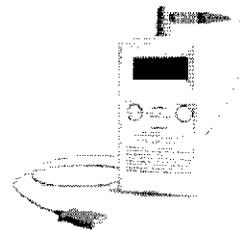


# Patient LABELING



# New Humanitarian Device Approval



Picture of Device

FDA approved this device under the Humanitarian Device Exemption (HDE) program <http://www.fda.gov/cdrh/ode/hdeinfo.html>. See the links below to the Summary of Safety and Probable Benefit (SSPB) and other sites for more complete information on this product, its indications for use, and the basis for FDA's approval.

**Product Name:** NeuRX DPS™, RA/4 Respiratory Stimulation System

**Manufacturer:** Synapse Biomedical Inc.

**Address:** 300 Artino Street, Oberlin, OH 44074

**Approval Date:** June 17, 2008

**Approval Letter:** A link to web for the approval letter

## What is it?

The NeuRX DPS™, RA/4 Respiratory Stimulation System is a diaphragm (muscle that controls breathing) pacing system.

## How does it work?

The NeuRX DPS™, RA/4 Respiratory Stimulation System works by providing an electrical stimulus to the diaphragm, thus initiating movement and allowing the patient to breathe.

## When is it used?

It can be used for at least for at least 4 hours a day by patients as an alternative to mechanical ventilation.

## What will it accomplish?

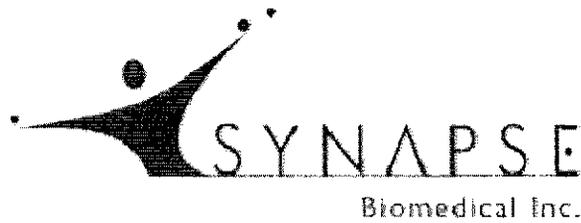
It may allow the patients to be free of mechanical ventilation for at least 4 continuous hours a day.

## When should it not be used?

This device can not be used if the patient's diaphragm is not capable of being stimulated.

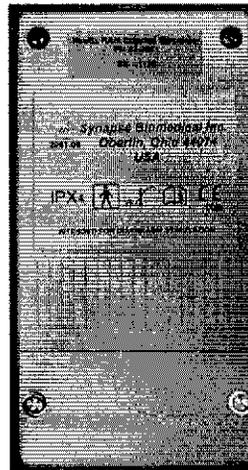
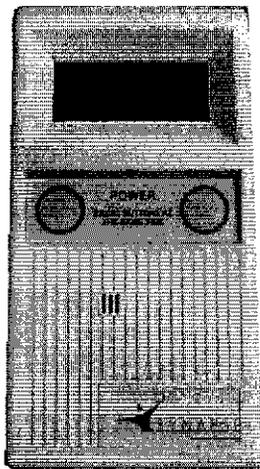
## Additional information:

**SSPB and Labeling:** A link to web



## Patient Instruction Manual

### NeuRx RA/4 Pacing System



#### **HUMANITARIAN DEVICE:**

**Authorized by Federal law for use in the treatment of respiratory insufficiency for high-level spinal cord injured patients. The effectiveness of this device for this use has not been demonstrated.**

Synapse Biomedical, Inc.  
300 Artino St.  
Oberlin, OH 44074  
Tel: (440) 440774-2488  
Fax (440) 774-2572

## Key Contact Information

Doctor \_\_\_\_\_

Nurse \_\_\_\_\_

Contact Name \_\_\_\_\_

Center Name \_\_\_\_\_

Telephone \_\_\_\_\_

Fax # \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_

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# LABEL SYMBOLS

Below is an explanation of the symbols used on this product and its packaging. Refer to the appropriate product to see symbols that apply.

## CONTROL SWITCH SYMBOLS

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### **CAUTION**

ON/OFF switch buttons. Must be pressed simultaneously to activate and deactivate the Stimulator.

## SYMBOL EXPLANATIONS

---



FOLLOW INSTRUCTIONS FOR USE



IEC 60601-1, Type BF Equipment



Conformite Europeene (European Conformity)  
This symbol means that the device fully complies with Medical Device Directive 93/42/EEC.

IPX4

The device is protected from splashing water.



Output voltages may approach 50 volt D.C. during operation.



Serial Number



Moustapha Diop  
6 Allée Paul Verlaine  
95350 Saint Brice Sous Foret  
France

## **WARNINGS AND CAUTIONS**

**Caution: Federal Law (USA) restricts this device to sale, distribution and use by or on the order of a physician**

**Caution: The long-term effects of chronic electrical stimulation are unknown.**

**Caution: Safety has not been established for the use of the device during pregnancy.**

**Warning: This device is electrically powered and may produce tissue damage or electrical hazard if improperly used.**

**Warning: This device should be kept out of the reach of children.**

**Do NOT attempt to open the Stimulator case; the device has NO patient-accessible controls. Doing so can result in damage to the device.**

**Do NOT use in patients with an implanted electronic device (Insufficient clinical data is available, at this time, to establish safety with a cardiac pacemaker).**

**Do NOT connect the patient to high-frequency surgical equipment while connected to the external stimulator. Doing so can result in burns at the site of the stimulator electrodes and possible damage to the stimulator.**

**Do NOT subject Patients implanted with the NeuRx RA/4 Pacing System to Magnetic Resonance Imaging (MRI).**

**Do NOT use this device if skin in the electrode implant area is swollen, infected, or inflamed or if there are skin eruptions such as phlebitis, thrombophlebitis, or varicose veins.**

**Avoid operating this device in close proximity (for example 3 feet) to shortwave or microwave therapy equipment that may produce instability in the stimulator output.**

**Avoid accidental contact between connected but unused applied parts (cable or leads) and other conductive parts including those connected to ground (protective earth).**

## **ELECTROMAGNETIC INTERFERENCE WARNING**

**Do follow the EMC information provided. The NeuRx RA/4 Stimulator needs special precautions regarding electromagnetic compatibility (EMC).**

**Use Caution around portable and mobile RF communications equipment as these can affect the NeuRx RA/4 Stimulator.**

**Do NOT use cables or accessories other than those specified. Doing so may result in increased emissions or decreased immunity of the NeuRx RA/4 Stimulator.**

## **FLAMMABILITY WARNING**

**Do NOT use the NeuRx RA/4 Stimulator in an oxygen enriched environment or near a flammable anesthetic mixture with air, oxygen or nitrous oxide. The NeuRx RA/4 Stimulator is not categorized as AP (anesthetic-proof) or APG (anesthetic-proof category G - gas) type of equipment.**

# **PRECAUTIONS**

**Spinal Cord Injury (SCI) patients must have a mechanical ventilator available at all times. If you do not feel that you are receiving adequate ventilation or if any malfunction of the pacing device is suspected, you should be placed on mechanical ventilation immediately and the pacing system turned off. Caregiver availability and monitoring should be consistent with when a ventilator is used.**

**Do NOT expose the device to excessive moisture or severe mechanical shock. If display indicates system failure, pain is felt at the electrode site, or device is exposed to moisture or shock, disconnect the cable and contact Synapse Biomedical.**

**Do NOT conduct diathermy treatment or electro cauterization in the area of the implanted electrodes.**

**Do NOT have the stimulator connected during any type of electrical diagnostic treatment such as EMG or ECG.**

**Precautions should be observed when there is a tendency to hemorrhage following acute trauma or fracture, following recent surgical procedures when muscle contraction may disrupt the healing process, or where sensory nerve damage is present.**

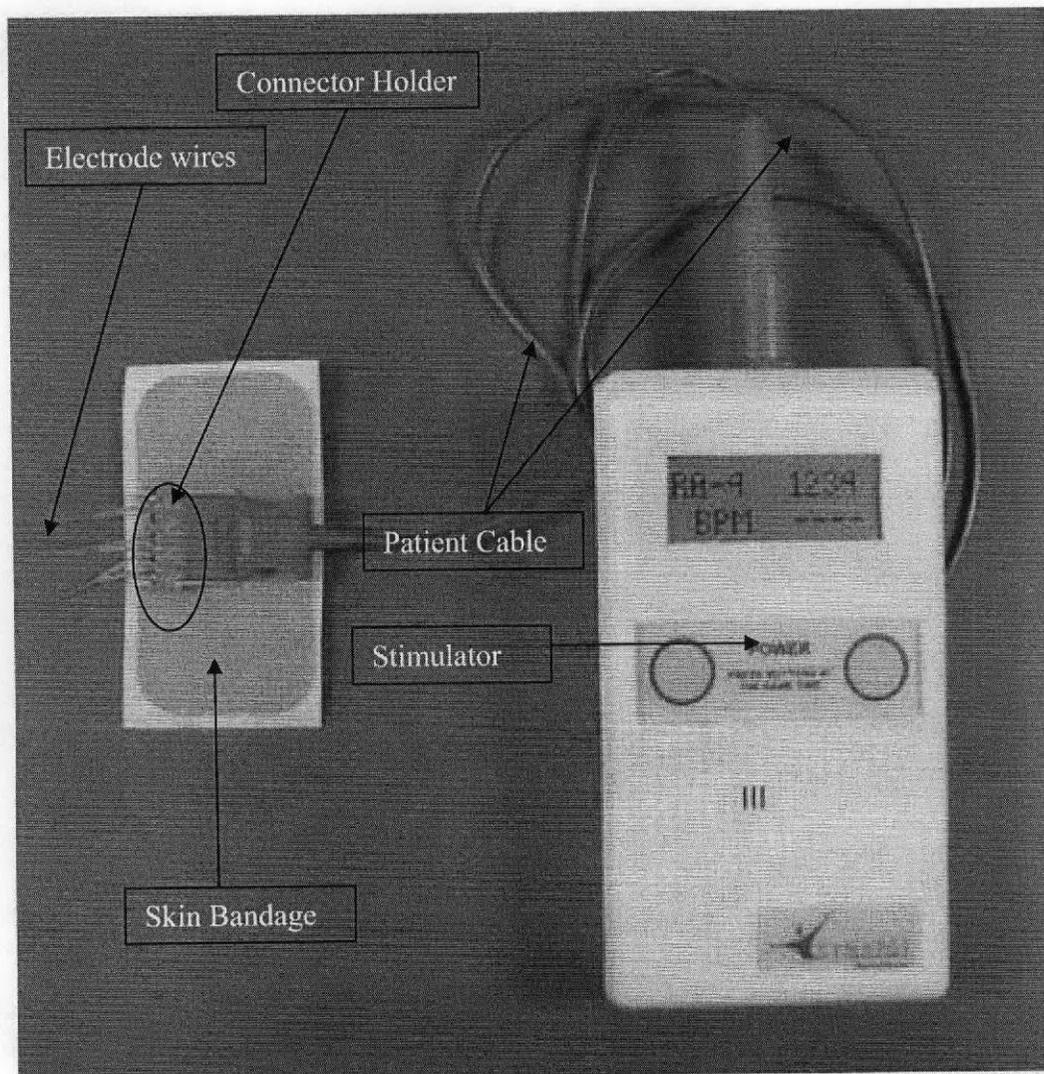
**Some patients may experience skin irritation or hypersensitivity due to the electrical stimulation, the adhesive on the skin bandage, or the transparent dressing (Tegaderm™ and Op-Site™ are examples of transparent dressings) used over the gauze that covers the electrodes. Contact your physician or center if this occurs as irritation can usually be reduced by changing the stimulus parameters or removing the adhesive.**

## DEVICE DESCRIPTION

The NeuRx RA/4 System is a system designed to help patients breathe by stimulation of their diaphragm muscles.

It is implanted using standard laparoscopic surgical techniques in an outpatient procedure.

The implanted intramuscular diaphragm electrodes are connected to the NeuRx RA/4 external stimulator through the Patient Cable and the Connector Holder site.



The stimulator provides repetitive electrical stimulation to the implanted electrodes to cause the patient's diaphragm to contract and cause the patient to draw breath in a manner similar to natural breathing.

A physician will program the Stimulator so that it produces the right stimulation patterns. If the stimulation is uncomfortable, tell the physician as he or she can adjust the Stimulator to reduce or eliminate the discomfort.

The user simply connects the device to the implanted electrodes and turns it on for use; no other controls are available or necessary for operation.

During use, the stimulator should be kept close to the patient's body to avoid pulling on the cable and electrodes.

The stimulator can be placed in a pocket of the patient's clothing, a fanny pack or simply placed on a table or other convenient location.

## FUNCTIONAL FEATURES

The cable should be securely inserted into the exit site connector and the top of the stimulator. The stimulator is programmed with parameter data that satisfies the patient's specific requirements.

To turn the stimulator ON: Depress the two buttons on the front of the stimulator simultaneously.

To turn the stimulator OFF: Depress the two buttons on the front of the stimulator simultaneously.

The buttons must be depressed simultaneously as a safety feature guarding against inadvertent activation.

The stimulator has a Liquid Crystal Display (LCD) that provides stimulator operational information.

RA-4	1234
15 BPM	AAAA

The stimulator indicates the Breath-per-Minute (BPM) rate and when the individual electrodes are active.

During the inspiration phase, a letter 'A', 'B' or 'C' is shown below each output number indicating that the stimulator is working well.

During the expiration phase, a '-' character is shown below each output number indicating that the stimulator is not active.

In the event that an 'X' appears below an output number, then a problem exists and your physician, center or Synapse Biomedical should be contacted.

The backup Stimulator may be carried with the patient as a spare Stimulator. It can be used at any time and may be helpful when diagnosing Stimulator or patient cable issues. The backup Stimulator should be cleaned and stored just like the Stimulator used daily. Your physician, center or Synapse Biomedical should be contacted when issues are discovered.

In the event that a '?' appears below an output number, it should be immediately followed by a letter. This can occur normally when the pulse modulation parameter is set at a high value or when the pulse width parameter is less than 50  $\mu$ sec. Each stimulator is programmed with settings that were established during the conditioning session. This is considered a normal event.

## **SCI PATIENT INFORMATION**

Patients with high-level spinal cord injuries typically experience chronic ventilatory insufficiency due to respiratory muscle paralysis. These patients historically have been supported predominantly through positive pressure mechanical ventilation. Alternatively, patients may be ventilated through activation of the nerves that cause the diaphragm to contract and create an inspiration. A device such as the NeuRx RA/4, that is surgically implanted in the diaphragm, does this and has given SCI patients the ventilatory support and freedom to experience a normal breathing pattern with the NeuRx RA/4 device as long as they have an intact phrenic nerve.

The first step in using the NeuRx RA/4 device is the process of increasing diaphragm muscle strength. Patients who have long standing and significant respiratory paralysis will require conditioning of the diaphragm muscle in order to sustain ventilation. The more the diaphragm is conditioned, the stronger the diaphragm will become.

Conditioning can happen every hour. In the beginning, the recommended stimulator usage for SCI patients is 15 to 30 minutes each session. As the diaphragm gets stronger, the length of sessions should increase and the number of daily sessions should decrease. Allow 45-60 minutes between sessions to allow the diaphragm to fully recover. Always consult your physician before making any changes to daily pacing sessions.

# CONDITIONING SESSIONS

The following describes the process of one conditioning session:

- Secretions should be cleared prior to conditioning and managed throughout the conditioning session.
- Connect patient cable to orange connector block and to the stimulator.
- Place pulse oximeter on patient and continuously monitor throughout conditioning session.
- Turn stimulator on and remove from ventilator.
- Allow patient to get comfortable on stimulator (2 – 3 minutes) and measure tidal (breath) volumes with Respirometer. Make note of tidal volume, pulse oximeter reading and any comments, complaints, or discomforts.
- At the midway point of a conditioning session, measure tidal (breath) volumes with Respirometer. Compare to initial readings and, using the BORG scale below, determine the effort to breathe. Make note of tidal volume, pulse oximeter reading and any comments, complaints, or discomforts. If the effort to breathe on the BORG scale is 4 or greater, discontinue the session and return to the mechanical ventilator. If the pulse oximeter reads below 90%, discontinue the session and return to the mechanical ventilator.
- Prior to ending a conditioning session, measure tidal (breath) volumes with Respirometer. Make note of tidal volume measurements, pulse oximeter reading, breathing effort, and any comments, complaints, or discomforts.
- When conditioning session is over, place back on the ventilator and turn the stimulator off.
- Allow approximately 45-60 minute rest period between sessions.
- Conditioning notes should be reviewed with the physician to determine increases in conditioning time.

## **BORG Scale (breathing effort):**

- 0 = No Breathlessness at all
- 1 = Very Slight Breathlessness
- 2 = Slight Breathlessness
- 3 = Moderate Breathlessness
- 4 = Somewhat Severe Breathlessness
- 5 = Severe Breathlessness
- 7 = Very Severe Breathlessness
- 10 = Maximum Breathlessness

## CONDITIONING WARNINGS

STOP conditioning session and be placed back on the ventilator:

- If you notice any change in heart rate or feeling of chest discomfort
- If signs of shortness of breath or any discomfort persists or worsens.
- If oxygen level drops below 90%.
- If management of secretions becomes difficult.
- Your Borg scale is 4 or greater.

CAUTION: Always wear a Passy-Muir™ valve while sleeping to help prevent obstructive sleep apnea. Contact your physician if you do not already have one.

CAUTION: Use caution when eating and drinking while conditioning. A Passy-Muir™ valve should be worn during these conditioning sessions to reduce the risk of aspiration.

USE an abdominal binder when you are in your chair as this may improve your tidal (breathing) volumes.

WARNING: External electrical stimulation should not be done in the chest area.

## ALARMS

The stimulator initiates an audible alarm if it detects any of the following problems:

- If the connection from the cable to the box or the cable to the electrode wires becomes loose or disconnects a beep lasting the duration of an inhaled breath will sound. The alarm will repeat at each programmed inhalation until the cable is reconnected.
- A 10 second long beep, audible alarm will sound when the stimulator switches to the internal backup battery. The 10 second alarm repeats once every hour.
- A 20 second long beep, audible alarm will sound when the internal backup battery is low. The 20 second alarm repeats once every minute.

## CARE OF CABLE

- The cable connects the exit site connector (wires) to the stimulator.
- Do not cut, kink or pull the cable
- Do not manipulate the metal pins in the end pieces of the cable
- Do not immerse in water
- Keep extra cables in a dry secure location
- When in use, the cable should fit securely into the exit site connector and the stimulator
- The length of the cable should be long enough to provide comfort and allow range of motion without pulling on the exit site connector
- Notify your physician or center if the cable gets cut, kinked, falls in water, or has a loose connection to the exit site connector or stimulator

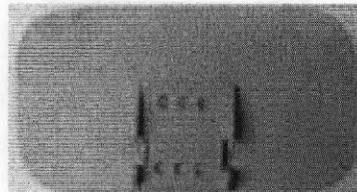


## CARE OF LEADS

- Do not pull on the wires coming through the skin
- Do not cut the wires
- Use extreme caution when shaving skin area around wire site

## CARE OF EXIT SITES & CONNECTOR

- Keep the skin at the exit sites clean and dry
- Do not scratch skin at exit sites
- Clean the exit sites with alcohol wipe, allow alcohol to dry, place gauze dressing over the exit site. Be sure to cover all the wire with the gauze. Place a transparent dressing over the gauze. (Tegaderm™ and Op-Site™ are examples of transparent dressings)
- Change the dressings every 3 days or more often if the dressing becomes wet or otherwise soiled
- If the area becomes red, swollen, painful or drainage appears: notify your physician.
- Do not manipulate the metal pins in the connector
- The exit site connector should lie flat against the surface of the skin
- Observe that the electrode leads are properly positioned within the connector
- This connector will snap into a skin bandage (provided by the research team)
- Notify your physician if there is a change in the appearance of the connector
- You should change the skin bandage weekly or if it becomes soiled



## CLEANING OF COMPONENTS

- The surfaces of the Stimulator may be cleaned and disinfected with a solution of ¼ teaspoon of household bleach (3-6% bleach) to 1 pint of water. Rubbing alcohol (isopropanol) may be used in place of the bleach. Typical cleaners such as glass or multi-surface spray cleaners are adequate. Do NOT use these cleaners on parts that will contact the skin (for example, electrodes at the exit sites).
- The surfaces of the Patient Cables may be cleaned with a mild anti-bacterial hand soap solution.

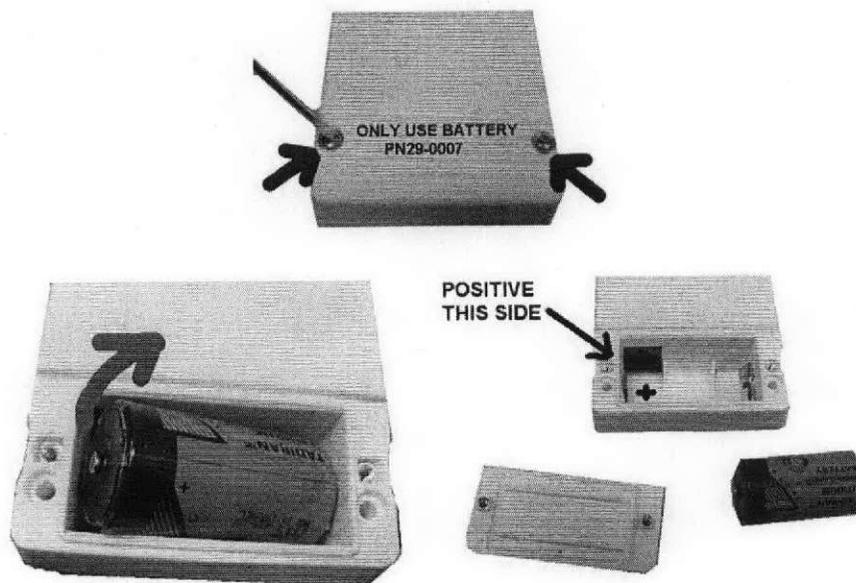
# BATTERY INSTALLATION

## WARNINGS

- If the stimulator displays "LOW BATTERY" then replace the battery immediately!
- Ensure that the Stimulator is turned OFF prior to battery replacement.
- The device contains a permanently installed back-up lithium-ion battery and is not replaceable.
- The device contains a replaceable lithium-ion battery and replacement by inadequately trained personnel could result in an explosion. Follow the following procedure:

## BATTERY REPLACEMENT

- ✓ Use only SPECIAL size "C" Lithium batteries. Do not use a standard alkaline battery in the Stimulator. The size "C" Lithium batteries can be obtained from Synapse Biomedical.
- ✓ It is very important to install battery in the correct orientation
- ✓ It should be replaced every 500 hrs (3 weeks of full time pacing)
- ✓ The stimulator will initially display "REPLACE BATT" when your battery needs replaced.
- ✓ To change the battery, use the provided flat blade screwdriver to remove the battery cover located on the back bottom of the stimulator. Remove old battery and replace with new.
- ✓ Replace the battery cover and secure with mounting screws.
- ✓ Dispose of depleted batteries according to local regulations.



## TROUBLESHOOTING

The following guide can be helpful in determining the source of problems with the DPS system:

Problem	Action
Pacing of the diaphragm stops	<ol style="list-style-type: none"> <li>1. Check the connections of the electrode leads to the Connector Holder</li> <li>2. Check the connection of the Patient Cable to the Connector Holder</li> <li>3. Check the connection of the Patient Cable to the Stimulator</li> </ol>
Patient is not receiving adequate ventilation	Disconnect the Stimulator and return the patient to a ventilator
Patient Discomfort during pacing	Contact your physician. The Stimulator program may need adjustment
Bleeding, bruising, or infection of the electrode implantation site(s)	Contact your physician.
Patient feels pain at the electrode site	Disconnect the Stimulator first, then contact your physician
Skin irritation or hypersensitivity to stimulation	Contact your physician
Multiple "X"s appear on the Stimulator display	Disconnect the Patient Cable from the Stimulator and insert Test Plug. If problem persists then contact Synapse Biomedical
The Stimulator is exposed to substantial amount of water or fluid	Disconnect the Stimulator first, then contact Synapse Biomedical
A continuous audio alarm during the Inspiration Interval.	<ol style="list-style-type: none"> <li>1. Check the connections of the electrode leads to the Connector Holder</li> <li>2. Check the connection of the Patient Cable to the Connector Holder</li> <li>3. Check the connection of the Patient Cable to the Stimulator</li> </ol>
The Stimulator beeps every hour	The Stimulator is running on its internal battery. Replace the main battery as described in this manual.
The Stimulator beeps every minute	The Stimulator is running on its internal battery and the internal battery is getting low. <b>Replace the main battery immediately</b> as described in this manual.

## SERVICE

The RA/4 External Stimulator has no user serviceable parts and it is recommended that if the unit becomes inoperable it is returned to Synapse Biomedical, Inc. for service.

## REPLACEMENT PARTS

The following standard replacement parts may be ordered directly from Synapse Biomedical, Inc. as required.

