings or issues which might be appropriate to discuss (such as Sudden Unexplained Death in Epilepsy or SUDEP).

PRECAUTIONS

⚠ **Throat pain** may result from stimulation.
People who smoke may have an increased risk of throat pain.

⚠ **Shortness of breath** may result from stimulation.
People with chronic pulmonary disease (breathing difficulties) may have an increased risk of shortness of breath from stimulation.

Complications of NCP System therapy could include those related to:

- Possible implantation complications
- Possible NCP Pulse Generator malfunctions
- Possible complications associated with loss of stimulation
- Possible complications associated with manipulation of the NCP Pulse Generator and NCP Lead

Although most people have considered the side effects and complications associated with implantation and stimulation to be minor, the following information is given so that you will have a complete understanding of treatment with the NCP System.

Possible Implantation Complications
Implantation of the NCP Pulse Generator is similar to implantation of a heart pacemaker, with the addition of the neck incision for the NCP Lead. Along with scarring and the normal risks associated with any surgical procedure, complications which may be associated with NCP System implantation include, but may not be limited to:

- skin irritation
- pain at the incision site
- infection

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- breaking out through the skin or movement of the NCP Pulse Generator and/or NCP Lead
- unplugging of the NCP Lead from the NCP Pulse Generator
- breakage or disolving of the NCP Lead
- blood clot
- pocket of fluid
- solid tissue formation
- inflammation
- tissue reactions
- damage to neck or facial nerves or muscles (paralysis)

All of these conditions may occur on a temporary (short term) or permanent (long term) basis.

Implantation of the NCP Lead may be associated with nerve constriction (squeezing of the nerve). Constant hoarseness within a few days after implant could indicate nerve constriction. ⚠ Your doctor should be notified **immediately** if you notice a constant hoarseness.

Possible NCP Pulse Generator Malfunctions
Pulse Generator malfunction, although unlikely, is possible. Stimulation associated with a malfunction may cause intense pain in the neck, hoarseness, choking, and difficulty in breathing. ⚠ If at any time you notice any of these symptoms, or if stimulation is occurring continuously, is painful or irregular, the magnet should be placed and held over the NCP Pulse Generator to stop stimulation (see **Stopping Stimulation with a Magnet** section below). You should then notify your doctor **immediately**. Stimulation due to a malfunction could possibly damage the nerve, leading to permanent hoarseness or other adverse effects, and cause the NCP Pulse Generator to last less time than was expected.

Possible Complications Associated with Loss of Stimulation
As the Pulse Generator battery loses power, the Pulse Generator may not stimulate at the same strength as it did before. You may notice this as irregular stimulation. When the battery of the NCP Pulse Generator completely loses power, stimulation will stop. See **Daily Stimulation Check** section for information on checking for stimulation. ⚠ Your seizure frequency and/or seizure intensity and/or seizure length may increase after stimulation stops. It is possible that your seizures may increase to levels greater than those before stimulation was started. If you suspect that the NCP Pulse Generator may not be stimulating properly, you should call your doctor.

Possible Complications Associated with Manipulation of the NCP Pulse Generator and NCP Lead
⚠ Never move or twist the NCP Pulse Generator as it may damage the NCP Lead or possibly damage your vagus nerve.

⚠ Possible Side Effects
The most common side effect associated with stimulation is hoarseness during stimulation (hoarseness should only occur during the ON time, which is usually 30 seconds). Most people tolerate the hoarseness well. ⚠ YOU SHOULD NOTIFY YOUR DOCTOR ANY TIME

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THE HOARSENESS BECOMES PERSISTENT, BOTHERSOME (uncomfortable) OR CONTINUOUS.