<u>ITEM</u>	<u>PART NUMBER</u>	<u>ORDER QUANTITY</u>
Lithium Battery	29-0007	6
Patient Cable	22-0003	1
Connector Holder	22-0004	15

## ACCESSORY

The following accessory may be ordered directly from Synapse Biomedical, Inc.

<u>ITEM</u>	<u>PART NUMBER</u>	<u>ORDER QUANTITY</u>
Screwdriver	29-0018	1

## SPECIFICATION

Power Source	3.6-volt lithium battery
Battery Life	500 hours
Operating Temperature	+41 to +104 F
Storage Temperature	+20 to +140 F
Relative Humidity	10% to 85%
Pulse Waveform-type	Regulated-current biphasic
Pulse Amplitude	5mA to 25mA
Pulse Width	10usec to 200usec
Pulse Period	20msec to 250msec
Inspiration Interval	0.8sec to 1.5sec
Inspiration Rate	8 to 18 Breaths per Minute

## GLOSSARY

The following definitions are helpful in understanding the procedure and components of NeuRx RA/4 Pacing System.

**Alcohol Wipe** – individually packaged pad saturated with 70% Isopropyl Alcohol used to cleanse the skin's surface. For single use only.

**Connector Holder** – a bandage with a special plastic "shell" attached that is used to end of the Patient Cable

**Covering Bandage** – an adhesive bandage that covers the electrodes that exit the skin

**Diathermy** – treatment procedure that uses high frequency energy waves to generate a deep heat of body tissues. Can be used as a treatment for pain relief

**Electrode (or Percutaneous Electrode)** – specially made thin wire, which is placed through the skin into the diaphragm and used to deliver electrical stimulation.

**Electrode Connector** – a plastic strip that the doctor connects one end of the Electrodes to, after implanting the other ends of the electrodes into the diaphragm

**EMG** – Electromyography is a method for measuring muscle activity via the electrical signals produced by muscles when they are stimulated.

**ECG** – Electrocardiogram is a recording of the electrical activity of the heart.

**IEC** – International Electrotechnical Commission (IEC) is an international standards organization dealing with electrical, electronic and related technologies.

**Patient Cable** – the covered wire that connects the Stimulator to the electrodes at the connector holder

**Programming** – the process of entering personalized parameter data that satisfies the patient's specific requirements into the stimulator

**Spasm** – sudden involuntary or uncontrolled muscle tightening

**Stimulator** – a battery-operated controller that is programmed to generate a controlled amount of electrical stimulation

NOTES



300 Artino St  
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USA

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Tel: (888) 767-3770

Fax (440) 774-2572

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77-0017 Rev C5



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## Synapse Biomedical

### NeuRx RA/4 Diaphragm Pacing Stimulation System

#### Patient Information

#### HUMANITARIAN USE DEVICE

Authorized by Federal Law for use in the treatment of respirator insufficiency for high-level spinal cord injured patients. The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

#### INTENDED USE

The NeuRx™ RA/4 is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older.

#### PROCEDURE

Your doctor has determined that you have chronic respiratory insufficiency due to a high-level spinal cord injury. Your doctor feels that you might benefit from the use of the NeuRx RA/4. The NeuRx RA/4 is a diaphragm pacing stimulation system. Diaphragm pacing provides an electrical signal to activate the main muscle responsible for breathing. The muscle responsible for breathing is called the diaphragm and it is activated by branches of the phrenic nerve. With this system, the electrodes are not placed directly on the nerves, but placed in the diaphragm muscle during a surgical procedure called a laparoscopy.

In this procedure, four small incisions (0.5 - 2.0 cm long) will be made in your abdomen. A tube will be placed into the first incision and carbon dioxide gas will be pumped through the tube to fill your abdomen. Next, a small tube containing a camera (called a laparoscope) will be inserted into your abdomen to allow the surgeon to see your diaphragm muscle.

The surgeon will find the best location to place the electrodes in the diaphragm. To do that, he will use a probe that temporarily places an electrode on the surface of the diaphragm. The probe will be used to stimulate your diaphragm muscle at several locations. Once the best locations are found, the probe will be removed and two or more electrodes will be placed in the right and left halves of the diaphragm muscle. The lead wires from these electrodes will travel under the skin to the chest region and exit through the skin nearby. An additional electrode will be placed just beneath the skin. The wires will be trimmed so that the ends sticking out of your skin are only 2 - 6 inches in length. An x-ray will be taken following the surgery to check the position of the wires. After the surgical procedure, you may have to recuperate in the hospital and will continue to use a mechanical ventilator to help you breathe. You will need to use the ventilator until your diaphragm has been fully reconditioned. The time it will take to wean you off of the ventilator is dependant on a number of factors; including your age, the time that has past since injury, and the duration and number of condition sessions that you can tolerate. It has taken patients, studied as part of a clinical investigation of the DPS System, approximately six weeks to get to four continuous hours of respiratory support from the device.

## PROCEDURE RISKS

- There is a risk of diaphragm penetration during the procedure, which could cause a condition known as capnothorax
- There is a risk of infection and/or inflamed tissue at the electrode implantation sites
- There is a risk of bleeding at the electrode implantation sites
- There is a risk of nerve, tissue or organ damage as a result of the procedure
- There is a risk that the electrode wires could break off in your body leading to reduced or intermittent diaphragm pacing or failure of the pacing system
- There is a risk of cardiac arrhythmia being caused by the placement of the electrodes in the chest cavity
- There is a risk of skin irritation or hypersensitivity from the electrical stimulation or from the tape used with the electrodes or from the skin bandage that holds the electrode connections
- There is a risk that your body may not be compatible with the materials used in the electrodes and their wires
- There is a risk of choking during eating and of sleep apnea if a Passy-Muir™ valve is not used during the training period

- There is a risk of discomfort during the conditioning period. Be sure and inform your physician if you notice pain, discomfort, or shortness of breath
- There is a risk that you may not have sufficient muscle reaction when using the stimulator and the product may not work for you
- At this time, there is insufficient clinical data to determine safety in implanting patients with cardiac pacemakers, therefore, you should not be implanted with this device if you have a cardiac pacemaker or other implanted electrical device
- This product should not be used by patients with suspected or real heart problems or who have epilepsy
- The safety of this device in use during pregnancy is unknown
- The long-term effects of electrical stimulation of the diaphragm are unknown

#### **RISKS AND PROBABLE BENEFITS OF USING THE NEURX RA/4**

There is a risk that during electrode placement, the electrodes may go all the way through the diaphragm muscle, which could cause air to gather in your chest and cause a capnothorax. If this occurs, air in your chest may cause both discomfort and hinder your ability to breathe. In a worst-case situation, one or both of your lungs could collapse. If a lung does collapse, it will be re-inflated immediately using a tube that is placed in your chest. There may be some discomfort and/or bruising at the site where the lead wires go through the skin. This is temporary and should go away in a few days.

It is possible that stimulation from the diaphragm pacing system could stop either due to electrode breakage, cable disconnection, or stimulator failure. If one of these happens, breathing will stop. Without prompt attention, this could result in permanent disability or death. This risk is reduced by using back-up electrodes and sounding an alarm whenever the stimulator detects improper operating conditions.

There is a risk of aspiration when using the device. While becoming used to the stimulation and timing, it is recommended that a one-way (Passy-Muir™) valve on your tracheostomy is used while eating or drinking when on the pacing device. It is also recommended to use the one-way valve while sleeping to avoid upper airway obstructions. The Passy-Muir™ speaking valve looks like a plug with holes in it. The valve fits directly onto the end (hub) of your tracheostomy tube. It opens during inspiration to let air into your lungs and closes during exhalation to allow air to pass your vocal cords and out of through your nose and/or mouth. The valve allows for more normal respiration, improves swallowing and may reduce your risk of aspiration.



You may experience increased spasms with the stimulation while your body becomes used to the stimulation. This typically subsides within a few days of use.

Over fifty patients have been implanted with the NeuRx RA/4 DPS System at five implanting clinical sites. The ability of the device to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day has been demonstrated in 96% of patients that have been through diaphragm conditioning. Only one patient was unable to derive benefit from the device, as a result of a false positive inclusion criteria test. No patients have abandoned use of the device. There are a total of 45 patients actively using the device, four patients having died, from causes unrelated to the device, and one delayed in starting use due to spasms from a malfunctioning baclofen pump. There are 48 patients that have been able to pace for longer than four consecutive hours and 49 patients that have achieved tidal volumes greater than their basal metabolic requirements.

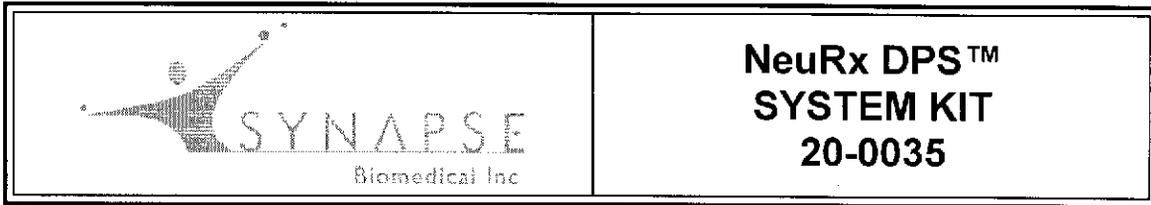
## **PRECAUTIONS**

- Be sure that a mechanical ventilator is available for you at all times even if you are routinely using this device. Caregiver availability and monitoring should be consistent with when a ventilator is used.
- Wear an abdominal binder when sitting in a chair as it will help your breathing
- Do not use this device in oxygen-enriched environments
- Avoid using abdominal stimulation electrodes, commonly used to avoid 'quad gut' while using the NeuRx RA/4 Pacing System.
- Do not undergo Magnetic Resonance Imaging (MRI) after being implanted with the NeuRx RA/4 Pacing System.

## **ALTERNATIVE PRACTICES AND PROCEDURES**

Alternative methods exist for treatment of chronic respiratory insufficiency include positive pressure mechanical ventilation or using electrodes placed on the nerves instead of in the diaphragm muscle. This treatment (phrenic nerve pacing) is a different method of contracting the diaphragm to create an inspiration than is used by the NeuRx RA/4. The primary difference is the electrodes are placed around the phrenic nerves in the neck or chest during a surgical procedure.

# Professional LABELING



**INTENDED USE**

The NeuRx™ RA/4 is intended for use in patients with stable, high spinal cord injuries with stimlatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older.

**HUMANITARIAN USE DEVICE**

Authorized by Federal Law for use in the treatment of respiratory insufficiency for high-level spinal cord injured patients. The effectiveness of this device for this use has not been demonstrated.

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

<b>Contents</b>
-----------------

Description	Part Number	Qty
<b>Sterile Surgical Kit</b>	<b>20-0028</b>	<b>1</b>
Sterile Mapping Probe	21-0001-99	1
Sterile Indifferent Electrode	21-0004-99	1
Sterile Lead Tuner Set	21-0007-99	1
Sterile Blue Cable Set	21-0009-99	1
Sterile Trocar to Transducer Tubing	21-0010-99	1
Sterile Peterson Electrode, 60cm	21-0017-99	4
Sterile Green Cable	21-0023-99	1
Sterile Orange Cable	21-0024-99	1
Sterile Yellow Cable	21-0025-99	1
Sterile White Cable	21-0026-99	1
<b>Patient Kit</b>	<b>20-0002</b>	<b>1</b>
NeuRx RA/4 External Pulse Generator	23-0001	2
Patient Cable	22-0003	2
Battery	29-0007	6
Connector Holder	22-0004	15
Electrode Connector Socket Kit	22-0005	1
Screw Driver	29-0018	1
Test Plug	60-0001	1
Patient-Caregiver Instruction Manual	77-0017	1
Patient Information Sheet	77-0038	1



## **Surgeon Instruction Manual**

### **NeuRx RA/4 Diaphragm Pacing System**

#### **HUMANITARIAN DEVICE:**

**Authorized by Federal law for use in the treatment of respiratory insufficiency for high-level spinal cord injured patients. The effectiveness of this device for this use has not been demonstrated.**

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Fax (440)774-2572**

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Additional instructions delivered with the NeuRx DPS™ System that physicians should be familiar with:

PN 77-0017 Patient / Caregiver Instruction Manual  
PN 77-0038 Patient Information Sheet  
PN 77-0043 Electrode Delivery Instrument Instructions  
PN 77-0016 Clinical Station Instructions

## **1.0 INTENDED USE**

The NeuRx™ RA/4 is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older.

## **2.0 WARNINGS AND CAUTIONS**

- Caution: Federal Law (USA) restricts this device to sale, distribution and use by or on the order of a physician
- Caution: The long-term effects of chronic electrical stimulation are unknown.
- Caution: Safety has not been established for the use of the device during pregnancy.
- Warning: This device is electrically powered and may produce tissue damage or electrical hazard if improperly used.
- Warning: This device should be kept out of the reach of children.
- Do NOT attempt to open the Stimulator case; the device has NO patient-accessible controls. Doing so can result in damage to the device.
- Do NOT use in patients with an implanted electronic device (Insufficient clinical data is available, at this time, to establish safety with a cardiac pacemaker).
- Do NOT connect the patient to high-frequency surgical equipment while connected to the external stimulator. Doing so can result in burns at the site of the stimulator electrodes and possible damage to the stimulator.
- Do NOT subject Patients implanted with the NeuRx RA/4 Pacing System to Magnetic Resonance Imaging (MRI).
- Do NOT use this device if skin in the electrode implant area is swollen, infected, or inflamed or if there are skin eruptions such as phlebitis, thrombophlebitis, or varicose veins.
- Avoid operating this device in close proximity (for example 3 feet) to shortwave or microwave therapy equipment that may produce instability in the stimulator output.
- Avoid accidental contact between connected but unused applied parts (cable or leads) and other conductive parts including those connected to ground (protective earth).

#### FLAMMABILITY WARNING

- Do NOT use the NeuRx RA/4 Stimulator in an oxygen enriched environment or near a flammable anesthetic mixture with air, oxygen or nitrous oxide. The NeuRx RA/4 Stimulator is not categorized as AP (anesthetic-proof) or APG (anesthetic-proof category G - gas) type of equipment.

#### ELECTROMAGNETIC INTERFERENCE WARNING

- Do follow the EMC information provided. The NeuRx RA/4 Stimulator needs special precautions regarding electromagnetic compatibility (EMC).
- Use Caution around portable and mobile RF communications equipment as these can affect the NeuRx RA/4 Stimulator.
- Do NOT use cables or accessories other than those specified. Doing so may result in increased emissions or decreased immunity of the NeuRx RA/4 Stimulator.

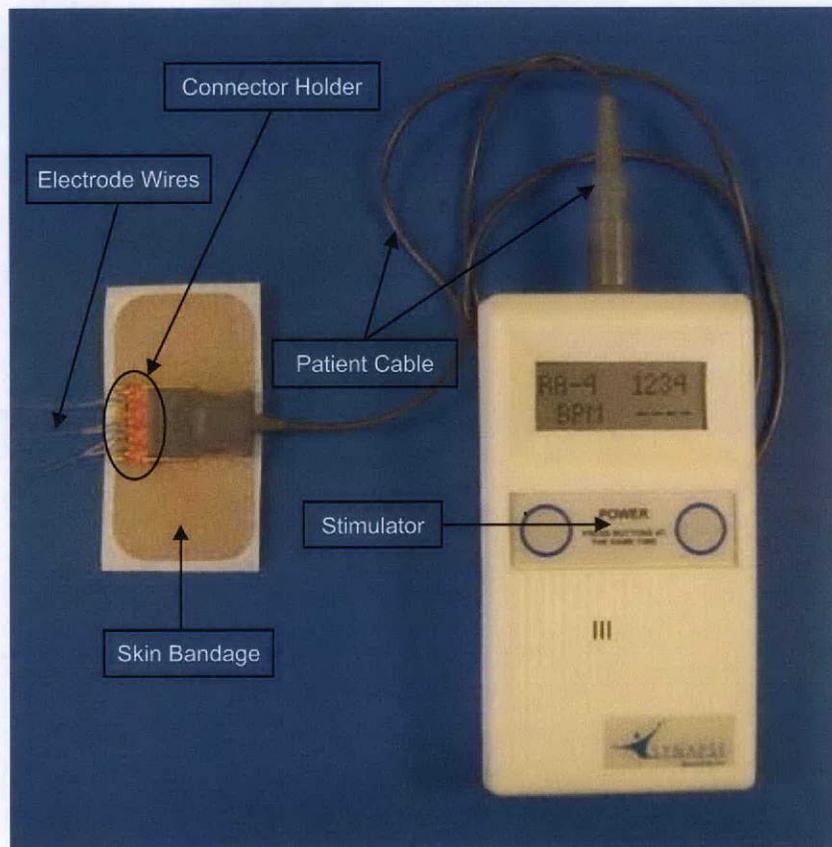
### 3.0 PRECAUTIONS

- Spinal Cord Injury (SCI) patients must have a mechanical ventilator available at all times. If the patient does not feel that they are receiving adequate ventilation or if any malfunction of the pacing device is suspected, they should be placed on mechanical ventilation immediately and the pacing system turned off. Caregiver availability and monitoring should be consistent with when a ventilator is used.
- Do NOT expose the device to excessive moisture or severe mechanical shock. If display indicates system failure, pain is felt at the electrode site, or device is exposed to moisture or shock, disconnect the cable and contact Synapse Biomedical.
- Do NOT conduct diathermy treatment or electro cauterization in the area of the implanted electrodes.
- Do NOT have the stimulator connected during any type of electrical diagnostic treatment such as EMG or ECG.
- Precautions should be observed when there is a tendency to hemorrhage following acute trauma or fracture, following recent surgical procedures when muscle contraction may disrupt the healing process, or where sensory nerve damage is present.
- Some patients may experience skin irritation or hypersensitivity due to the electrical stimulation, the adhesive on the skin bandage, or the transparent dressing (Tegaderm™ and Op-Site™ are examples of transparent dressings) used over the gauze that covers the electrodes. Skin irritation can usually be reduced by changing the stimulus parameters or removing the adhesive.

- Patients should wear an abdominal binder when sitting in a chair as it will help their breathing
- Do not use this device in oxygen-enriched environments
- Avoid using abdominal stimulation electrodes, commonly used to avoid 'quad gut' while using the NeuRx RA/4 Pacing System.
- Patients should not undergo Magnetic Resonance Imaging (MRI) after being implanted with the NeuRx RA/4 Pacing System.

#### 4.0 DEVICE DESCRIPTION AND PRINCIPLES OF OPERATION

- The NeuRx RA/4 System is a system designed to help patient's breath by stimulation of their diaphragm muscles.
- It is implanted using standard laparoscopic surgical techniques in an outpatient procedure.
- The implanted intramuscular diaphragm electrodes are connected to the NeuRx RA/4 external stimulator through the Patient Cable and the Connector Holder site.



- The stimulator provides repetitive electrical stimulation to the implanted electrodes to cause the patient's diaphragm to contract and cause the patient to draw breath in a manner similar to natural breathing.

- A physician will program the Stimulator so that it produces the right stimulation patterns. If the stimulation is uncomfortable, the physician can adjust the Stimulator to reduce or eliminate the discomfort.
- The user simply connects the device to the implanted electrodes and turns it on for use; no other controls are available or necessary for operation.
- During use, the stimulator should be kept close to the patient's body to avoid pulling on the cable and electrodes. The stimulator can be placed in a pocket of the patient's clothing, a fanny pack or simply placed on a table or other convenient location.

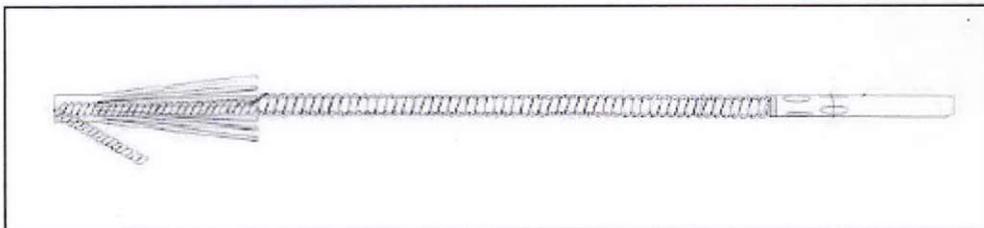
#### 4.1 DETAILED DESCRIPTION OF THE SYSTEM

The NeuRx RA/4 System is an intramuscular, percutaneous, motor point diaphragm stimulation system. It is implanted using standard laparoscopic surgical techniques in an outpatient procedure. The implanted intramuscular diaphragm electrodes are connected to a four channel external stimulator at a percutaneous exit site. The stimulator provides a capacitively coupled, charge balanced, biphasic stimulation to each electrode with a common indifferent electrode that is placed subcutaneously. The stimulator controls the charge delivered through clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. The clinician uses a clinical station to characterize electrode response to stimulation and program the external stimulator with the patient specific parameters. The user simply connects the device and turns it on for use; no other controls are available or necessary for operation.

##### 4.1.1 IMPLANTABLE COMPONENTS

The stimulation is delivered to the phrenic nerve motor point through four intramuscular electrodes implanted into the diaphragm. Two electrodes are placed into each hemi-diaphragm at locations, found during surgical mapping, that elicit the greatest contraction of the diaphragm. This may be obtained by a single motor point, where the main trunk of the phrenic nerve enters the diaphragm, to produce a diffuse contraction or at two individual branches that recruit the anterior and posterior portions of the diaphragm. The electrodes are tunneled directly to the percutaneous exit site on the chest.

##### 4.1.1.1 Intramuscular Electrode



The intramuscular electrode is a double helix wound lead with exposed 316LVM stainless steel stimulating surface and polypropylene reinforced

core and barb. The body of the lead is insulated with PFA (perfluoroalkoxy) fluoropolymer coating and terminated in a 316L stainless steel pin with a silicon reinforcing sleeve. All of the materials have a history of long-term implantable use as part of previously approved products. The lead is 61cm in overall length, 0.75mm in diameter, and has a 9mm de-insulated stimulating tip.

#### 4.1.1.2 Indifferent Electrode

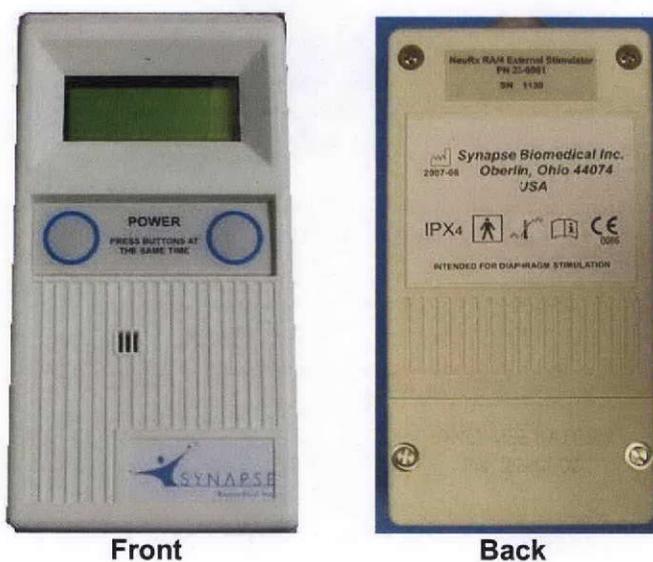
The indifferent electrode provides a common return current path for all of the electrodes implanted in the diaphragm. It is implanted in the subcutaneous tissue of the lateral chest region and is tunneled to the percutaneous exit site. The lead is fabricated of the same double helix wound 316LVM stainless steel as the intramuscular electrode and percutaneous extension lead. It is also terminated in a 316L stainless steel pin at one end and 7cm de-insulated for the return electrode tip. The overall length is approximately 12cm with a 0.75mm diameter.

### 4.1.2 EXTERNAL COMPONENTS

#### 4.1.2.1 RA/4 Stimulator

The RA/4 patient stimulator is an external four channel, battery powered device that controls the stimulus output and respiratory timing. The four output channels are independently controlled, capacitively coupled, biphasic outputs with a common return. The device is packaged in an impact resistant plastic enclosure with patient cable connector on the top, display and power buttons on the front and replaceable battery compartment on the back. A programming connector is located in the battery compartment for connection to the clinical station.

RA/4 External Stimulator

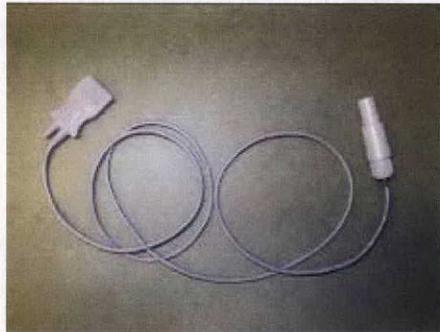


The device has no controls that allow modification to any parameter settings. On-off power control consists of redundant switches that require actuation at the same time to provide protection from accidental actuation by incidental contact.

The device is powered from a user replaceable primary 3.6v, 7200mA-H lithium battery and a secondary 3.6v, 650mA-H rechargeable battery. The internal secondary battery recharges from the primary battery upon replacement. This configuration allows a charged backup battery in the unit at all times to allow sufficient time for the user to replace the primary battery. The display will indicate when the device is operating from the internal backup battery and provide an audio indicator when the internal backup battery reaches low charge remaining. Additional indicators are given for impedance of each channel on the display and an audio indicator in the event of an impedance too high for the constant current supply.

#### **4.1.2.2 Patient Cable**

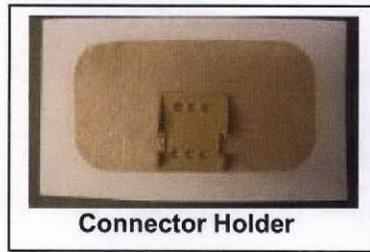
A five conductor cable is provided that connects from the external stimulator to the electrode connector socket. The stimulator end of the cable is a positive locking medical grade plastic shell connector. The cable is a multi-conductor, shielded cable that is 1m in length. The electrode connector end is a custom molded five conductor connector. It is a precision mated strip of pins embedded in molded medical-grade PVC.



**Patient Cable**

#### **4.1.2.3 Connector Holder**

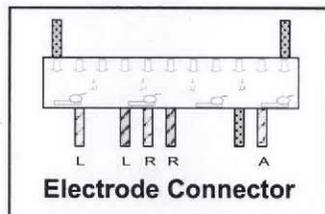
A disposable holder secures the electrode connector socket on the chest. A custom molded clip is secured to a 7.5 x 2.5cm spunlace tape. The spunlace tape is MED5322 hypoallergenic fabric medical tape intended for applications to the skin for sustained periods.



Connector Holder

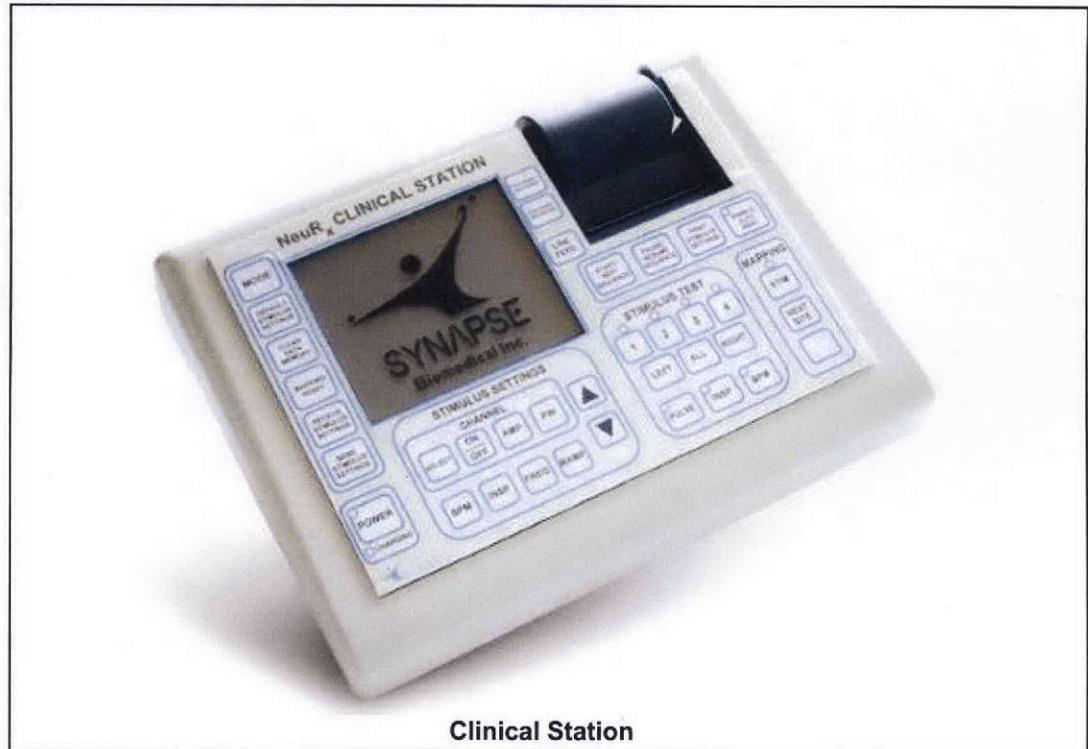
#### 4.1.2.4 Electrode Connector Socket Kit

Each electrode is terminated into a precision ITT Canon socket. The individual sockets are crimped onto the electrodes and inserted into a carrier strip. The sockets are inserted into the carrier strip in a set sequence to mate with the patient cable. The crimp connections are strain relieved with medical grade silicone tubing.



Electrode Connector

#### 4.1.2.5 Clinical Station



Clinical Station

There are three primary aspects of the device implementation that the clinical station provides. The station provides intra-operative mapping functionality and electrode characterization, incorporates RA/4 stimulator functionality, and external RA/4 stimulator programming capability.

The first application of the station in the device implementation is to provide intra-operative stimulation and sensing of stimulated response. This surgical mapping mode utilizes the surgical components listed below to provide twitch or burst stimulation to record and display the abdominal pressure response through the solid state pressure sensor. A stimulator mode is used to test the channels individually and in combination at the end of the surgery to make sure that all electrodes are intact and providing the anticipated response.

The station is then used to characterize the response from each electrode utilizing the four stimulus output channels. The amplitude, pulse width, frequency, and pulse ramping response are each characterized to optimize the tidal volume and patient comfort on a per breath basis. The inspiration time and respiratory rate are set for appropriate minute ventilation. The stimulator mode can be used to fine tune the settings for the patient.

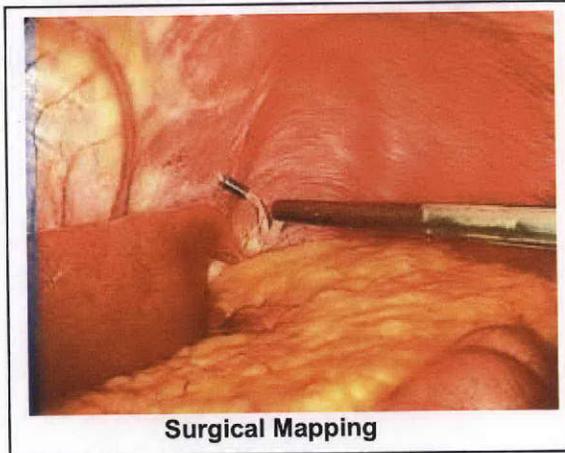
Finally, the station sends the desired stimulus and respiratory timing parameters to the external stimulator in the programming mode. The station can also read the currently programmed parameters from an external stimulator to verify the settings.

Reference the Synapse Biomedical Clinician Manual (PN 77-0016) for instructions on operation of the Clinical Station.

### **4.1.3 SURGICAL COMPONENTS**

#### **4.1.3.1 Mapping Instrument**

The initial step in the surgical implementation is the laparoscopic mapping of the diaphragm. This is performed by introducing a specialized 5mm mapping instrument to stimulate the inferior surface of the diaphragm in a grid pattern to identify optimal implantation sites of the intramuscular electrodes. The mapping instrument is applied to sequential sites on the diaphragm by the surgeon and secured by applying the operating room vacuum through the central lumen of the probe. Stimulation is applied in either a twitch or burst mode from the clinical station to elicit an abdominal pressure change.



**Surgical Mapping**

#### **4.1.3.2 Transducer to Trocar Pressure Tube**

A one meter section of PVC tubing, with male luer lock connectors on either end is used to connect a Trocar port to the solid state pressure sensor.

#### **4.1.3.3 Solid State Pressure Sensor**

A differential, 1 PSI full scale, pressure sensor transduces the abdominal pressure changes to an electrical signal for the clinical station. It connects to the pressure tube with a female luer lock and to the clinical station with a positive locking medical grade connector.

#### **4.1.3.4 Cable Set**

A set of cables with touch-proof connectors are used to connect off the sterile field from the mapping instrument to the clinical station. A set of 3m meter cables connect to the mapping instrument or clip leads to test implanted electrodes. Another cable connects from the surface anode to the Clinical Station.

#### **4.1.3.5 Surface Anode**

A standard 2" x 3.5" electrotherapy surface electrode is used during intra-operative mapping.

#### **4.1.3.6 Electrode Delivery Instrument**

An 11mm durable laparoscopic instrument is used for implantation of the electrodes in the diaphragm. The barbed intramuscular electrode is loaded in the lumen of the instrument with the de-insulated barb extending out of the needle. The skirt of the polypropylene barb is loaded inside of the needle. When the needle is extended and inserted between the muscle fibers, parallel to the diaphragm surface, the de-insulated barb catches on the fibers and the lead is drawn out of the lumen as the instrument is withdrawn.



#### 4.1.3.7 Tunnelers

A set of 304 stainless steel 12 gauge cannulae are used to tunnel implanted leads to the percutaneous exit site.

### 5.0 PATIENT INFORMATION

See the document "Synapse Biomedical NeuRx RA/4 Diaphragm Pacing Stimulation System Patient Information" (PN 77-0038) provided with the device. This document is meant to be provided to the patient.

### 6.0 PROCEDURE RISKS

- There is a risk of diaphragm penetration during the procedure, which could cause a condition known as capnothorax
- There is a risk of infection and/or inflamed tissue at the electrode implantation sites
- There is a risk of bleeding at the electrode implantation sites
- There is a risk of nerve, tissue or organ damage as a result of the procedure
- There is a risk that the electrode wires could break off in the body leading to reduced or intermittent diaphragm pacing or failure of the pacing system
- There is a risk of cardiac arrhythmia being caused by the placement of the electrodes in the chest cavity
- There is a risk of skin irritation or hypersensitivity from the electrical stimulation or from the tape used with the electrodes or from the skin bandage that holds the electrode connections
- There is a risk that the body may not be compatible with the materials used in the electrodes and their wires
- There is a risk of choking during eating and of sleep apnea if a Passy-Muir™ valve is not used during the training period

- There is a risk of discomfort during the conditioning period.
- There is a risk that a patient may not have sufficient muscle reaction when using the stimulator and the product may not work for every patient
- At this time, there is insufficient clinical data to determine safety in implanting patients with cardiac pacemakers, therefore, patients should not be implanted with this device if they have a cardiac pacemaker or other implanted electrical device
- This product should not be used by patients with suspected or real heart problems or who have epilepsy
- The safety of this device in use during pregnancy is unknown
- The long-term effects of electrical stimulation of the diaphragm are unknown
- It is possible that stimulation from the diaphragm pacing system could stop either due to electrode breakage, cable disconnection, or stimulator failure. If one of these happens, breathing will stop. Without prompt attention, this could result in permanent disability or death. This risk is reduced by using back-up electrodes and sounding an alarm whenever the stimulator detects improper operating conditions.
- There is a risk of aspiration when using the device. While becoming used to the stimulation and timing, it is recommended that a one-way (Passy-Muir™) valve on the tracheostomy be used while eating or drinking when on the pacing device. It is also recommended to use the one-way valve while sleeping to avoid upper airway obstructions. The Passy-Muir™ speaking valve looks like a plug with holes in it. The valve fits directly onto the end (hub) of the tracheostomy tube. It opens during inspiration to let air into the lungs and closes during exhalation to allow air to pass the vocal cords and out through the nose and/or mouth. The valve allows for more normal respiration, improves swallowing and may reduce the risk of aspiration.
- Patients may experience increased spasms with the stimulation while their body becomes used to the stimulation. This typically subsides within a few days of use.

## 7.0 SUMMARY OF CLINICAL STUDIES

The goal of this trial was to assess the NeuRx DPS for patients with high-level spinal cord injury resulting in dependence on positive pressure mechanical ventilation. Implantation for up to fifty patients was approved with an analysis after the thirtieth patient reached the three month time-point. This summary of data and analysis for safety and probable benefit is on fifty implanted patients with forty-eight having reached the three month time-point.

### 7.1 Objectives

The primary endpoint for demonstration of probable benefit is the ability of the NeuRx DPS to provide clinically acceptable tidal volume for at least four continuous hours of pacing. For a male patient, the tidal volume to meet the basal metabolic requirement ( $V_{T-bmr}$ ) is defined at 7ml/kg body weight. For a

female patient, the  $V_{T-bmr}$  is defined at 6ml/kg body weight.

The study would be considered a success if the NeuRx DPS is able to achieve the primary endpoint without unacceptable complications, device related adverse events, or deficits in the quality of life of the study population.

## **7.2 Methods**

The implementation of the NeuRx DPS can be divided into four categories:

### **7.2.1 Inclusion pre-screening**

Candidates are patients with high level spinal cord injury resulting in dependence on mechanical ventilation. The candidate must have bilateral intact phrenic nerves below the level of the spinal cord injury. The candidate must be in otherwise generally good health.

#### **7.2.1.1 Inclusion Criteria**

- Age 18 years or older
- Cervical spinal cord injury dependant on mechanical ventilation
- Clinically stable following acute spinal cord injury
- Bilateral phrenic nerve function clinically acceptable as demonstrated with EMG recordings and nerve conduction times
- Diaphragm movement with stimulation visible under fluoroscopy
- Clinically acceptable oxygenation on room air (>90%)
- Hemodynamically stable
- No medical co-morbidities that would interfere with the proper placement or function of the device
- Committed primary caregiver
- Negative pregnancy test in females of child-bearing potential
- Informed consent from patient or designated representative

#### **7.2.1.2 Exclusion Criteria**

- Co-morbid medical conditions that preclude surgery
- Active lung disease (obstructive, restrictive or membrane diseases)
- Active cardiovascular disease
- Active brain disease
- Hemodynamic instability or low oxygen levels on room air
- Hospitalization for or a treated active infection within the last 3 months
- Significant scoliosis or chest deformity
- Marked obesity
- Anticipated poor compliance with protocol by either patient or primary caregiver.
- Currently breastfeeding

## **7.2.2 Surgical Implantation**

Surgery is completed in four phases: exposure, mapping, implantation, and routing.

**7.2.2.1** The exposure consists of the setup for the standard four port laparoscopy to visualize the diaphragm. During this phase any abdominal adhesions are released and any gastronomy tubes may be replaced or removed if needed.

**7.2.2.2** The next phase consists of the mapping of the diaphragm on a grid pattern for response to twitch stimuli. Locations on each hemi-diaphragm are stimulated with each site recorded on a grid that is overlaid on the laparoscopic video display. The magnitude of the abdominal pressure change, to the applied stimuli, is recorded at each location. The primary electrode site is identified at the location of maximal pressure change in each hemi-diaphragm. A secondary electrode site is identified as either a backup to the primary site or at a location in each hemi-diaphragm that recruits another phrenic nerve motor point region (e.g. anterior, lateral, or posterior) of the diaphragm at a similar magnitude.

**7.2.2.3** Once the primary and secondary electrode sites are identified in each hemi-diaphragm the implantation phase begins. An intramuscular electrode is introduced into the abdominal cavity with the electrode delivery instrument. The electrode is inserted into the diaphragm, at an angle so that the electrode lead travels parallel to the plane of the diaphragm prior to exit, and the delivery instrument is withdrawn. The electrode is then tested to assure the desired response to twitch stimuli is achieved and the procedure is repeated for the remaining electrodes. If the response is not adequate when tested, the electrode may be withdrawn and another implanted.

**7.2.2.4** Electrode leads are then routed to the percutaneous exit site. The indifferent electrode (or anode) is placed from the percutaneous exit site. The electrodes are then retested to make sure that all of the connections have been made properly. An EKG strip is recorded with all four electrodes active to be sure there is no capture of the cardiac rhythm. The port incisions are then closed and the patient is transferred to recovery.

## **7.2.3 Reversal of Disuse Atrophy & Conditioning**

At one to two weeks post surgery the patient returns to the hospital for the initiation of stimulation. Each electrode is characterized over the range of stimulus parameters using the Clinical Station. Tidal volumes are recorded with a calibrated Wrights Spirometer and oxygen saturation is monitored with a pulse oxygen monitor. It should be noted that the tidal volumes are measured with the patient's tracheotomy, which in most cases is a cuff-less trach. This means that tidal volumes recorded (and subsequently reported below in the results) with the Wrights Spirometer are lower than the actual inspired air volume due to air leaks around the patients stoma and through

their upper airway. An EKG rhythm strip is recorded at maximal stimulus parameters to assure that there is no capture of the cardiac waveform. Initial parameter settings are determined and the RA/4 External Stimulator is programmed. Initial conditioning sessions are performed while the patient is at the hospital to assure the patient and their caregivers understand and are comfortable with the operation of the DPS.

The patient returns home and logs their use and changes in tidal volume with the Wrights Spirometer. Pulse oximetry and a rank scale indication of respiratory effort are recorded with any comments on the log sheets for each use of the DPS. The clinical team follows up with the patients on a weekly basis during the initial weeks, reviewing the log sheets and making any changes as necessary. Log sheets are maintained until the patient has reached, or is capable of, full time use. Electrodes are characterized again at 3, 6, and 12 month intervals post surgery, if the patient has not reached a steady-state plateau or full time use of the system.

#### 7.2.4 Chronic Use

Once the patient has achieved full time use of the DPS or is using it at a level that is consistent with their desired level of activity, they are free to use the system as desired. The DPS includes two external stimulators, two patient cables, extra batteries and percutaneous connector site tapes. The clinical team follows up with the patients periodically and the patients contact the clinical team, or Synapse Biomedical, for additional supplies (batteries, cables, and percutaneous connector tapes) as needed.

### 7.3 Description of Enrolled Subjects

Patients in our study group have all suffered from high-level spinal cord injury and were full-time dependant on positive pressure mechanical ventilation prior to inclusion. The enrolled patients include the longest time since injury of twenty-seven years and shortest time of three months. The gender ratio of thirty-seven males to thirteen females, or 74% male, is fairly consistent with the national database statistics of 81.2% male overall in spinal cord injury. The predominant source of injury was motor vehicle accidents (40%), followed by sports injuries (40%) and all others (20%). Additional demographics are given in Table 1 and the level of injury of the implanted patients in Table 2.

**Table 1: Demographics (n=50)**

	Average	Stdev	Min	Max
Age (years)	36	16	18	74
Weight (kg)				
Males	83	16	57	127
Females	59	13	40	84
Time Since Injury (years)	5.6	6.9	0.2	26.9

**Table 2: Level of Spinal Injury**

Level of Injury	# of Patients	Percent of Total
C1	3	6%
C1/C2	14	28%
C2	24	48%
C2/C3	1	2%
C3	3	6%
C3/C4	3	6%
C4	1	2%
C4/C5	1	2%

The basal metabolic requirements (BMR) and positive pressure mechanical ventilator settings for the implanted patients is given in Table 3.

**Table 3: Mechanical Ventilation (n=50)**

	Average	Stdev	Min	Max
Basal Metabolic Requirement (ml)				
Male (7ml/kg)	578	109	399	889
Female (6ml/kg)	355	79	240	504
Tidal Volume (ml)				
Male	1025	233	400	1500
Female	837	341	170	1500
Minute Ventilation (liters / min)				
Male	12	3	6	21
Female	10	4	4	18

Subjects entered into the study met the inclusion criteria of spinal cord injury with a successful phrenic nerve conduction study, with the exception of one compassionate use patient. This inclusion criteria was modified, subsequent to the failure to pace with the second patient enrolled in the study, to have fluoroscopic confirmation of diaphragm excursion as a condition of inclusion. Ten of the patients have cardiac pacemakers.

#### 7.4 Results

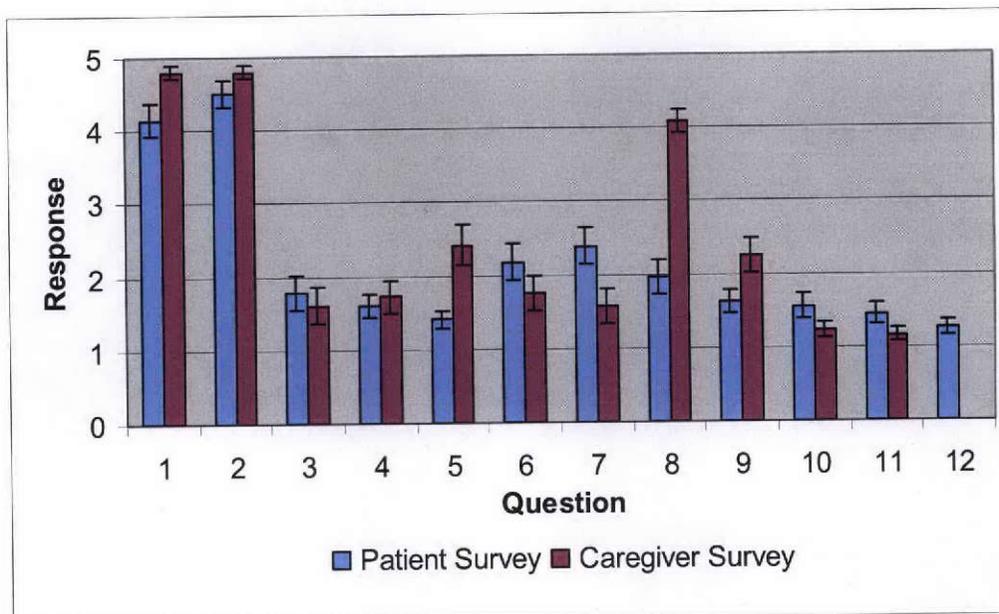
Fifty patients have been implanted with the NeuRx DPS at five implanting clinical sites. There has been over 97 years of active implant time with the average follow-up of  $2.0 \pm 1.5$  years (median = 1.6, range 0.5 – 8.0).

**Table 4: Summary Results**

Category	NeuRx DPS	
	#	% of Total
<b>Success</b>	<b>48</b>	<b>96%</b>
$V_T > \text{Basal Req.}, \text{Continuous use} > 4 \text{ hrs}$	48	96%
$V_T < \text{Basal Req}$ or use < 4hrs, Still conditioning	0	0%
<b>Partial Success</b>	<b>1</b>	<b>2%</b>
$V_T > \text{Basal Req.}, \text{max use} < 4 \text{ hrs}$	1	2%
<b>Failure (Never Paced)</b>	<b>1</b>	<b>2%</b>
<b>TOTAL</b>	<b>50</b>	<b>100%</b>

The summary results given in Table 4 show the NeuRx DPS achieving 96% deemed as successful based on their ongoing use (with tidal volumes greater than basal requirements) or progress (with evidence of increasing tidal volumes and continuous time of use) post implant. One patient was able to achieve tidal volumes greater than basal requirements during initial conditioning but, due to a malfunctioning baclofen pump, did not initiate conditioning for fatigue resistance of her diaphragm until two years after her implant date and is listed as a "Partial Success". There are a total of 45 patients that are actively using the device. Four patients have died from causes unrelated to the device, all of whom had achieved the success criteria of tidal volumes greater than basal requirements and more than four hours of continuous use. One patient was never able to pace. There are a total of 48 patients that have been able to pace for longer than four consecutive hours and 49 patients that have achieved tidal volumes greater than their basal metabolic requirements.

Results from a follow-up survey given to patients and their caregivers are shown below. Initially the survey was completed after implantation then repeated at follow-ups to have the patients and caregivers to assess DPS effect on their activities. Thirty-six surveys have been completed by twenty-eight different patients / caregivers. The results were overall positive in all patients responding. In all cases the patients reported that the surgical implantation was not as painful as expected. 59% of patients report fewer secretions with 50% of caregivers reporting less suctioning (6% of patients reported an increase in secretions upon initial use of the device. See section 8.0 for further discussion of secretions). 74% of patients report "more normal breathing". 68% of caregivers state caring for the paced patient is less work than the mechanical ventilator. 96% of caregivers say the pacer is easy to use. Other comments included: DPS as life saving during hurricanes and power outages; the silence of pacing enabled sleeping well for the first time since their injury; attending classes or church easier; traveling for the first time ever since injury; transfer from ventilator ward to assisted living or home and air travel now possible. 78% of patients report more freedom and feeling of independence. All of patients would recommend the DPS to other tetraplegics.