Other side effects likely associated with stimulation include:

- throat pain
- muscle tingling
- muscle pain
- nausea
- choking sensation
- vomiting
- coughing
- muscle movement
- shortness of breath
- stomach discomfort
- aspiration (fluid in lungs)
- difficulty swallowing

Stimulation may worsen conditions such as breathing disorders (asthma and bronchitis). Discomfort, including breathing difficulty, can occur if NCP Pulse Generator settings are increased too rapidly. Ask your doctor to decrease or change the stimulation settings anytime the side effects become intolerable. ⚠Also, the magnet settings should be tested while you are in the doctor's office to make sure you are **able to tolerate the settings.** Stimulation, or the stoppage of stimulation, may possibly cause a worsening of seizures.

⚠ENVIRONMENTAL HAZARDS

While the system is designed to minimize the possibility that electrical noise will affect the system's operation, environmental sources of noise may damage the NCP Pulse Generator or interfere with its proper functioning. The probability of interference or damage varies with the strength and nature of the noise source.

Properly operating cellular telephones, microwave ovens, electrical ignition systems, power transmission lines, theft prevention devices, and metal detectors should not affect the Pulse Generator. Similarly, most routine diagnostic procedures such as fluoroscopy and X rays should not affect system operation. However because of higher energy levels, sources such as transmitting antennas may interfere with the system.

Make sure that medical personnel are informed that you have an implant in your chest. Some medical equipment and procedures, such as therapeutic radiation, lithotripsy, procedures for heart problems, and surgery with certain electrical instruments could damage the NCP Pulse Generator and Lead. Also, Magnetic Resonance Imaging (MRI, a type of x-ray used in imaging the inside of the body) of the NCP System using a **body coil** could damage your vagus nerve. Most other routine diagnostic procedures (such as fluoroscopy, X rays, and diagnostic ultrasound) should not affect your NCP System. **Contact your doctor before having any medical tests performed so that any necessary precautions may be taken.**

⚠Strong magnets, hair clippers, vibrators, loudspeaker magnets, and other similar equipment can cause inadvertent activation. Do not place these things near your chest.

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⚠MRI can be performed if a head coil is used. MRI using the whole body coil is not recommended because it could damage the vagus nerve. Contact your doctor before having an MRI performed so that it can be discussed with the MRI personnel.

⚠Avoid areas in which pacemaker warning signs are posted.

Properly operating microwave ovens, electrical ignition systems, power transmission lines, theft prevention devices, and metal detectors SHOULD NOT affect the Pulse Generator. However strong sources such as transmitting antennas could interfere with the NCP System.

NCP Pulse Generator Effects on Other Devices

During stimulation the NCP Pulse Generator may interfere with devices such as pocket transistor radios and hearing aids but SHOULD NOT trigger airport metal detectors or theft prevention devices. The NCP Pulse Generator may also interfere with ECG/EKG recordings or affect the operation of other implanted devices (such as heart pacemakers and implantable defibrillators). Contact your doctor if you need to have other devices implanted.

Magnet Effects on Other Equipment

The magnet provided for activation or inhibition of the NCP Pulse Generator MAY DAMAGE televisions, computer disks, credit cards, and other items affected by strong magnetic fields. Do not store magnets near these types of equipment.

USES OF THE MAGNET

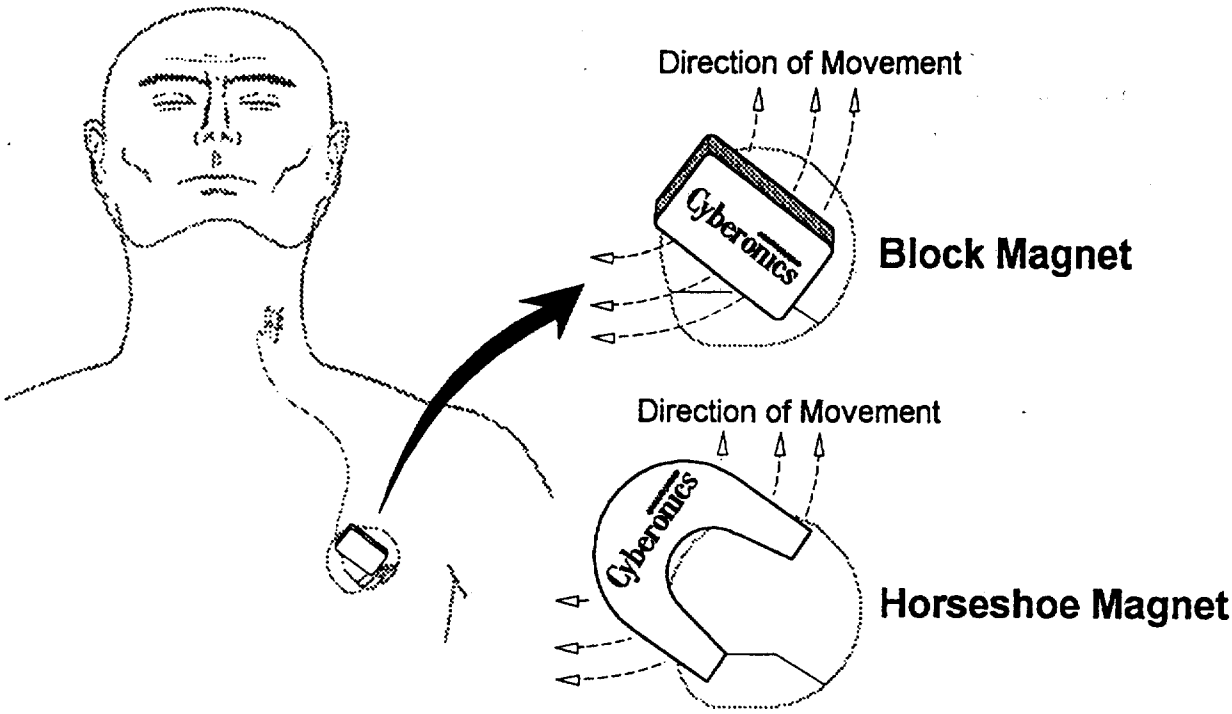
A magnet can be used to either start or stop stimulation. One of the most important uses of the magnet is to start stimulation and verify operation of the device. Cyberonics recommends that this be done daily.

The magnet may be used to start stimulation during an aura or at the beginning of a seizure. Although many people do not benefit from starting stimulation with the magnet, some report that their seizures are stopped, less intense and of a shorter duration. Magnet activation may be started by placing a magnet near the NCP Pulse Generator and then removing the magnet. Two differently shaped magnets are available from Cyberonics. The horseshoe magnet is strongest, but is also the largest. The block magnet is not as strong, but it is smaller and easier to store and manipulate. Both of these magnets can be used to start and stop stimulation. Proper magnet placement techniques for the magnets are shown in Fig. 2.

⚠ **Avoid Excessive Stimulation**: Continuous magnet use (> 8 Hours of <u>continuous</u> magnet activation) should be avoided because of the possibility of nerve damage.

Magnet Placement

Fig. 2. Magnet Placement{tc "Fig. 2. Magnet Placement" \f g}



NOTE: All magnets may lose their effectiveness over time. Avoid dropping the magnets. Do not store magnets near other magnets or near the equipment listed under the **Magnet Effects on Other Equipment** section.

Starting Stimulation with a Magnet

To start stimulation, put the magnet near the NCP Pulse Generator for at least one second and then immediately remove it. Removal of the magnet causes the NCP Pulse Generator to start operating at the settings your doctor set for magnet use. Ask your doctor to test your magnet settings before you leave the office to be sure you can tolerate the settings.

Daily Stimulation Check

Cyberonics recommends that you use the magnet to check that your Pulse Generator still works. This should be done once every day as discussed above.