1 = strongly agree, 5 = strongly disagree

Patient Survey	Caregiver Survey
1. The pre-surgical testing was difficult.	1. I feel learning how to use the pacer was difficult.
2. The surgery was more painful than I expected.	2. I feel caring for the pacer is difficult.
3. I feel my breathing is more normal with the pacer.	3. I feel replacement parts are easy to change.
4. I feel I get good breaths with the pacer.	4. I feel caring for the patient that is paced is less work than caring for the patient on a ventilator.
5. I feel the stimulator gives me more freedom than the ventilator.	5. I feel I suction less.
6. I feel I have fewer secretions with the pacer.	6. I feel my life is better with the pacer than with the ventilator.
7. I feel I am suctioned less with the pacer.	7. I can get replacement parts easily.
8. I feel my voice is stronger and more normal sounding.	8. I have had to request replacements parts frequently.
9. My life is better with the pacer than with the ventilator.	9. I feel it is easier to obtain and train caregivers.
10. I feel more independent with the pacer.	10. I am satisfied with the pacer.
11. I am more satisfied with the pacer.	11. I would recommend this to others.
12. I would recommend this procedure to others.	

### 7.5 Outcomes

At least twenty-six patients (52%) have progressed to full-time use of the system, although three are deceased from causes unrelated to the DPS. Another twenty-two patients (44%) are able to use the DPS for significant portions of the day or night. One of those patients is deceased from unrelated device cause and had achieved up to twenty hours per day of use. The reason for part-time use varies by patient but is not due to an inability to sustain adequate stimulated tidal volumes. One patient was able to achieve stimulated tidal volumes greater than her basal requirements, but has not commenced conditioning to obtain fatigue resistance due to a malfunctioning baclofen pump.

Thirty-eight of the patients receiving the NeuR<sub>x</sub> DPS were implanted at University Hospitals of Cleveland. The remaining twelve patients were implanted at three additional sites, with the majority of those implanted at Shepherd Center.

The pacing activity achieved by successfully implanted patients demonstrates the ability of patients to integrate the use of the DPS into their lives. All of the patients successfully implanted with the device have achieved tidal volumes greater than their basal requirements. Full time use (demonstrated by the successful ability to pace 24 or more straight hours) has been achieved by 59% (n=20) of patients implanted over one year and 38% (n=13) use the device either for their daytime, night or otherwise for the majority of their ventilatory support. Of the patients that are between 0.5 and 1 year since implant, 40% (n=6) have achieved full-time use and the other 60% (n=9) are still increasing the amount of time per day that they use the device.

No response to stimulation was observed in Patient #2. His inclusion was probably due to a false positive phrenic nerve conduction study (PNCS). Intra-operatively his diaphragm appeared very transparent, in retrospect, indicating severe denervation. He was implanted in very posterior location where a change in abdominal pressure was measured during mapping. Viewing the laparoscopic video, afterward, indicated that this placement was recruiting abdominal muscles and not diaphragm muscle. He was initially seen at MetroHealth Medical Center to initiate diaphragm conditioning, but as no response from the diaphragm was achieved he was not setup with a pacing device. The inclusion criterion was subsequently changed to reduce the possibility of a false positive PNCS. The movement of the diaphragm is now visually observed under fluoroscopy during the PNCS to corroborate that sufficient innervation of the diaphragm muscle exists.

The ultimate goal of the NeuR<sub>x</sub> DPS is to replace mechanical ventilation for the patients on a chronic use basis. The indicators of achieving this objective are the ability to spend significant time off of the ventilator and the measured tidal volume ( $V_T$ ) during chronic stimulation. Standard of care for ventilated patients indicates that the basal  $V_T$  requirements for an adult male are typically 7ml / kg of body weight and 6ml / kg for adult females. Due to ventilator circuit dead space, tracheotomy leakage, and duration/volume of speech concerns, spinal cord patients are typically mechanically ventilated at much higher settings than their basal  $V_T$  requirements. Particularly, since minute ventilation is comprised of the sum of the alveolar and dead space ventilation the higher ventilator  $V_T$  is required to overcome the dead space volume and meet the estimated basal required  $V_T$ . Table 3 identified the initial ventilator settings for each of the patients and their resultant minute ventilation. As expected, for most of the patients, the minute ventilation is well above the normal minute ventilation of 5 – 10 liters/min. The average minute ventilation for the implanted patients is  $10 \pm 4$  liters / min (n=13) for females and  $12 \pm 3$  liters / min (n=36) for males, which is significant difference between males and females. The basal

requirements also show a significant difference between males and females. The males require  $575 \pm 109$  ml (n=36) of tidal volume to maintain basal requirements whereas the females require  $355 \pm 79$  ml (n=13).

With the DPS and the resultant negative pressure ventilation, the higher tidal volumes are not necessary since the ventilator dead space and any concerns about leakage around the tracheotomy are eliminated. Also the duration of speech follows the natural speaking pattern of the patient although the volume of speech is still a concern since the DPS stimulation parameters are set for a constant  $V_T$ . All the patients that meet our current inclusion criteria (e.g. visual verification of diaphragm movement under fluoroscopy with PNCS) and have completed the initial conditioning have been able to exceed their basal  $V_T$  requirements. Furthermore, all of these patients have acceptable minute ventilation, either in or above the normal range (of 5 – 10 liters / minute). Table 5 provides the stimulated tidal volume and minute ventilation for the patients using the DPS. Use of the DPS is at the patients' preference and comfort. Thus, the part-time patient, although physiologically capable of supporting full-time ventilation, choose to use it on a limited basis to support the level of independence that they desire and are comfortable with, given their caregiver support.

**Table 5: Stimulated Ventilation (n=49)**

	Average	Stdev	Min	Max
Basal Metabolic Requirement (ml)				
Male (7ml/kg)	575	109	399	889
Female (6ml/kg)	355	79	240	504
Stimulated Tidal Volume (ml)				
Male	816	207	540	1500
Female	528	97	350	680
Minute Ventilation (liters / min)				
Male	10	3	6	18
Female	6	1	4	9

Performing a paired comparison of the stimulated tidal volume with the basal metabolic requirement for each patient also shows that significant ( $p < 0.001$ ) tidal volumes may be obtained with the DPS. Given these results to date, this study has demonstrated probable benefit in this patient population. With no unexpected serious adverse events reported the NeuRx DPS has performed reliably and safely in this patient population.

## 8.0 ADVERSE EVENTS

	Adverse Event	# Events	# Affected Patients	% of Patients (n=50)
*	Capnothorax	21	21	42%
	<b>Equipment Failures</b>			
*	Broken External Wire	10	7	14%

	<b>Adverse Event</b>	<b># Events</b>	<b># Affected Patients</b>	<b>% of Patients (n=50)</b>
*	Broken Anode	3	3	6%
*	External Equipment Failure	2	2	4%
	<b>Infectious Diseases</b>			
	UTI	10	6	12%
	Pneumonia	6	3	6%
	Upper Respiratory Infection	8	3	6%
*	Localized Infection	2	2	4%
*	Spasms	5	5	10%
*	Pain/Discomfort with stimulation	5	3	6%
	<b>Airway Compromise</b>			
*	Aspiration	11	3	6%
*	Increased Secretions	3	3	6%
*	Airway Obstruction	3	3	6%
*	Low $V_T$ , $O_2$	5	3	6%
	<b>Deaths</b>			
	Death (while device not in use)	2	2	4%
	Death (while device was in use)	2	2	4%
	Pain - not device related	2	2	4%
	Nausea	2	2	4%
	Autonomic Dysreflexia	3	2	4%
	Ulcer	2	2	4%
	Elevated Temperature	3	2	4%
	Redness or Swelling	4	2	4%
*	Difficulty Eating with Device	1	1	2%
	Dizziness	1	1	2%
	Atelectasis	1	1	2%
	PEG Tube displaced	1	1	2%
	Excess Gas / Bloating	3	1	2%
	Pressure Sore	1	1	2%
	Blood with Exsufflation	1	1	2%

- **Spasms**

Spasticity is a side effect of paralysis that varies from mild muscle stiffness to severe, uncontrollable leg movements. Most individuals with SCI have some spasms. Device related spasms may occur upon initiation of stimulation with muscle spasms in the arms or legs. In the five patients that reported muscle spasms as a result of diaphragm stimulation there was an initial occurrence when the stimulation was turned on or it may have persisted and was controlled by turning reducing the level of stimulation on one or more channels. All five of the patients were able to continue the use of the device and in fact went on to full-time pacing with the device. The incidence of spasms has decreased since we began using higher levels of pulse modulation with initial settings. Pulse modulation involves the ramping up of the pulse width during each breath to make the breathe smoother.

- **Pain / Discomfort with stimulation**  
 Referred pain, particularly to the shoulder, or abdominal discomfort may sometimes be elicited with the stimulation. This can usually be eliminated through reduction in parameter settings. It may also be an initial response to a novel stimuli and the subject naturally accommodates with progressive sessions. In the three patients that reported temporary pain or discomfort with the stimulation it was controlled by either permanently or temporarily reducing the level of stimulation on one or more channels. Two of the three patients use the device full-time and one patient (that was implanted at 27 years post injury) has used the device for over twelve hours of continuous use.
- **Increased Secretions**  
 Because of a lack of abdominal muscle control, many spinal cord patients are unable to clear secretions naturally (i.e. by coughing). Many techniques are employed to assist these patients clear secretions including: manual assist, CoughAssist device, and The Vest. Mechanical ventilation exacerbates the problem by creating atelectic (collapsed) regions in the lungs (particularly in posterior regions). When diaphragm stimulation is initiated the atelectic regions of the lungs are expanded and the secretions may be mobilized. Diaphragm pacing utilizes the more physiologic posterior lung lobes than mechanical ventilation. This may result in a noticeable increase in secretions during initial use of the device. In three patients this was noted and was subsequently reduced with continued use of the device.
- **External Equipment Failure**  
 In the event of the availability of the supplied external diaphragm pacing equipment to provide ventilation patients must be returned to their backup positive pressure mechanical ventilator. Each patient is supplied with two external pacing devices and cables. In risk analysis, failure of both supplied components was considered a failure of the external equipment. This has happened in one case where both external stimulators failed due to memory corruption from improper battery changes. This was subsequently changed in the external pacer through a circuit modification and has not occurred since the engineering change notice went into effect. Another patient reported failure of both external devices to provide sufficient ventilation, but this was subsequently identified as an escalating pneumonia.
- **Localized infection**  
 The implanted components of the pacing device consist of five leads, four stimulating electrodes are implanted in the diaphragm and one is in the subcutaneous tissue as a current return (anodic) electrode. The four diaphragm electrodes are gathered at the epigastric trocar site and tunneled to the percutaneous exit site, where they exit the skin along with the anodic electrode. Two patients during the trial had localized infections of the diaphragm leads at the epigastric site that required treatment. The first case had his epigastric connector site externalized due to an infection from a

delayed wound granuloma. This patient also had pre-existing mastocytosis that caused a greater reaction because of histamine abnormalities. Once externalized there was no longer a problem. Most superficial wounds like this are only managed with surgical drainage, this patient did have a brief course of antibiotics from his local physician prior to simple externalization of the wires. As the third patient in the study, this patient also had a coil of excess wire at the epigastric site which added to the foreign body response. After this case an excess coil of wire was no longer left at the epigastric port, instead excess wire was either left in the abdomen or pulled out of the percutaneous exit site. The use of braided suture that led to the suture granuloma was also stopped. Also the connector system is no longer used with the sutures.

The second case also had a localized wound infection at the epigastric site. This patient had a chronic gastro-cutaneous fistula from a gastrotomy tube that was handled surgically at the diaphragm pacer implantation with a resultant open wound. This probably led to the infection which slowly occurred following implantation. The wires became exposed in the epigastric area where they were tunneled over the ribs to the exit site on the chest. This patient was extremely thin and perhaps the lack of subcutaneous tissue also affected this as a pressure point. This problem was easily handled by having the wires connected to the orange block at the epigastric site and removing the tunneled wires. This was done in an office setting. The patient did take oral antibiotics because of some cellulitis above the tunneled wires. Since the tunneled wires were removed the patient has had no further problems and is pacing fine.

A comparison of wire infections to the similar placement of a gastroparesis device (Forster, et.al., 2003 "Further Experience with Gastric Stimulation to Treat Drug Refractory Gastroparesis") identified a similar rate of infection with 4 of 55 patients (7.2%) having the device removed due to post-operative or later infections. Further, with the laparoscopic procedure classified as a contaminated operation, with the management of gastrostomies, the current rate of infection would be anticipated.

- **Low Tidal Volume ( $V_T$ ) / Oxygen ( $O_2$ ) Desaturation**

During initial conditioning of the diaphragm muscle fatigue occurs and is part of the conditioning process. The instructions for use indicate that tidal volumes and oxygen desaturation are to be monitored and used as a basis monitoring the conditioning session. Instructions indicate that the patients are to return to their mechanical ventilation when signs of shortness of breath or discomfort are identified. Two of the first five implanted patients identified low tidal volumes and oxygen desaturation during their conditioning sessions. Both of these patients were returned to their ventilator, as per instructions, and later continued with additional conditioning sessions. These patients eventually paced full-time with the device. One additional patient suffered a scorpion bite while pacing that resulted in a low tidal volume and oxygen

desaturation. Upon treatment for the scorpion bite the patient was able to return to pacing with no additional effects.

- **Death**

NOTE: None of the reported deaths during the clinical trial were device related. The life expectancy of a mechanically ventilated spinal cord injured patient is far lower than a non-ventilated spinal cord patient. The National Spinal Cord Injury Statistical Center (NSCISC) reports a reduction of ten years in a forty year old mechanically ventilated patient with a life expectancy of eleven years, if the patient has survived the first year post injury. The NSCISC identifies the leading causes of death are pneumonia, pulmonary emboli, and septicemia.

Of the four deaths reported of patients enrolled in the study, two occurred while the device was in use and two when the device was not in use. The first death occurred in a patient with systemic mastocytosis and was the result of an allergic reaction, resulting in multiple organ failure, to an antibiotic given for a purulent groin wound. This patient was not using the pacing device at the time of death or at the administration of the antibiotic. He was using the device for several hours per day prior to his death. The second patient that died had suddenly passed out at a party and, although still breathing with the pacer, a pulse could not be found. He was transported to a local hospital where he was pronounced dead from presumed cardiac origin. This patient had been a full-time user of the device. The third patient passed away in his sleep with death from presumed cardiac origin. This patient was not using the pacing device at the time of his death, although he had reported using the device for several hours per day prior to his death. The fourth patient developed significant sepsis with evidence of liver failure and renal failure. The patient began having seizures and the rapidly developed overwhelming septic shock and had a subsequent arrest. This patient was part of the cardiac pacer arm of the study and was a full-time user of the device. It was noted that the patient was using DPS for respiration prior to his hypotensive arrest and no diaphragm pacing to cardiac pacemaker interaction was noted while he was being monitored.

- **Broken External Wire**

The NeuRx DPS™ consist of four electrodes implanted in the diaphragm with leads extending to an external connector block for access to connect to the external pacer. The external block is secured in an assembly of a plastic clip mounted on a piece of hypoallergenic tape (the connector holder). The connector holder is intended to be changed by the caregiver every few days, such as after bathing. To change the connector holder the connector block, containing the crimped electrode leads, is removed from the old holder and placed into the new holder by the caregiver. This manipulation may result in breakage of external lead wires. The external pacer senses the lead impedance of each lead with each stimulus pulse and alerts the patient by providing an audible alarm and displaying an "X" on the device display. As

there are four electrodes in each patient, a break in an individual electrode lead may not result in a catastrophic loss of ventilation but rather a reduction. Also, since the break would typically occur during the manipulation of the connector block while the caregiver is changing the connector holder, the recognition of the event when the pacemaker is reconnected occurs while the caregiver is present.

We identified 10 broken external wires in 7 patients (14% of the patients). Recognizing this in review, we initiated a supplement to modify the termination of the external wires. We eliminated the percutaneous extension lead and increased the length of the intramuscular electrode lead to allow the strain relieved terminating pin to be directly crimped into the connector socket. This eliminated the stripping and crimping of the lead wire directly into the connector socket with a more consistent strain relief. This supplement was approved May 3, 2007. Eleven (22%) of the reported patients were implanted after this approval with no broken external leads or anodes in 7.7 cumulative years of implant time. During this time frame, two of the earlier implanted patients had broken external lead wires, indicating that the change was not due to other changes in instructions or handling of the connection.

- **Difficulty Eating with Device**

With initial use of the device the coordination between swallowing and breathing is not established. The instructions indicate the use of a passy muir (one way breathing) valve to allow the patient to eat or drink during stimulation until the coordination is established. In one instance the patient attempted to eat and drink prior to having that coordination established and did not use a passy muir valve. While the patient did not aspirate, he did report difficulty eating and drinking.

## **9.0 Training of Surgical Implantation**

New surgeons will be proctored in the implantation of the NeuRx DPS™ system by a qualified, trained surgeon. To be considered for training, the new surgeon must be credentialed for laparoscopic surgery at their institution. The training procedure will, minimally consist of the qualified trainer proctoring from outside of the surgical field, in the trainee's operating room. The trainer will review the procedure, using this manual, and the patient information to assure that appropriate candidate selection has been made. Specific precautions will be reviewed, including the identification of a capnothorax with preventive measures and steps to resolve, prior to the procedure. Any peri-operative morbidity, mortality, or device malfunctions will be reported according to the FDA Medical Device Reporting (MDR) procedures and reviewed by Synapse Biomedical. Upon completion of training the trainee may request additional onsite proctoring or the trainer may identify that additional proctoring is necessary. The training will be documented on a Surgeon Training Memo, to be kept on record at Synapse Biomedical.

## 10.0 DESCRIPTION OF LAPAROSCOPIC SURGICAL PROCEDURE

### 10.1 INCLUSION PRE-SCREENING

Candidates are patients with high level spinal cord injury resulting in dependence on mechanical ventilation. The candidate must have bilateral intact phrenic nerves below the level of the spinal cord injury. The candidate must be in otherwise generally good health.

The laparoscopic surgical procedure for implantation of the NeuRx Diaphragm Pacing Stimulation (DPS) System is expected to take two hours. The patient is implanted with four IM (Intra-Muscular) electrodes, two in each hemidiaphragm, using laparoscopic techniques. Pre-operatives tests are obtained for patients based on their needs prior to general anesthesia.

### 10.2 ESTABLISH LAPAROSCOPIC PORTS

The operation is done in the supine position with no neuromuscular blocking agents. The patient's abdomen and chest is prepped and draped in the usual sterile fashion. Four ports will need to be inserted into the abdominal cavity: one for optics, two lateral working ports for the mapping probe and one epigastric port for electrode insertion instruments and the exit site from the abdominal cavity for the electrode lead wires. During this phase any abdominal adhesions are released and gastrostomy tube tracts are removed if they are in the way of implantation of the diaphragm pacing system. The falciform ligament is divided which allows easier visualization of the medial aspect of the right diaphragm and easier exit of the pacing electrodes through the epigastric port. Standard laparoscopic principles are followed with a typical setup in figure 1.



Figure 1: 4 ports insertion

### 10.3 MAPPING OF THE DIAPHRAGM

Prior to mapping, a surface electrode is placed around the thigh region and is connected to the Clinical Station (see Clinical Station Operating Manual). Intra-abdominal pressure during test stimulation (mapping) will be measured externally through the insufflation port with tubing. This tubing will connect to a pressure sensor to go to the clinical station. Mapping involves finding the point

on the abdominal side of the diaphragm where stimulation causes the greatest diaphragm excursion. The mapping instrument has a suction port that allows it to temporarily attach to the diaphragm and deliver an electrical stimulus (Figure 2). Stimulation is applied in either a twitch or burst mode from the clinical station. Mapping allows qualitative and quantitative data to be obtained. Quantitatively, changes in abdominal pressures are measured. Qualitatively, observation of the diaphragm contraction is performed. The stronger the stimulated contraction the closer to the motor point of the phrenic nerve. During mapping the entire diaphragm is assessed in grid pattern to be sure the point of maximal contraction is not missed. These locations are recorded on transparency that is overlaid on the laparoscopic video display. (Figures 3a and 3b) The magnitude of the abdominal pressure change, to the applied stimuli, is recorded for each location. The primary electrode site is identified at the location of maximal pressure change in each hemi-diaphragm. A secondary electrode site is identified as either a backup to the primary site or at a location in each hemi-diaphragm that recruits another region (e.g. anterior, lateral, or posterior) of the diaphragm at a similar magnitude. The two locations are marked using a marker.

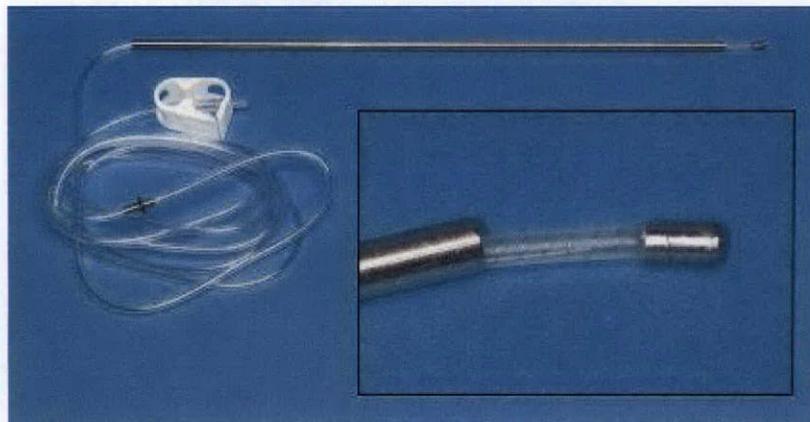


Figure 2: Mapping Probe



Figure 3a: Stimulation of the diaphragm

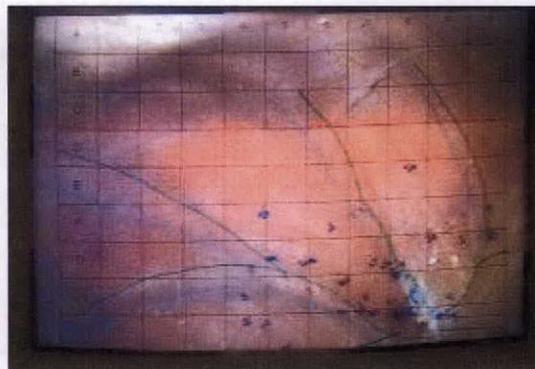


Figure 3b: Stimulation location recorded on Grid

#### 10.4 INSERTION AND PLACEMENT OF THE ELECTRODES

Once the primary and secondary electrode sites are identified in each hemidiaphragm the implantation phase begins. An intramuscular electrode is introduced into the abdominal cavity with the electrode delivery instrument (see figure 4).



Figure 4: Surgical Electrode Delivery Instrument

The electrode is inserted into the diaphragm, at an angle so that the electrode lead travels parallel to the plane of the diaphragm prior to exit, and the delivery instrument is withdrawn. (Figure 5a and 5b) A standard laparoscopic dissector may be used to assist in the positioning of the electrode at the desired site on the diaphragm and give counter-traction when the needle is being removed. The electrode is then tested to assure the desired response to twitch stimuli is achieved and the procedure is repeated for the remaining electrodes. If the response is not adequate when tested the electrode may be withdrawn and another implanted. A second electrode is implanted at the previously marked site during mapping. At the conclusion of the implantation a CXR will be obtained to be sure no intra-abdominal air will have tracked with the needle to the chest cavity- a capnothorax. If one is present it can be aspirated with a percutaneous catheter (such as an angiocatheter, small chest tube, or thoracentesis) at the end of the case.



Figure 5a: Electrode Insertion



Figure 5b: Electrode Insertion

Once all four electrodes are implanted they are brought out through the epigastric trocar location (figure 6).

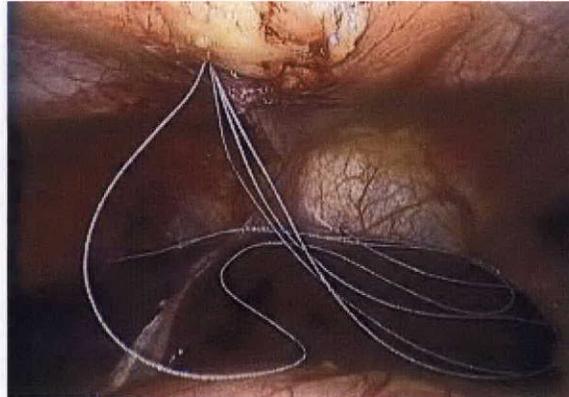


Figure 6

### 10.5 ROUTING

The electrode leads are then routed to the percutaneous exit site. These lead wires will be tunneled subcutaneously to an area in the upper chest at a site deemed appropriate by the surgeon and patient's caregivers. An additional indifferent electrode will be placed subcutaneously in the upper chest through a separate percutaneous exit site. The electrodes are then retested to make sure that all of the connections have been made properly. An EKG strip is recorded with all four electrodes active to be sure there is no capture of the cardiac rhythm. At this time if the patient needs a gastrostomy a standard percutaneous endoscopic technique can be done and the wires are once again checked. The port incisions are closed and the patient is transferred to recovery. The wire exit site is covered with a wound dressing.

### 10.6 REVERSAL OF DISUSE ATROPHY & CONDITIONING

At one to two weeks post surgery the patient returns to the hospital for the initiation of stimulation. Each electrode is characterized over the range of stimulus parameters using the Clinical Station. Reference the "Synapse Biomedical Clinical Station Manual" (PN 77-0016) for instructions on operation of the Clinical Station. Tidal volumes are recorded while using a calibrated Wrights Spirometer and oxygen saturation is monitored with a pulse oxygen monitor. It should be noted that the tidal volumes are measured with the patient's tracheotomy, which in most cases is a cuff-less trach. This means that tidal volumes recorded with the Wrights Spirometer are lower than the actual inspired air volume due to air leaks around the patients stoma and through their upper airway. An EKG rhythm strip is recorded at maximal stimulus parameters to assure that there is no capture of the cardiac waveform. Initial parameter settings are determined and the RA/4 External Stimulator is programmed. Initial conditioning sessions are performed while the patient is at the hospital to

assure the patient and their caregivers understand and are comfortable with the operation of the DPS.

The patient returns home and logs their use and change in tidal volume with the Wrights Spirometer. Pulse oximetry and a rank scale indication of respiratory effort are recorded with any comments on the log sheets for each use of the DPS. The clinical team follows up with the patients on a weekly basis during the initial weeks, reviewing the log sheets and making any changes as necessary. Log sheets are maintained until the patient has reached, or is capable of, full time use. Electrodes are characterized again at 3, 6, and 12 month intervals post surgery, if the patient has not reached a steady-state plateau or full time use of the system.

### **11.0 CHRONIC USE**

Once the patient has achieved full time use of the DPS, or is using it at a level that is consistent with their desired level of activity, they are free to use the system as desired. The DPS includes two external stimulators, two patient cables, extra batteries and percutaneous connector site tapes. The clinical team follows up with the patients periodically and the patients contact the clinical team, or Synapse Biomedical, for additional supplies (batteries, cables, and percutaneous connector tapes) as needed.

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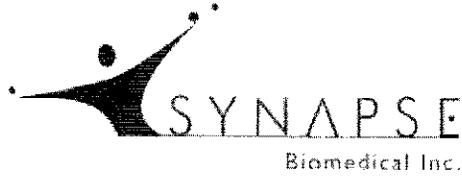
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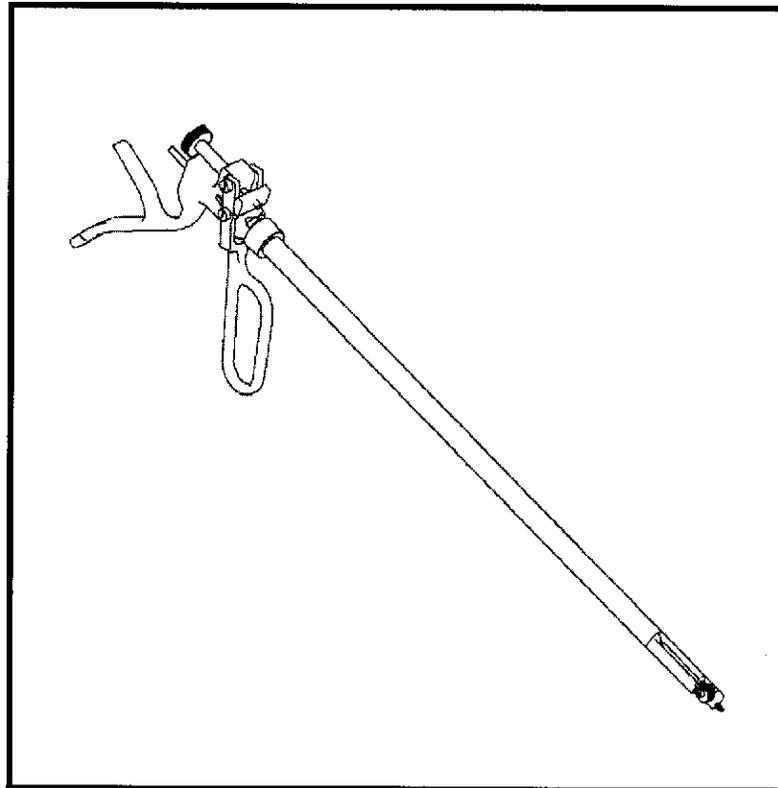
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77-0015 Rev 1E



# **ELECTRODE DELIVERY INSTRUMENT**



## **DISASSEMBLY FOR CLEANING**



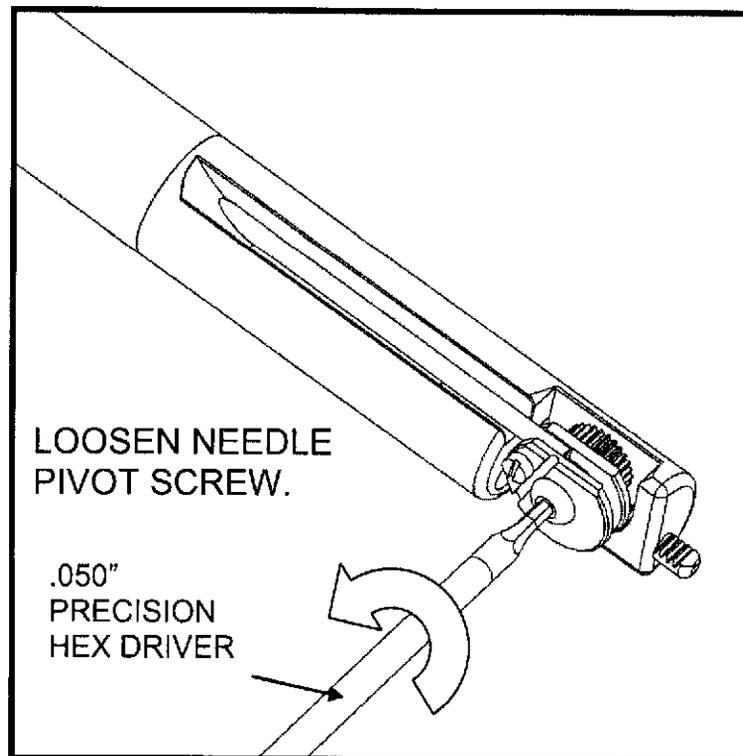
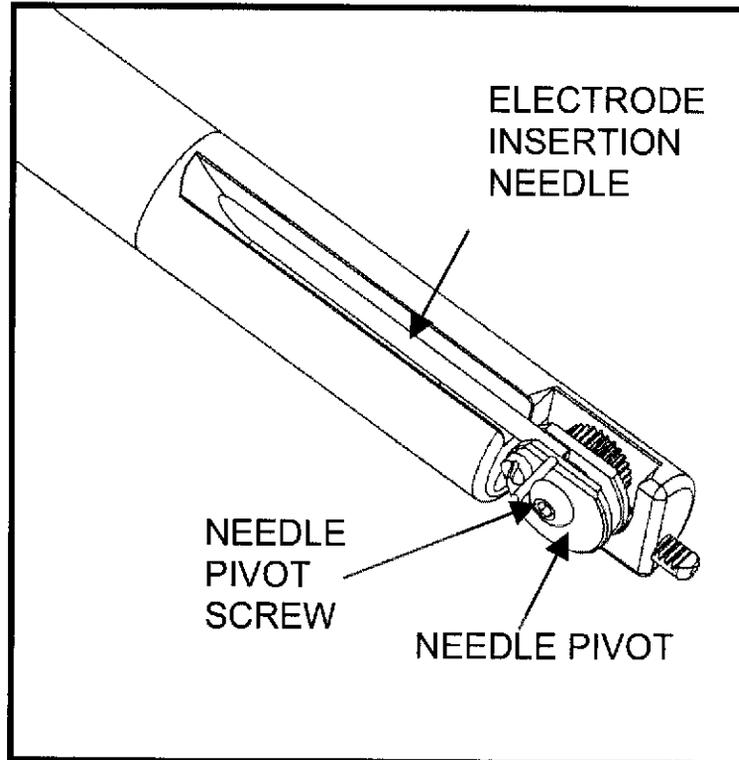
## **ASSEMBLY FOR USE**

### **HUMANITARIAN DEVICE:**

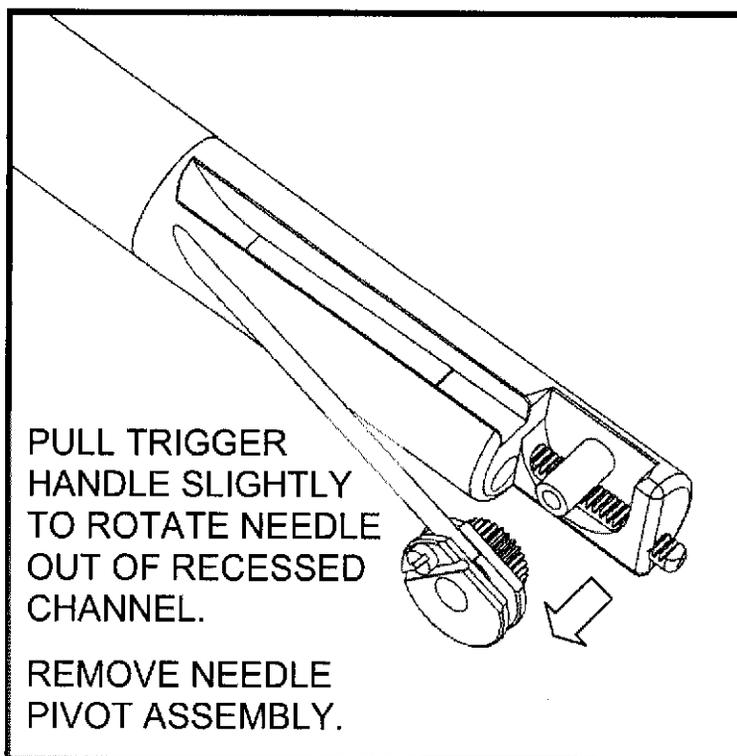
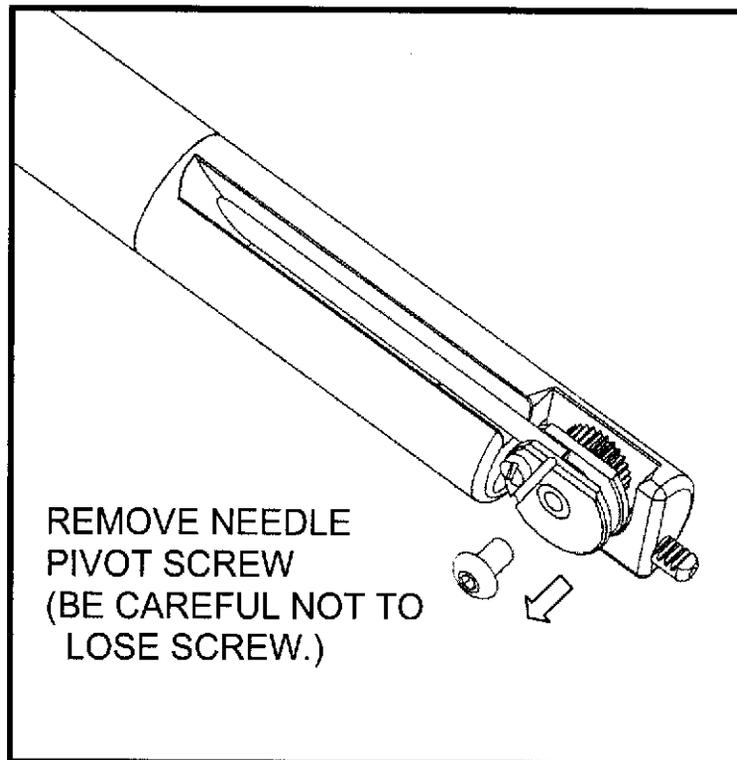
**Authorized by Federal law for use in the treatment of respiratory insufficiency for high-level spinal cord injured patients.  
The effectiveness of this device for this use has not been demonstrated.**

# INSTRUMENT DISASSEMBLY FOR CLEANING

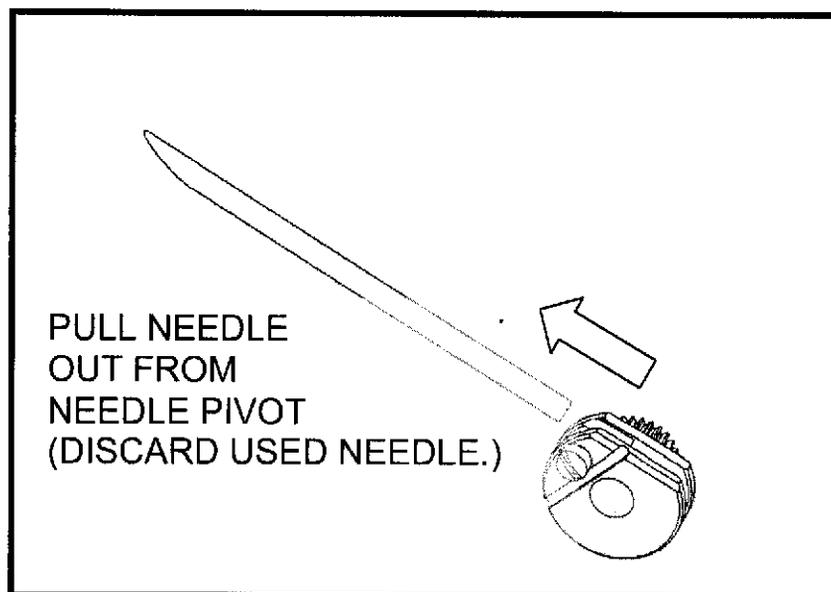
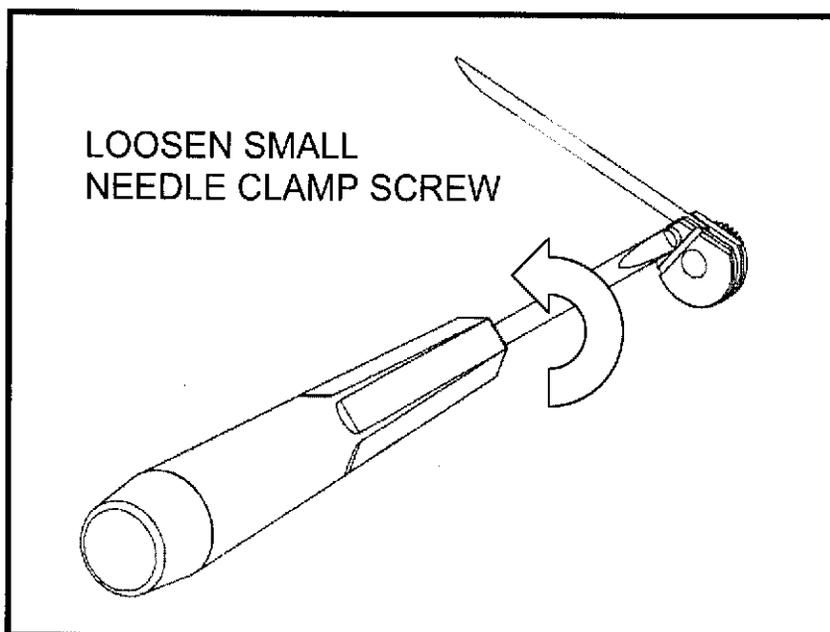
**STEP 1: REMOVE NEEDLE PIVOT**  
**USE CAUTION: ELECTRODE INSERTION**  
**NEEDLE IS VERY SHARP!!!**



**DISASSEMBLY  
STEP 1: REMOVE NEEDLE PIVOT  
(CONTINUED)**



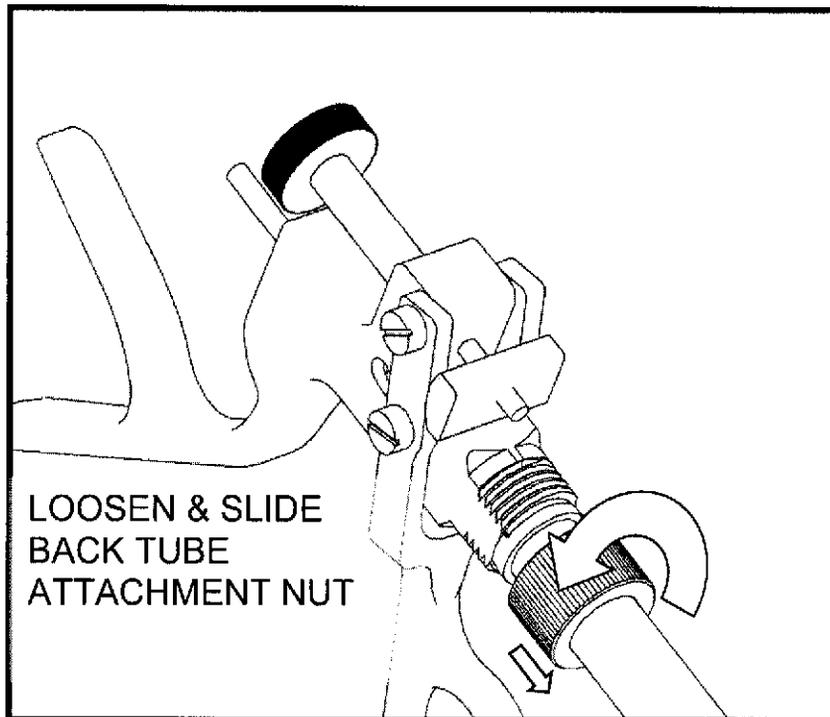
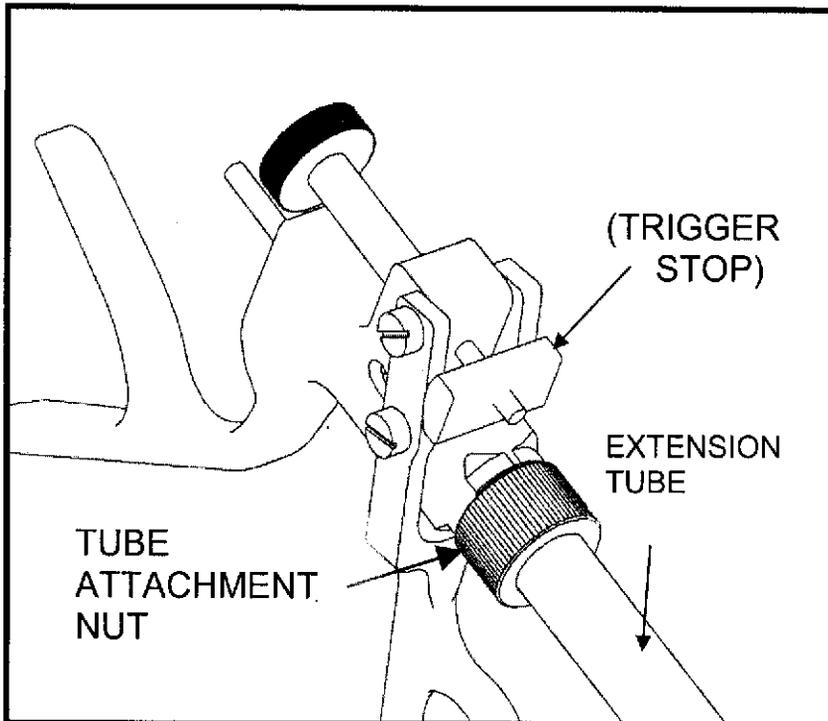
**DISASSEMBLY**  
**STEP 2: REMOVE ELECTRODE INSERTION NEEDLE**  
**FROM NEEDLE PIVOT**



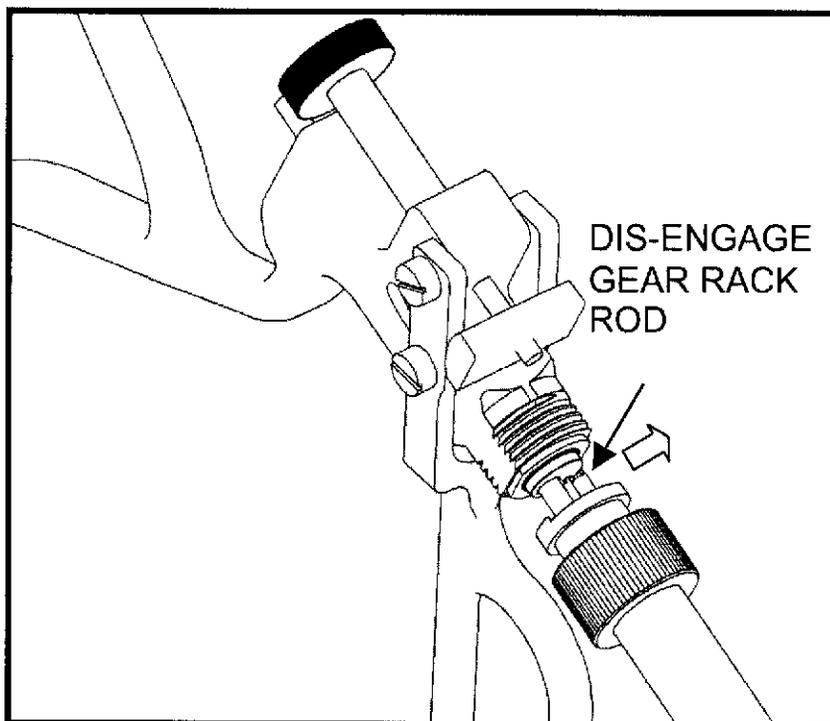
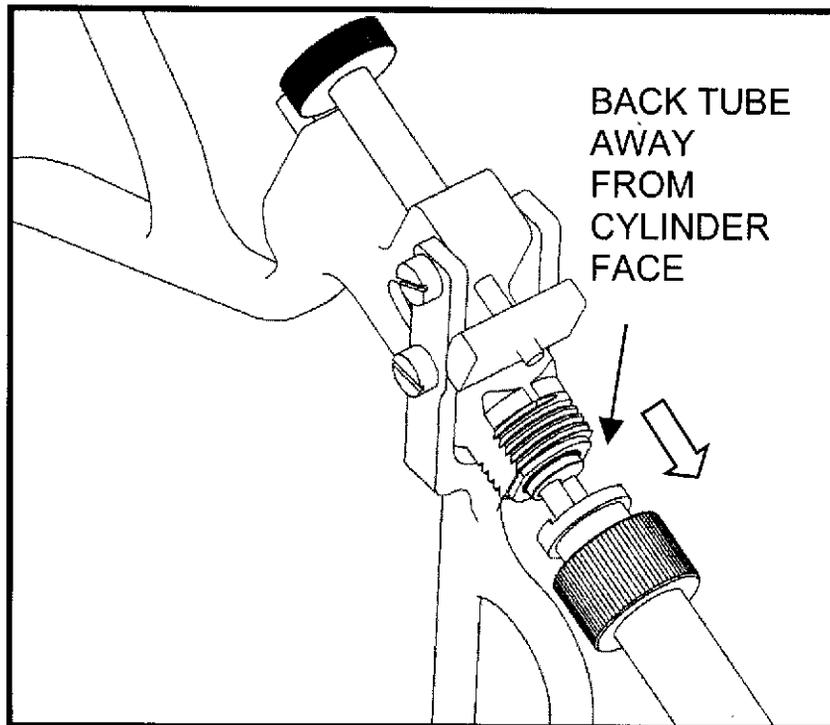
## DISASSEMBLY

### STEP 3: DISCONNECT EXTENSION TUBE

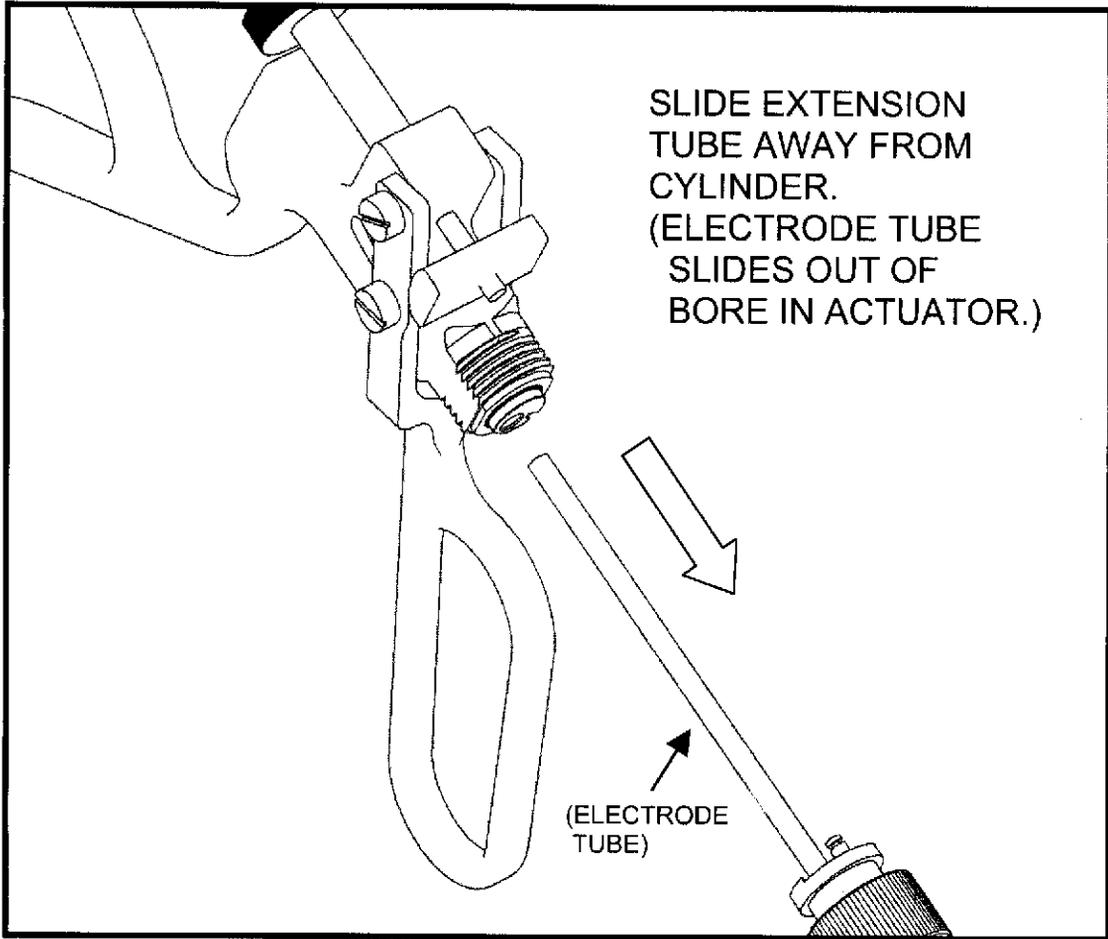
**NOTE:** Before starting this step, make sure the trigger stop is disengaged and the trigger handle is in the extended position.