⚠Stopping Stimulation with a Magnet

To stop stimulation put the block or horseshoe magnet over the NCP Pulse Generator and keep it there. The Pulse Generator will not stimulate while the magnet is over it. When the magnet is removed stimulation will start again in a short period of time. If you notice unusual or painful stimulation, use the magnet to stop stimulation by placing the magnet directly over your Pulse Generator and leaving it there. You may need to secure the magnet by taping it to your chest.

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Then contact your doctor immediately. Depending on Pulse Generator placement, some movement of the magnet may be needed.

REGISTRATION

A wallet-sized card should be given to you by your doctor or hospital personnel after your surgery. It contains information about your NCP Pulse Generator and NCP Lead. ⚠You should carry this card at all times. Cyberonics may contact you after your surgery to verify your address and phone number. Please send Cyberonics a change of address notice if you move.

This information will become part of the Cyberonics registry of individuals who have the NCP system and will be used as a permanent record of implant information. Cyberonics and all implantable device makers are required by government agencies to be able to contact people in case of device-related emergencies. Cyberonics maintains this information in confidential files and will release information only if required by law.

FOLLOW-UP INFORMATION

During the first few weeks following implantation you should see your doctor to check wound healing and proper Pulse Generator operation. Cyberonics recommends that the NCP Pulse Generator be turned off for about two weeks after implant to allow adequate healing. At this time your doctor will set your Pulse Generator to the settings he or she feels are appropriate.

At each visit your doctor will test the NCP Pulse Generator and NCP Lead to verify proper operation. You will be seen by your doctor according to a schedule that you both agree on. Cyberonics recommends that you be seen by your NCP doctor at least every 6 months.

BATTERY DEPLETION

The NCP Pulse Generator battery is expected to last 3 to 5 years, but its lifetime is highly dependent on the settings your doctor chooses and how the lead and nerve interact over time. When the battery is depleted, the NCP Pulse Generator will stop stimulating and the Pulse Generator must be replaced with a new Pulse Generator to continue stimulation. Replacement surgery usually takes about one hour and is typically done with a local anesthetic.

⚠Cyberonics recommends that you check the NCP Pulse Generator by using the magnet daily. This will allow you to know that stimulation is still working correctly.

⚠If you suddenly stop feeling stimulation, or it suddenly feels different, contact your doctor to have the NCP Pulse Generator tested. When stimulation stops your seizure frequency and/or seizure intensity and/or seizure duration may increase.

PULSE GENERATOR DISPOSAL

Patients should not be cremated without removing the NCP Pulse Generator, because it can explode if exposed to incineration or cremation temperatures.

When the device is explanted it should be returned to Cyberonics for safe disposal.

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TYPICAL QUESTIONS

How do most people respond to NCP System treatment?

In clinical studies most patients had a reduction in seizure frequency. However, some had no change or had an increase in seizure frequency.

Can I tell before being implanted with the NCP System whether I will be helped by the device?

There is no way of telling whether you are likely to be one of the patients who might benefit or get worse from this treatment.

What will the surgery be like?

You will be given anesthesia so that you can sleep during the surgery, which typically takes 1 or 2 hours. Your doctor will probably advise you to stay in the hospital that night, although outpatient surgery may be possible. Ask your surgeon to tell you more about the anesthesia and the surgery so you will know what to expect.

Are there risks associated with the surgery?

Any surgical procedure carries some type of risk. It is important that you discuss this question with your surgeon.

Will the scars be noticeable?

Every person has different healing and scarring results. Most people do not consider the scarring after implant to be a major concern. Your surgeon can use extra care when closing the incisions so the scars will be less noticeable. Discuss this with your surgeon.

Will people be able to see the implant through the skin?

The implantable NCP device is shaped like a circular disk, 55 mm in diameter and 13.2 mm thick. It's about the size of a thin pocket watch and weighs 55 grams. If you have a small frame or are very thin, the device will be visible as a bulge below your left collar bone.

What happens after the surgery?