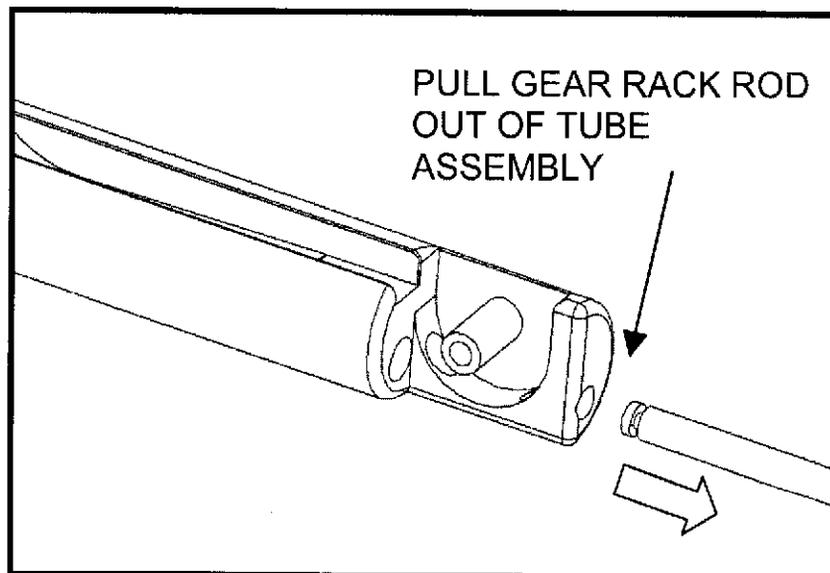
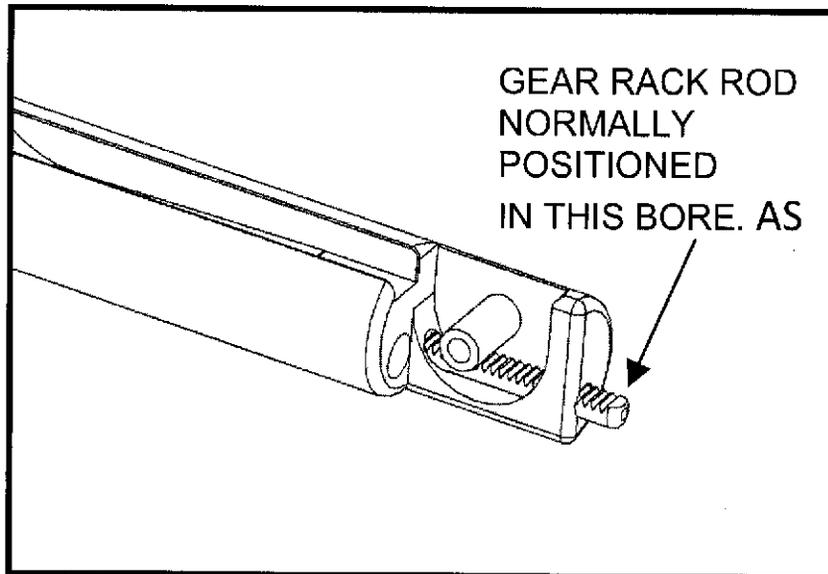
**DISASSEMBLY**  
**STEP 3: DISCONNECT EXTENSION TUBE**  
**(CONTINUED)**



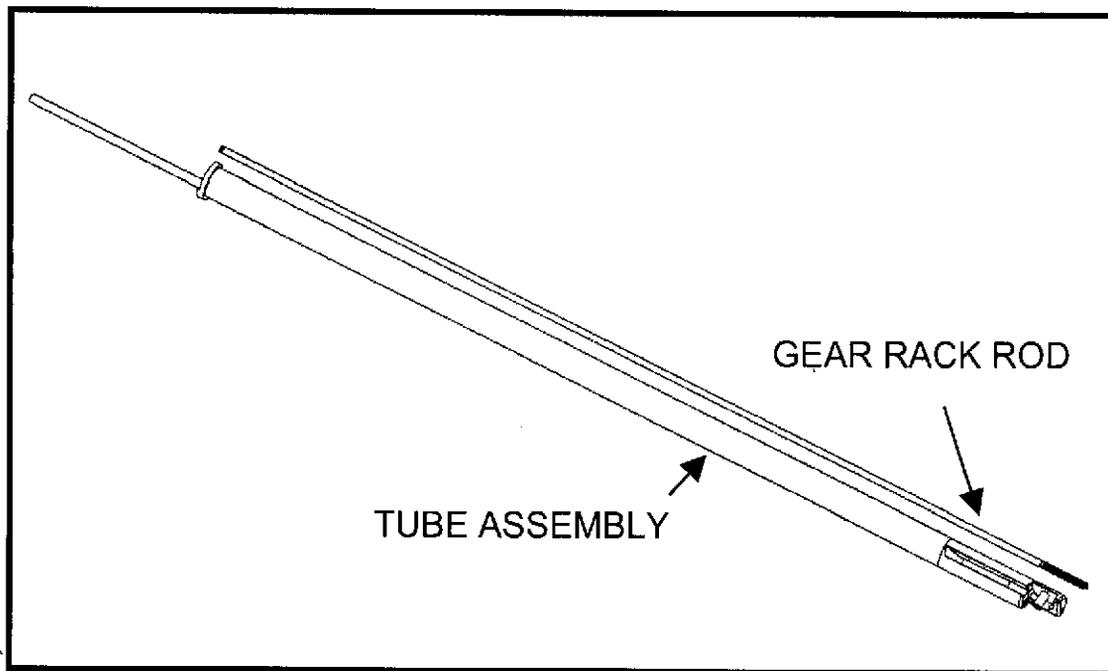
**DISASSEMBLY**  
**STEP 3: DISCONNECT EXTENSION TUBE**  
**(CONTINUED)**



**DISASSEMBLY**  
**STEP 4: REMOVE GEAR RACK ROD FROM TUBE**

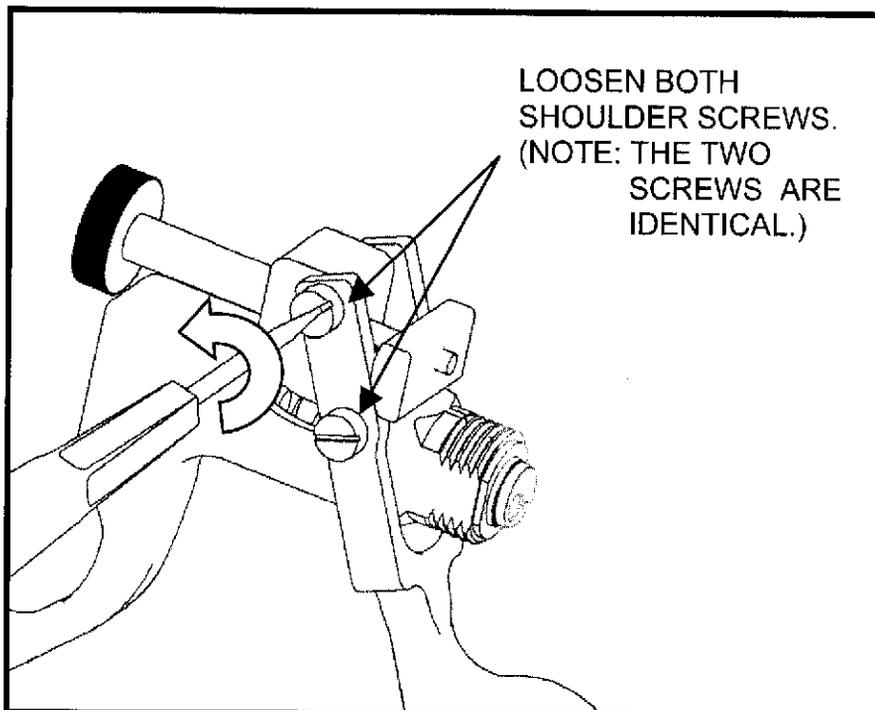
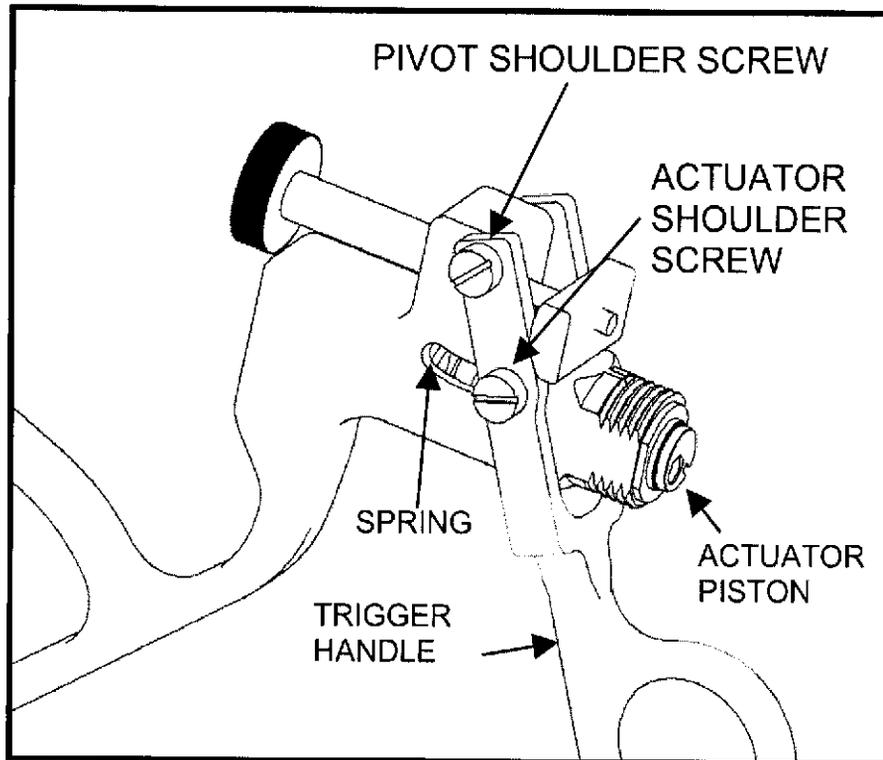


**DISASSEMBLY**  
**STEP 4: REMOVE GEAR RACK ROD FROM TUBE**  
**(CONTINUED)**



# DISASSEMBLY

## STEP 5: HANDLE DISASSEMBLY

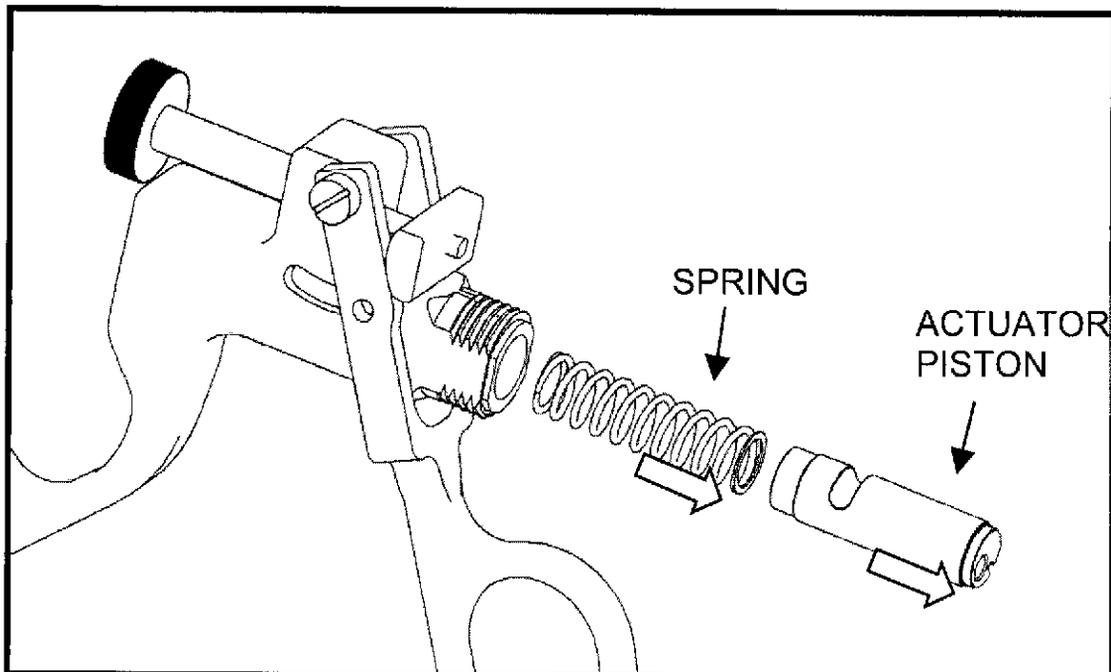
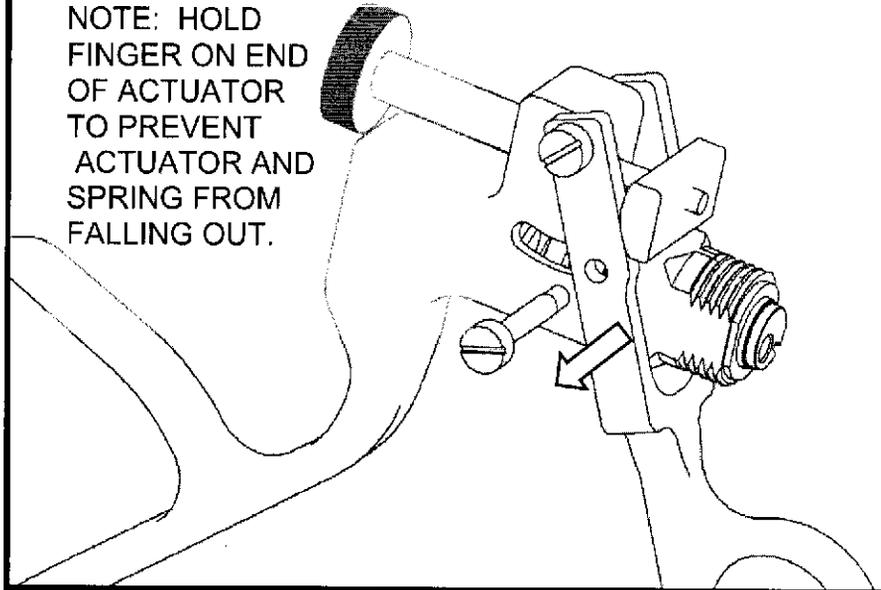


# DISASSEMBLY

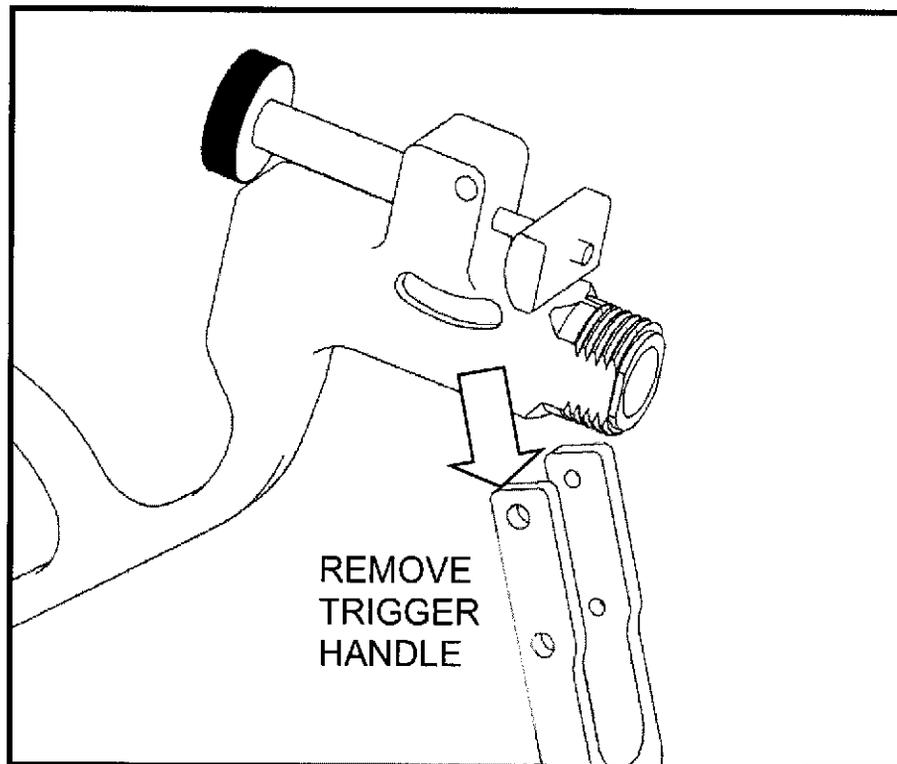
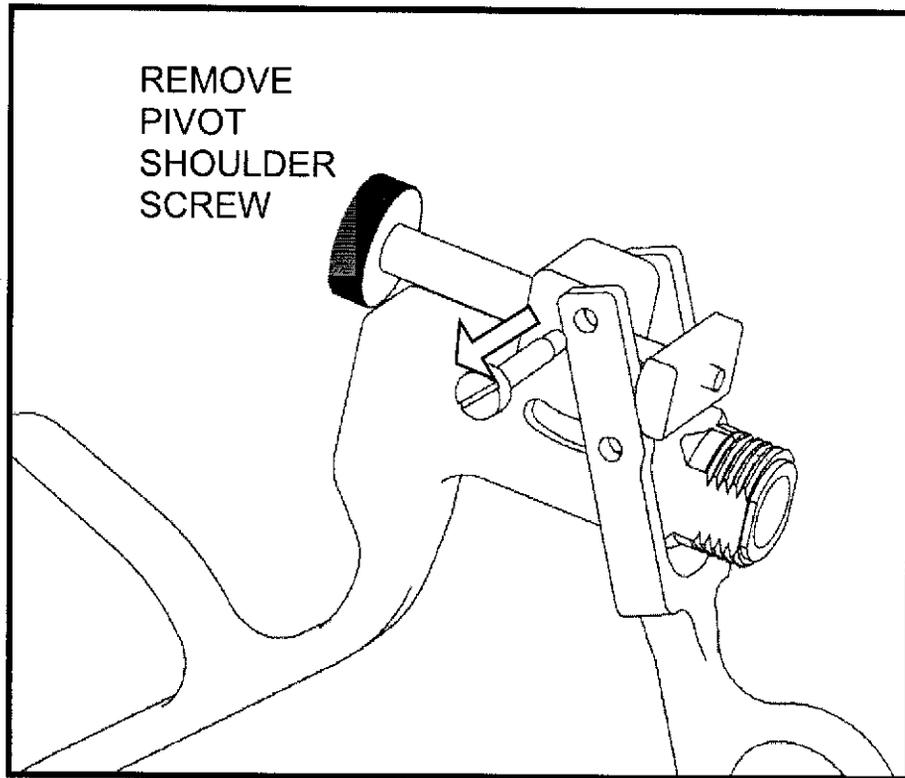
## STEP 5: HANDLE DISASSEMBLY (CONTINUED)

REMOVE ACTUATOR  
SHOULDER SCREW.

NOTE: HOLD  
FINGER ON END  
OF ACTUATOR  
TO PREVENT  
ACTUATOR AND  
SPRING FROM  
FALLING OUT.



**DISASSEMBLY  
STEP 5: HANDLE DISASSEMBLY  
(CONTINUED)**



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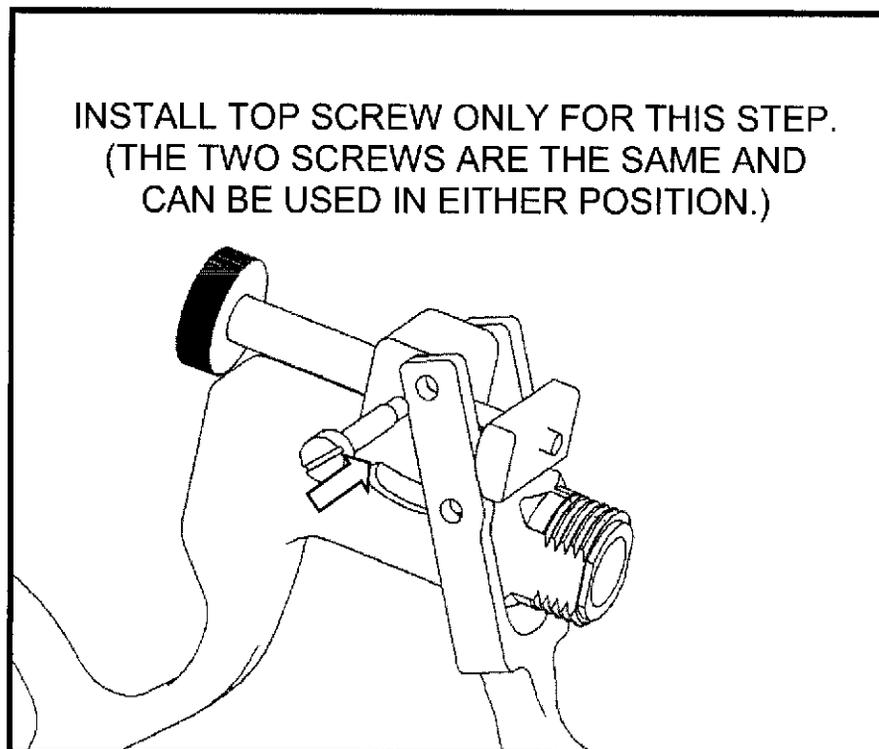
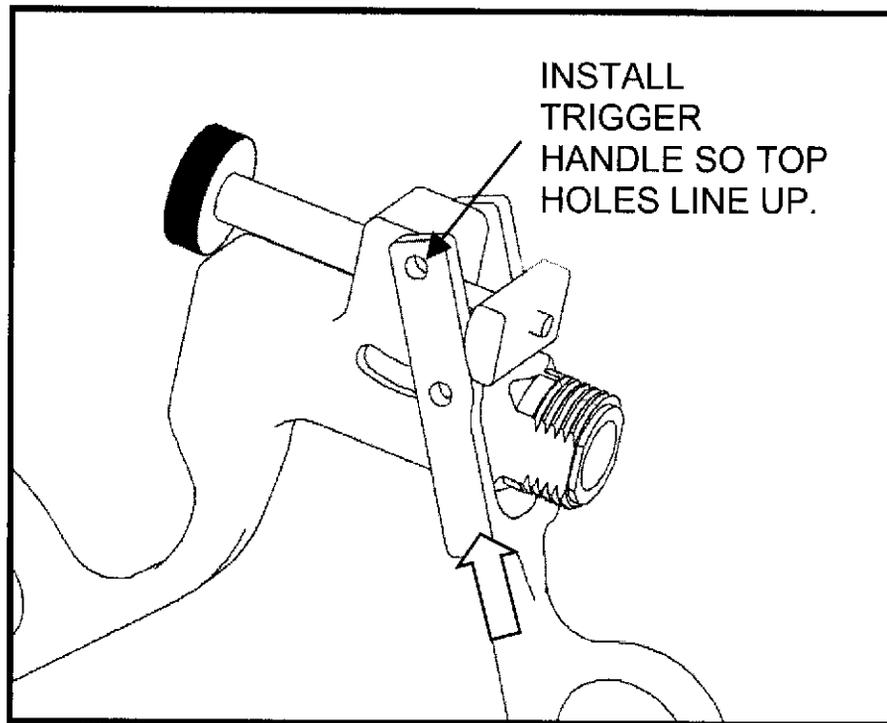
## **PARTS ARE NOW READY FOR CLEANING**

After each use, the needle, needle clamp screw and pivot wheel screw should be disposed of in appropriate sharps container and the instrument should be disassembled prior to cleaning. All parts should be cleaned within 2 hours to prevent fluid and debris from drying. Wear gloves and eye protection during the cleaning procedure. Place all parts in a container.

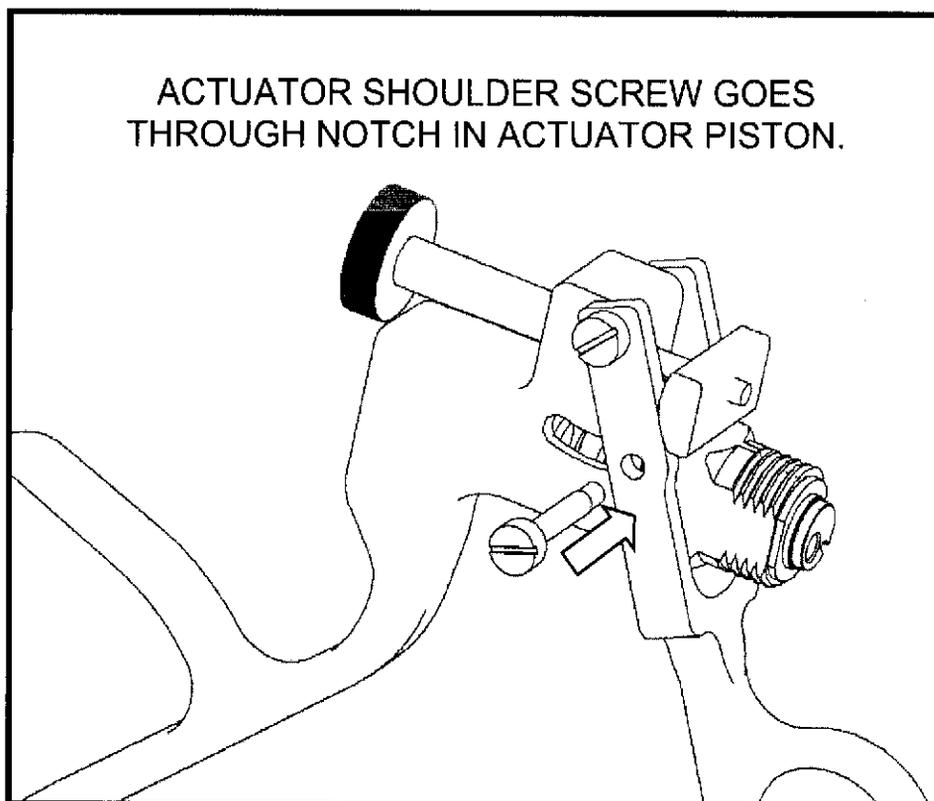
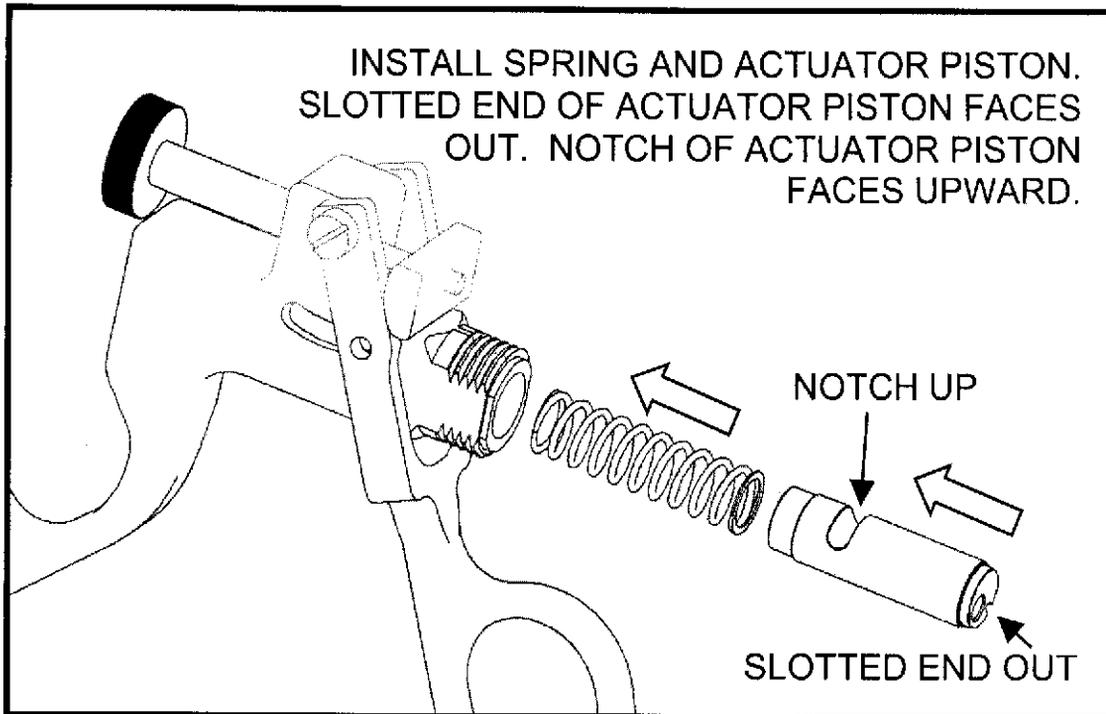
- Prepare a cleaning solution using an enzymatic detergent presoak-plus-cleanser, such as ENZOL™ or Cidezyme™. Prepare the solution according to manufacturers' recommendations.
- Place the parts in a container and prepare enough solution to completely cover all of the parts. The use of harsh or abrasive cleaning agents, such as chlorine bleach, is not recommended as it may affect the integrity of the surgical device, or may cause pitting or other forms of corrosion.
- Allow parts to soak in solution for 10 minutes. After this time, use a soft bristled brush and gently clean the exterior of the parts, paying attention to crevices and especially the needle pivot and gear rack rod until all visible soil has been removed.
- Visually inspect the parts to ensure the removal of soil.
- Flush the interior of the inner lumen of the electrode tube and gear rack exit hole located in the tip of the device.
- Use a soft bristled brush to clean the inner lumen of the tube assembly before proceeding.
- After soaking/washing, remove the parts from the cleaning solution and rinse with deionized water for 3 minutes.
- Visually inspect each part for cleanliness and re-clean if necessary.

# INSTRUMENT ASSEMBLY FOR USE

## STEP 1: HANDLE ASSEMBLY

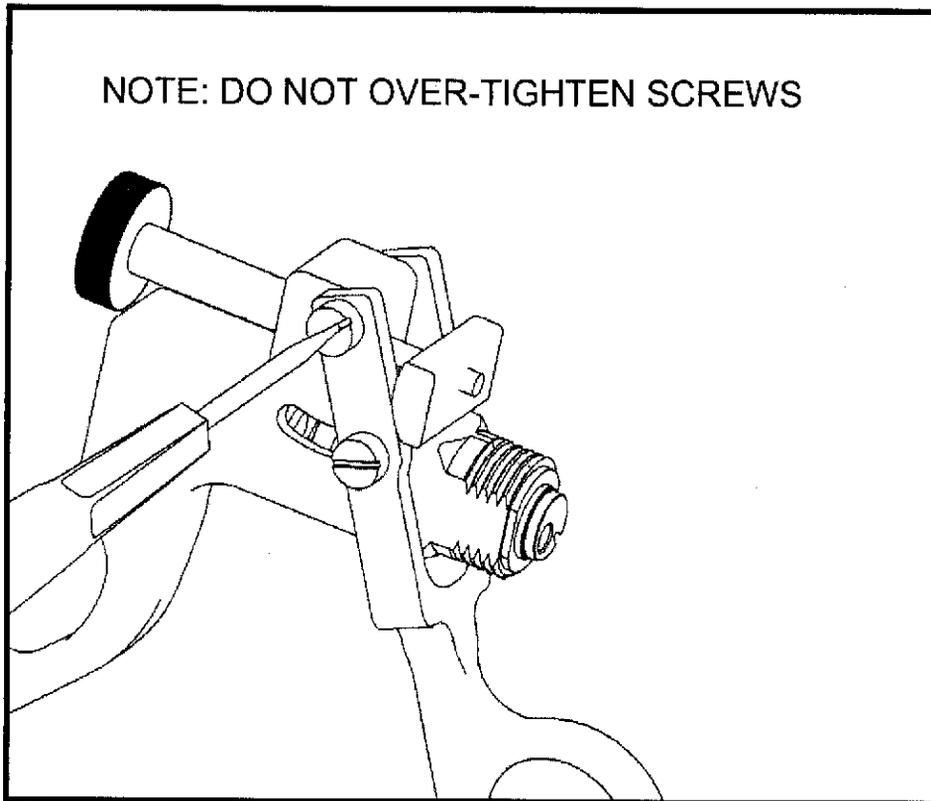


## STEP 1: HANDLE ASSEMBLY (CONTINUED)

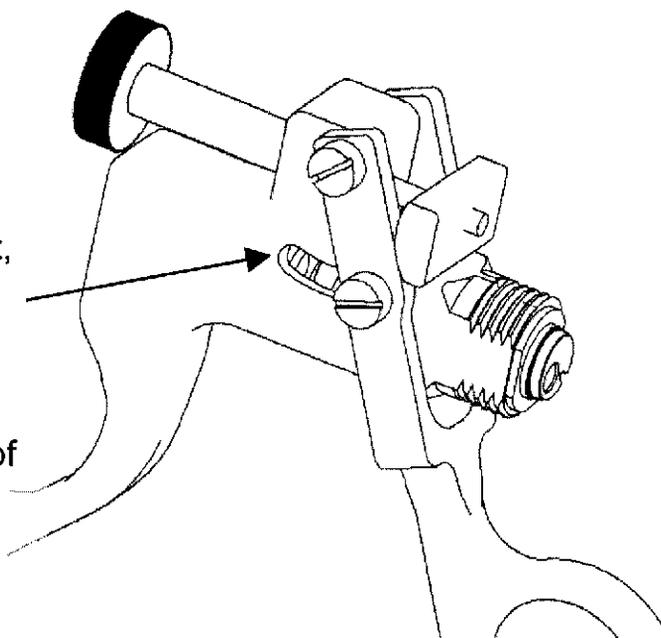


## STEP 1: HANDLE ASSEMBLY (CONTINUED)

NOTE: DO NOT OVER-TIGHTEN SCREWS



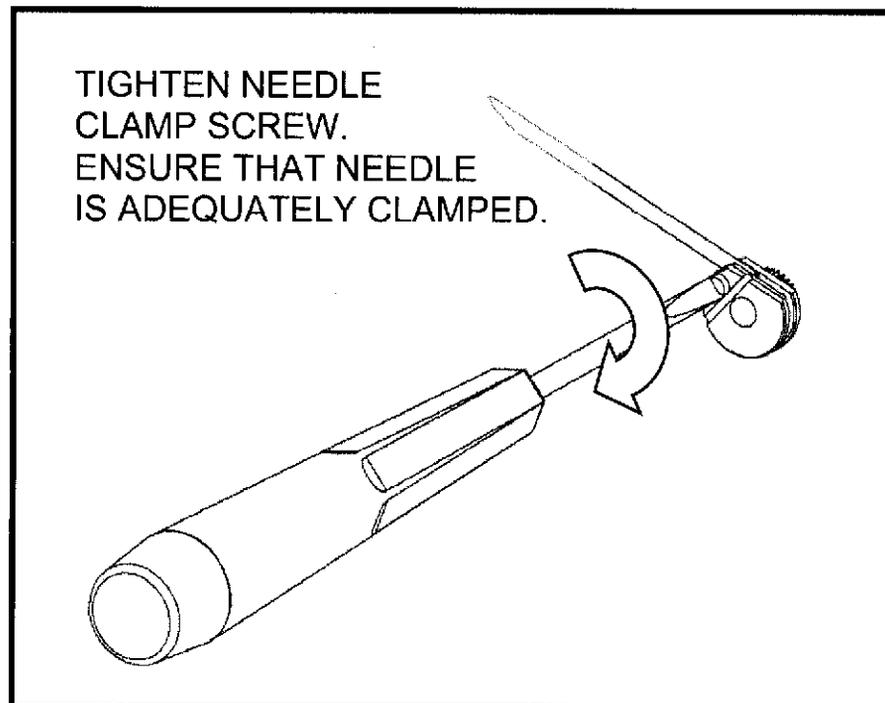
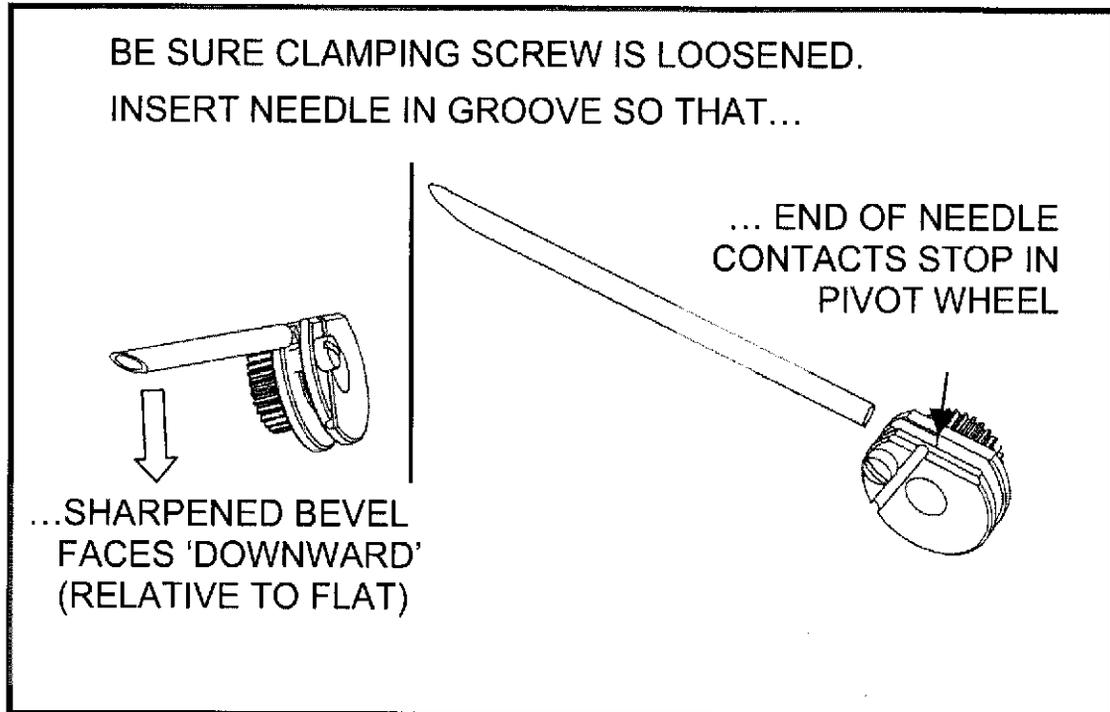
NOTE: Spray SPECTRA-LUBE™ Instrument Spray-on Lubricant, or equivalent, into slot and operate handle a few times to distribute lubricant. Wipe-off excess lubricant from exterior of handle.



## ASSEMBLY

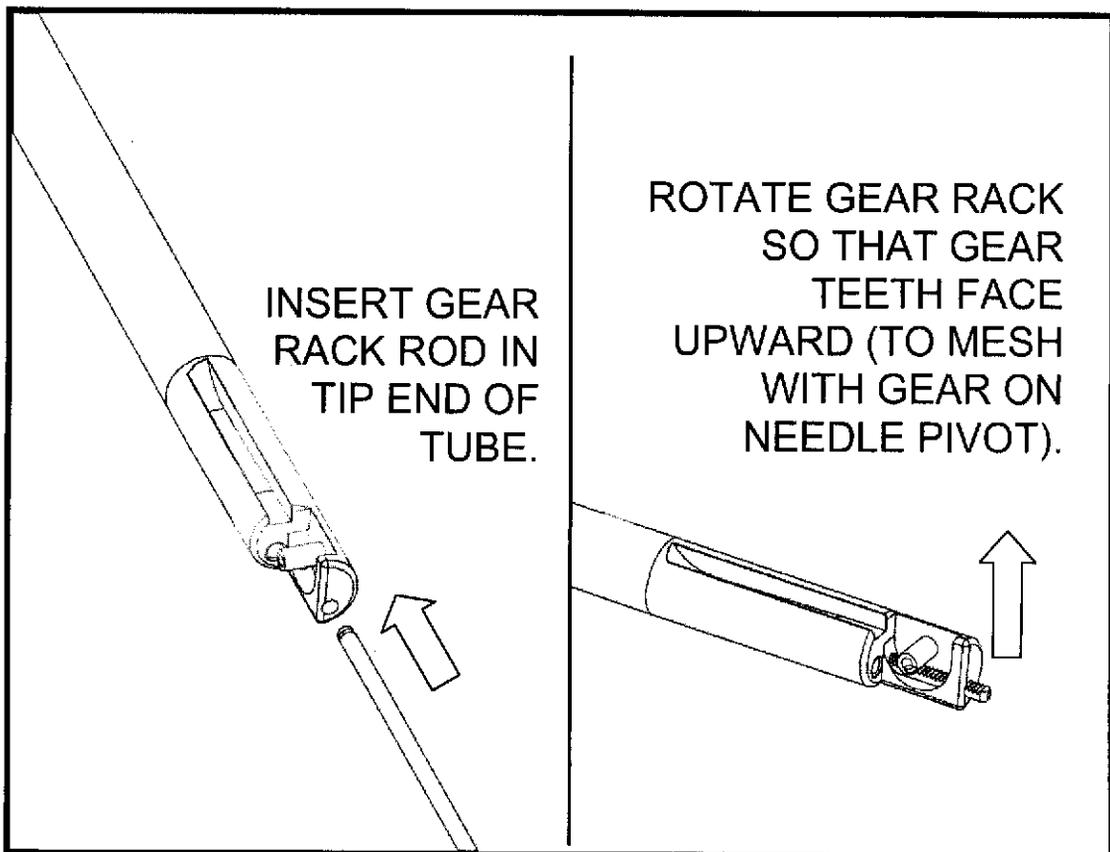
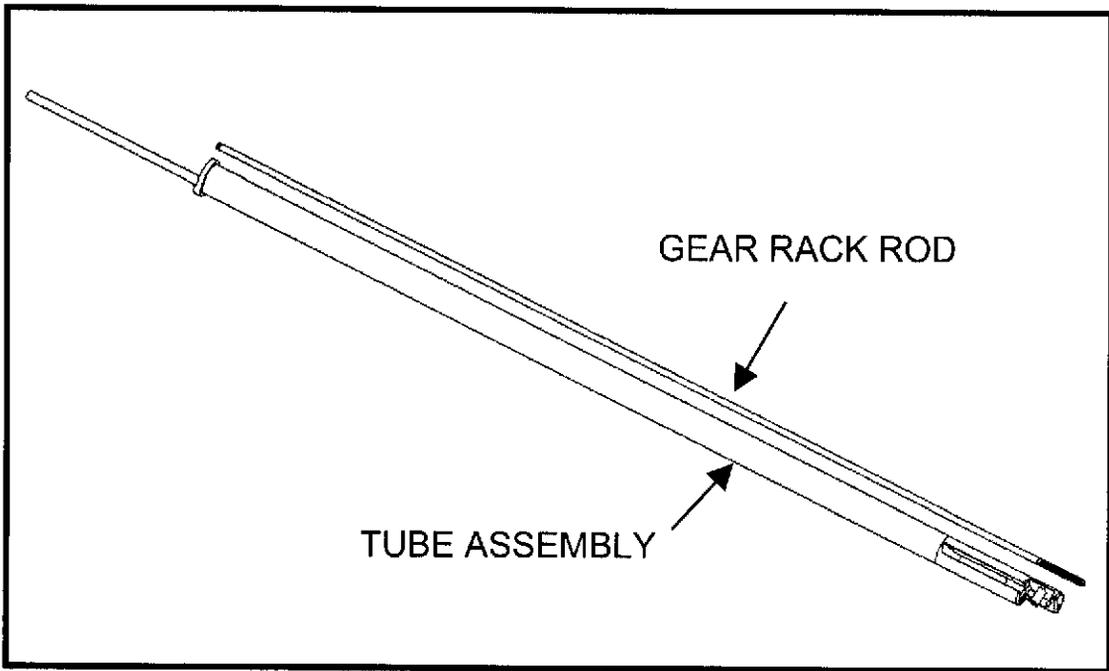
### STEP 2: INSTALL ELECTRODE INSERTION NEEDLE IN NEEDLE PIVOT

- USE CAUTION: ELECTRODE INSERTION NEEDLE IS VERY SHARP!!!
- BE CAREFUL NOT TO CONTACT SHARPENED TIP ON ANY SURFACE... IT IS EASILY DAMAGED.