Your doctor will program your treatment schedule into your NCP System. If the stimulation feels uncomfortable to you, your doctor can change it to make you more comfortable. Every time you visit your doctor, the wand can be used to check and fine tune your stimulation settings.

Your stimulator will work automatically without you having to do anything. However, if you wish, you can use the magnet to start stimulation also. Your doctor will give you the magnet and tell you how and when it can be used.

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Will I be able to tell when the stimulator is on?

Many people notice a tingling sensation and/or a change in their voice during stimulation (commonly described as hoarseness). This usually becomes less noticeable over time.

What are the side effects of VNS Therapy?

The most common side effects reported for the NCP System are a tingling sensation in the neck and mild hoarseness in the voice, both of which occur only during stimulation. Other less common adverse events are discussed in the sections above.

What are the results of the NCP System in clinical studies?

Your physician can provide you with information about the clinical studies to date, including published articles describing the results.

What does the magnet do?

If you put the magnet over the device in your chest and then take it off, it tells the NCP device to deliver an extra stimulation, regardless of your treatment schedule. You can easily use the magnet yourself, or it can also be used by your relatives, companions, or caregivers. Holding the magnet over the device in your chest will turn the stimulation OFF for as long as the magnet is kept over the device.

Can I stop all my seizures by using the magnet to activate the stimulation burst?

Every person experiences different results from magnet stimulation. Some report that the magnet stops or lessens most or all of their seizures. But for some people, the magnet has only limited or no effect.

When should I use the magnet?

The magnet should be used as soon as you believe that you are having a seizure. If you experience an aura before a seizure, apply the magnet immediately. The magnet may also be used at any time during a seizure. Also, you should use the magnet daily to test that the device is operating correctly.

Do I have to use the magnet?

No, not to start stimulation. Whether you use the magnet or not is completely up to you and your companion. However, Cyberonics recommends using the magnet daily to test that the device is operating correctly.

How does the magnet work?

The NCP device has electronic circuitry that recognizes the presence of the magnet and activates extra stimulation.

Can any magnet be used?

Only the Cyberonics magnet is recommended for use with your NCP System. If you lose your magnet or require extra magnets, contact your doctor. However, in an emergency situation, you can try other magnets.

Will the magnet affect my normal treatment schedule?

The magnet will always override your normal stimulation program, regardless of whether the device is currently stimulating or not. Once the magnet-activated stimulation ends, the NCP System will return to the treatment schedule set by your doctor.

How often can I use the magnet?

As often as you like provided you do not exceed more than 8 hours of continuous magnet activation. However, frequent use of the magnet will deplete the battery in the NCP device. If you find that you are using the magnet frequently, you may be better off having your normal stimulation parameters adjusted. If this happens, be sure to tell your doctor at your next appointment.

The magnet typically gives 30 or 60 seconds of stimulation each time you use it, depending on what your doctor decides to set. Therefore, there is no point in using the magnet again within the same time period.

What if the magnet is accidentally left over the NCP device for any period of time?

While the magnet is held over the device, no stimulation will be delivered. The magnet stimulation only starts after the magnet has been removed.

Is it possible to stop all stimulation using the magnet?

Yes. If you notice unusual or painful stimulation, hold the magnet in place and leave it there - the magnet will stop all stimulation while it is in place over the NCP device. You may need to secure the magnet by taping it to the chest. It is important that you contact your doctor immediately.

Who should carry the magnet and how?

You should carry the magnet, so that it is always available. Many people carry the magnet in a small pouch belt around their waist. You may also want relatives or caregivers to have access to an NCP magnet for use if they observe you having a seizure.

Is the magnet an environmental hazard?

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The NCP magnet may damage computer disks, credit cards, and other items affected by strong magnetic fields. Try to keep your magnet at least 8 to 10 inches away from any of these items if possible.

MORE QUESTIONS

If there are additional questions regarding the NCP System, any of its accessories, or general questions about vagus nerve stimulation, contact your doctor.

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