# ASSEMBLY

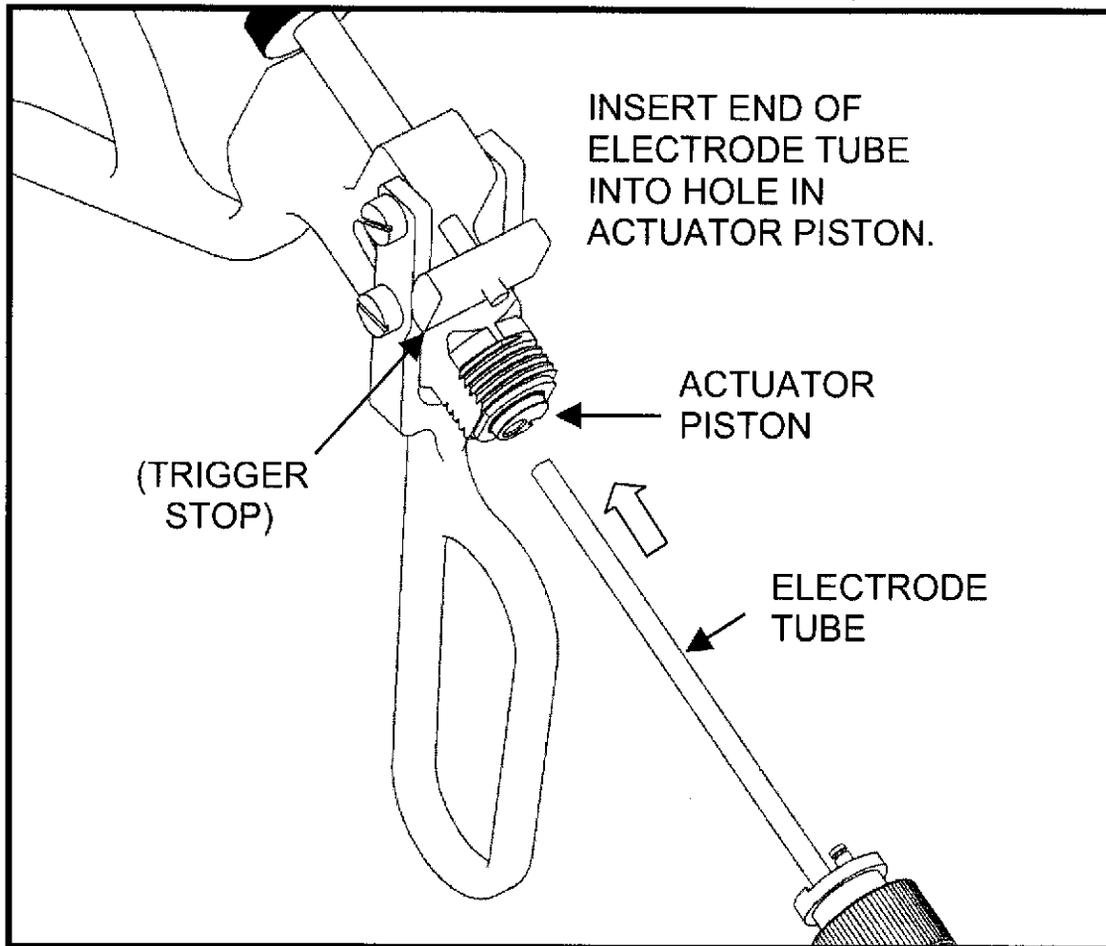
## STEP 3: INSTALL GEAR RACK ROD IN EXTENSION TUBE



## ASSEMBLY

### STEP 4: CONNECT EXTENSION TUBE TO HANDLE

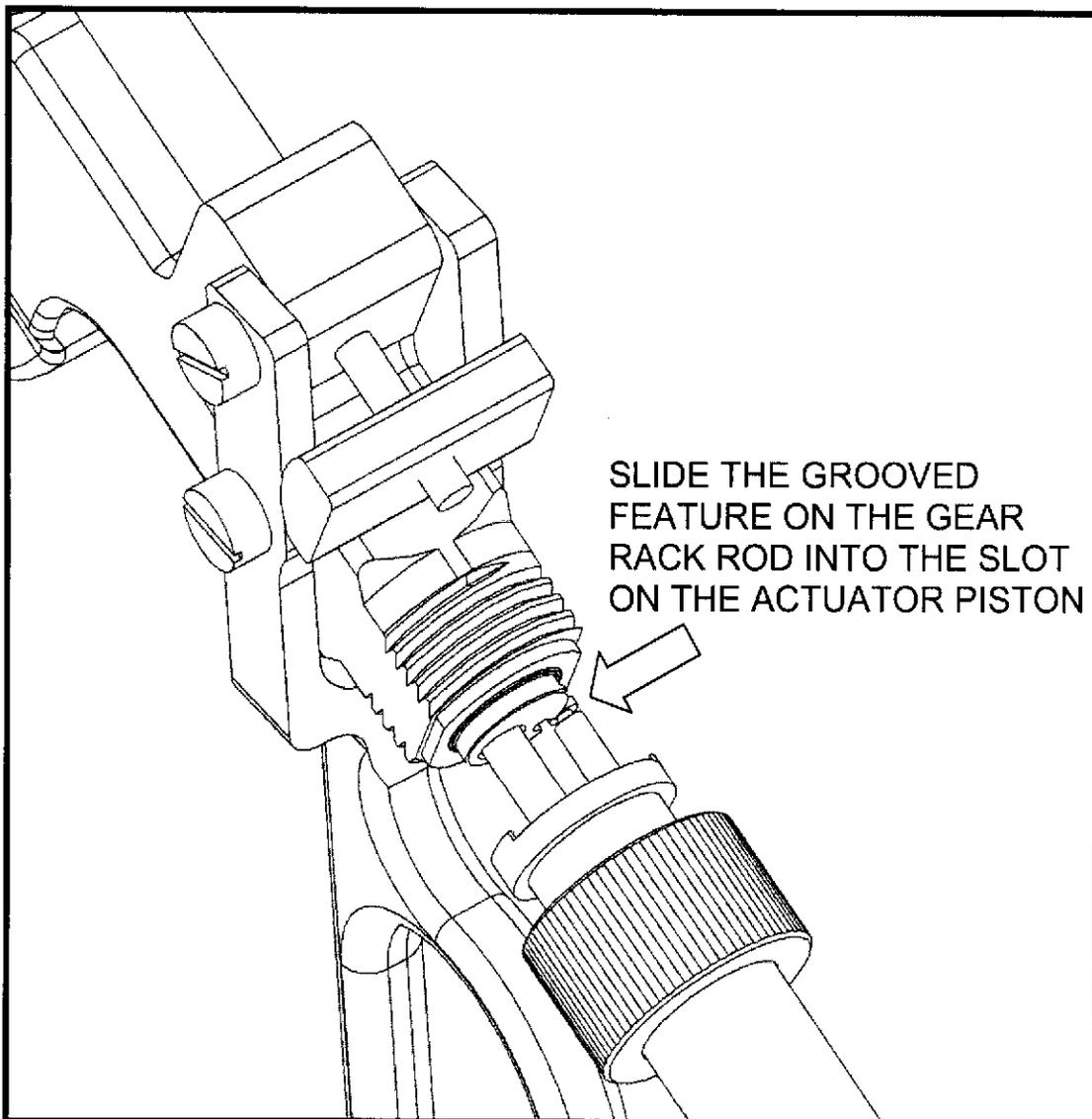
**NOTE:** Before starting this step, make sure the trigger stop is disengaged and the trigger handle is in the extended position.



## ASSEMBLY

### STEP 4: CONNECT EXTENSION TUBE TO HANDLE (CONTINUED)

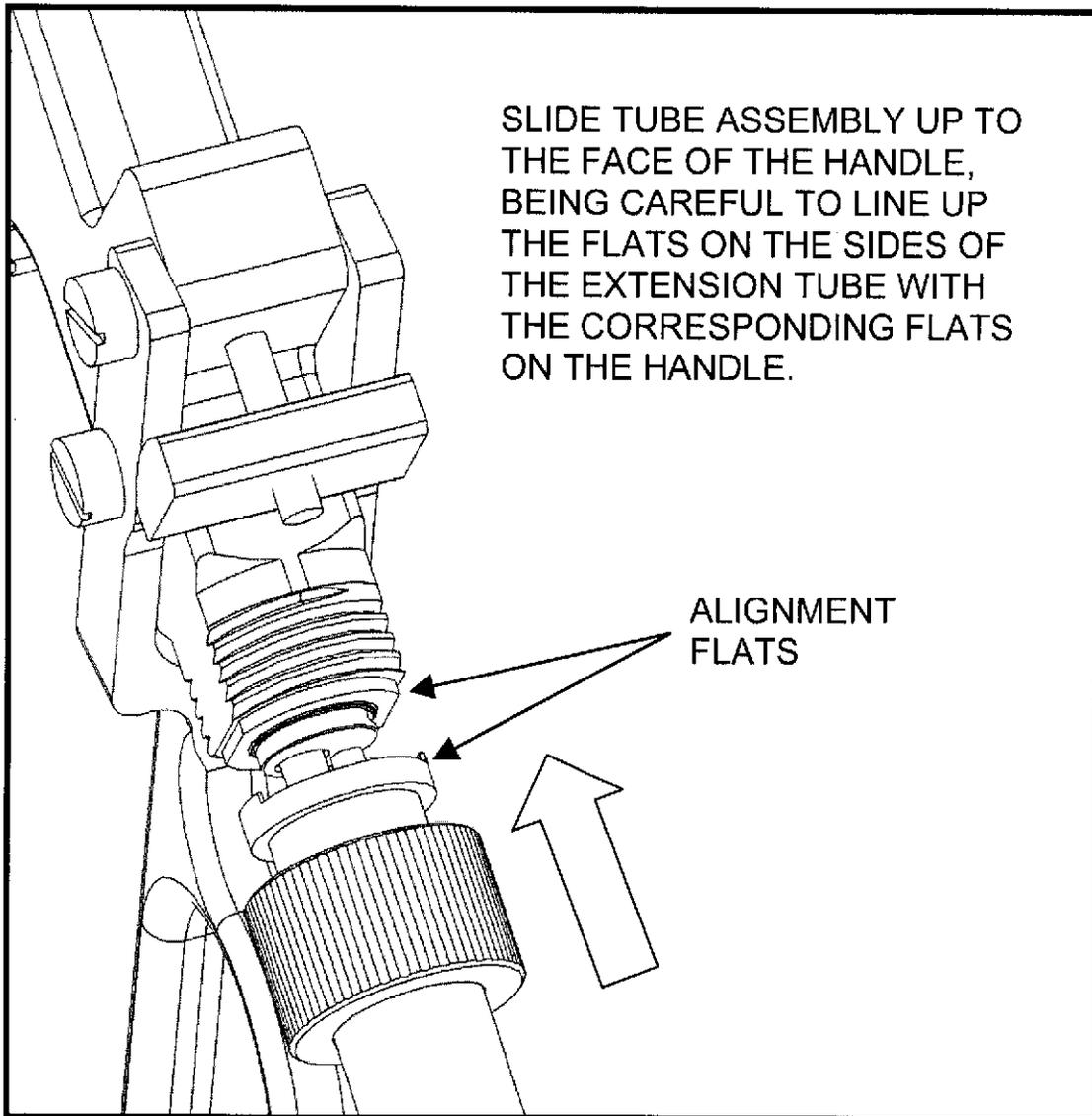
- Slide the electrode tube through the actuator piston until the end of the tube assembly is close to the actuator piston.
- Keep the tube assembly rotated so that the recessed pocket for the needle is facing upward, relative to the handle assembly.



## ASSEMBLY

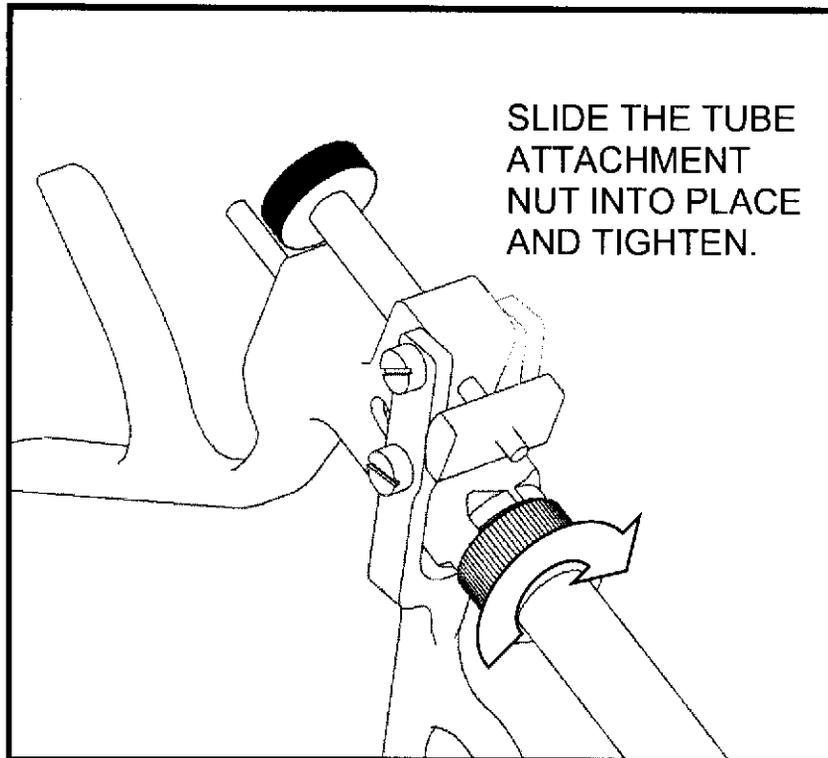
### STEP 4: CONNECT EXTENSION TUBE TO HANDLE (CONTINUED)

- Keep the tube assembly rotated so that the recessed pocket for the needle is facing upward, relative to the handle assembly.
- It may help to pull the trigger handle in slightly during this step, to get the end of the actuator piston into the cylinder.



**ASSEMBLY**  
**STEP 4: CONNECT EXTENSION TUBE TO HANDLE**  
**(CONTINUED)**

**Continue to be careful to keep the tube assembly rotated so that the recessed pocket for the needle is facing upward while tightening the tube attachment nut.**



At this point, check the following:

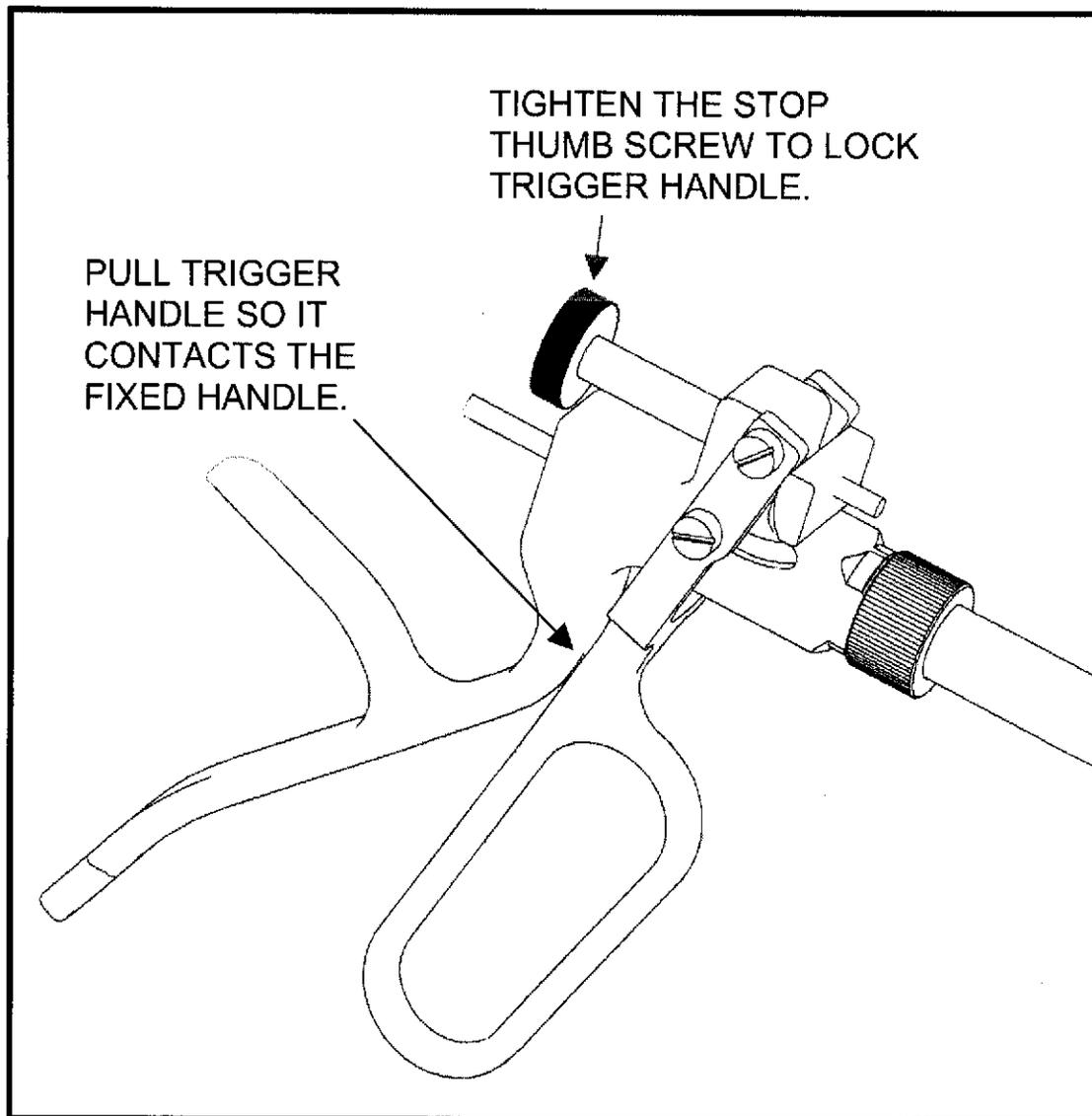
- Make sure that the recessed pocket for the needle is still facing 'upward'.
- Pull and release the trigger handle several times to ensure that the mechanism moves freely in both directions. If it does not, make certain that the tube alignment features are properly aligned and that the gear rack rod is correctly engaged, with the gear teeth facing upward. It may be necessary to partially or completely disassemble the instrument and start over.

## ASSEMBLY

### STEP 5: INSTALL NEEDLE PIVOT

**USE CAUTION: ELECTRODE INSERTION NEEDLE IS VERY SHARP!!!**

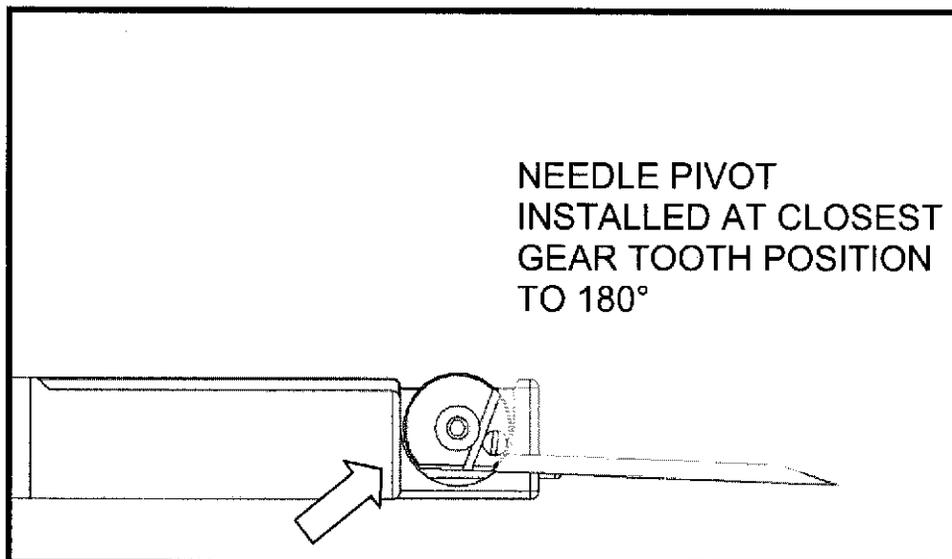
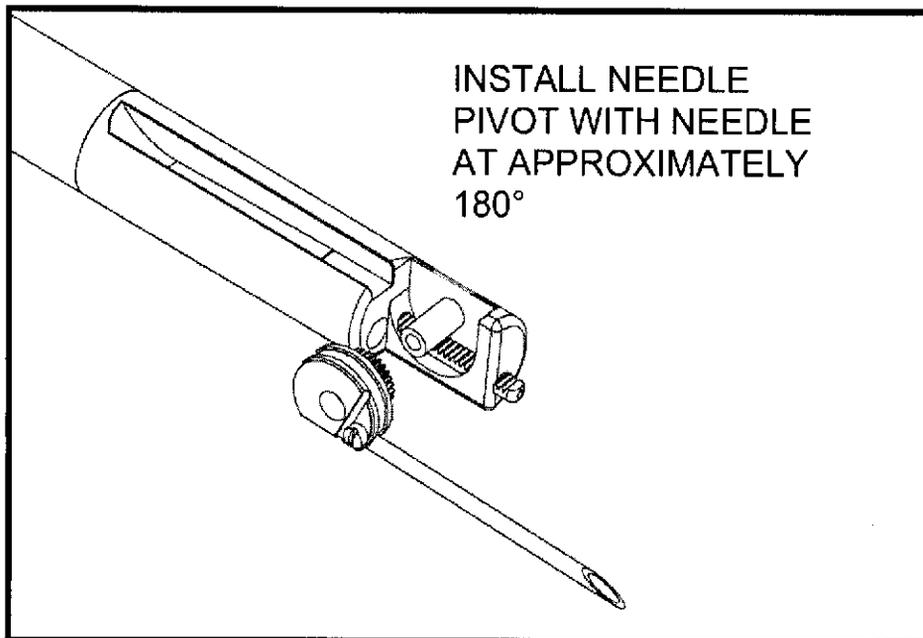
- Pull the trigger handle all the way until it contacts the fixed handle. This corresponds to the position where the needle should be fully extended, at approximately 180°.
- Tighten the stop thumb screw so the trigger handle stays in this position.



**ASSEMBLY**  
**STEP 5: INSTALL NEEDLE PIVOT**  
**(CONTINUED)**

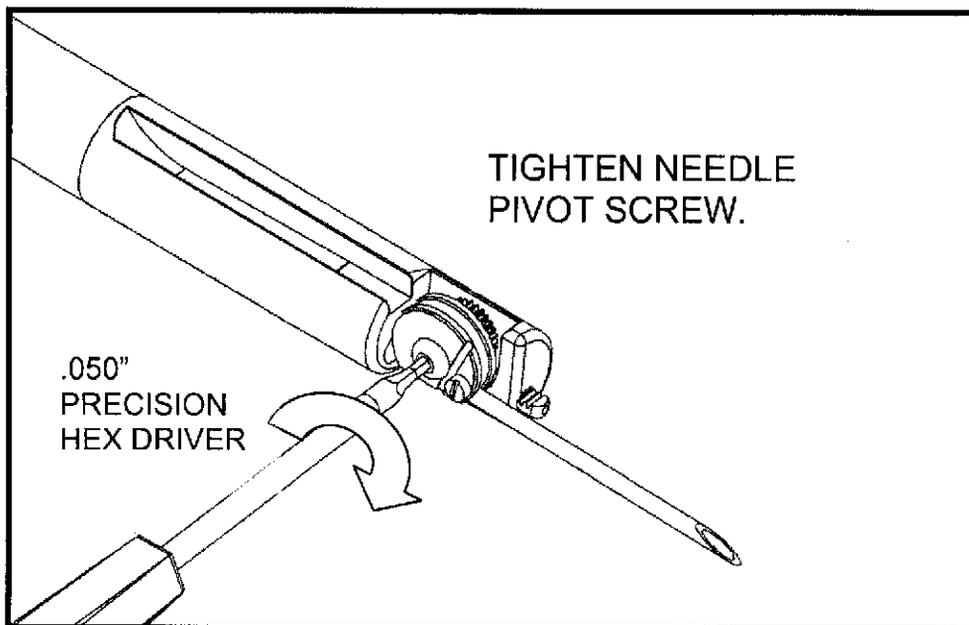
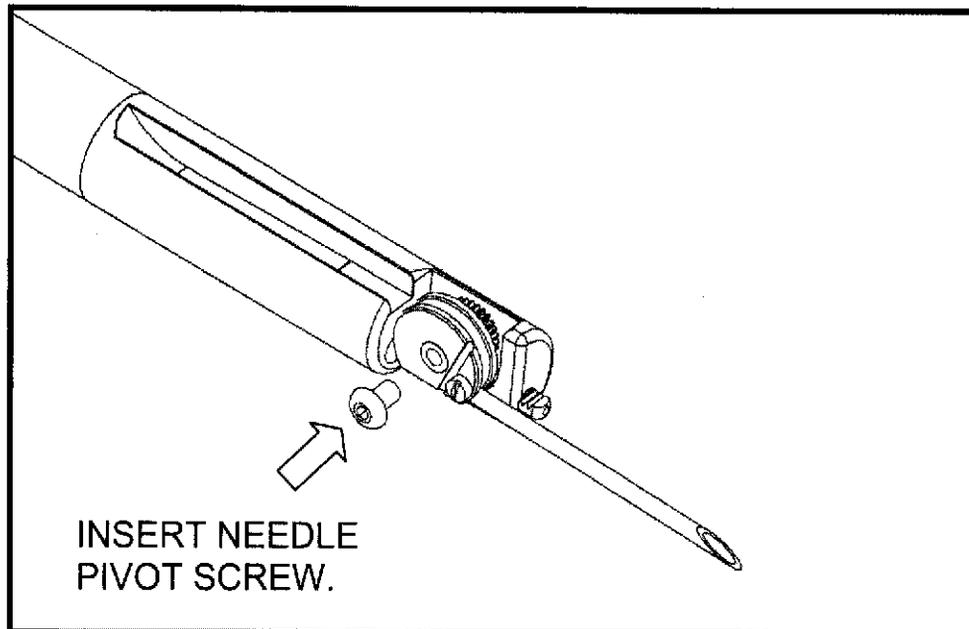
**USE CAUTION: ELECTRODE INSERTION NEEDLE IS VERY SHARP!!!**

The angle at which the needle is installed depends on the position of the gear rack rod and the orientation of the gear on the needle pivot. The gear has 28 teeth, so a single tooth amounts to about 13 degrees of rotation ( $360/28$ ). Install the needle at the closest tooth position to 180 degrees, which will likely be 180 plus or minus a few degrees.



**ASSEMBLY**  
**STEP 5: INSTALL NEEDLE PIVOT**  
**(CONTINUED)**

**USE CAUTION: ELECTRODE INSERTION NEEDLE IS VERY SHARP!!!**



At this point, release the stop (loosen the thumb screw) and pull and release the trigger handle several times to ensure that the mechanism moves freely, throughout the desired range of needle travel.

# STERILIZATION

Place the assembled device into appropriate individual sterilization containers such as self-sealable autoclavable pouches. The device must be double-pouched with proper labeling attached to outer packaging layer.

Sterilize using in-house sterilization procedures that meet AAMI TIR12-2004 parameters for dynamic-air-removal steam sterilization cycles.



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