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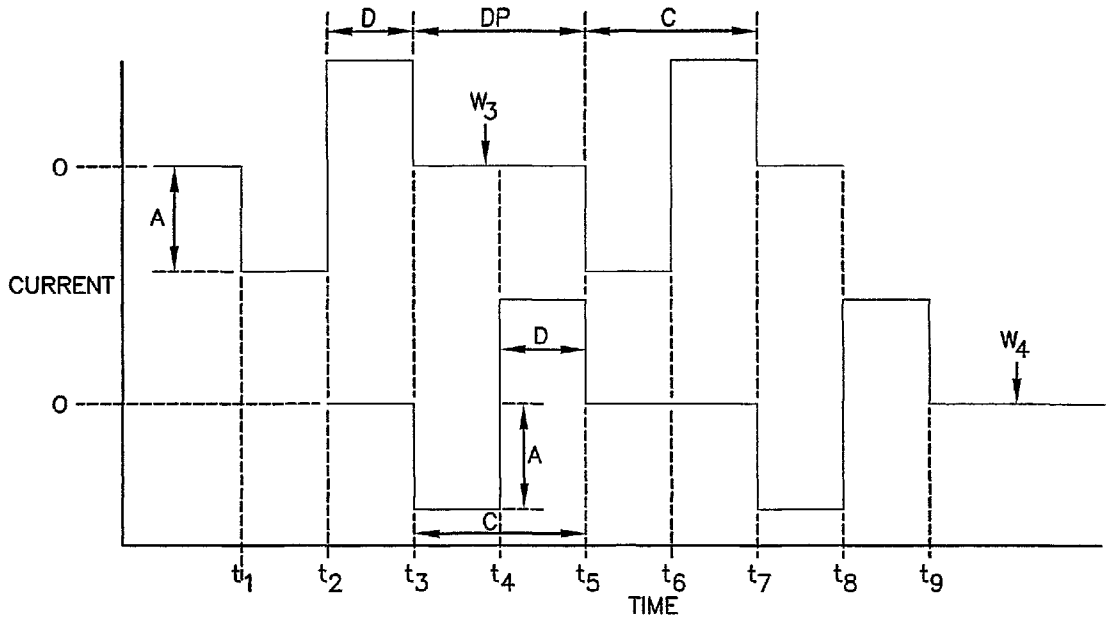
(54) **Title:** NEURAL ELECTRODE TREATMENT



(57) **Abstract:** An apparatus for applying a signal to a nerve for the treatment of a disorder includes a first electrode and a second electrode. Each of the electrodes is adapted to be secured to a nerve of a patient. A signal generator is electrically connected to each of the first and second electrodes. The signal generator is adapted to create a signal having a first waveform at the first electrode and a second waveform at the second electrode. The waveforms have parameters selected to block propagation of neural action potentials. The waveforms have a repeating pattern of cycles of pulses with a delay period between at least selected ones of said pulses. In one embodiment, the first and second waveforms are out of phase for a cycle of one of the waveforms to occur during a delay period of the other of the waveforms.

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NEURAL ELECTRODE TREATMENT

This application is being filed as a PCT International Patent Application on 01 August 2006, in the name of EnteroMedics Inc., a U.S. national corporation, applicant for the designation of all countries except the U.S.; and Adrianus P. Donders and Koen J. Weijand, both citizens of The Netherlands, and Mark B. Knudson, a U.S. citizen, applicants for the designation of the U.S. only, and claims priority to U.S. Application Serial No. 11/205,415, filed 17 August 2005.

I.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention pertains to electrodes for nerves and therapeutic signals to be applied to such electrodes. More particularly, this invention pertains to such electrodes and signals for placement on the vagus nerve for treatment of obesity.

2. Prior Art

a. Neural Conduction Block

The Assignee of the present application has a number of pending U.S. patent applications pertaining to application of a conduction block technology to a nerve for a treatment of a variety of disorders. These applications include the following (all filed September 29, 2003): US Patent Application Serial No. 10/674,330 (published September 2, 2004 as Publication No. US 2004/0172086 A1); US Patent Application No. 10/675,818 (published September 9, 2004 as US Patent Application Publication No. US 2004/0176812 A1) and US Patent Application Serial No. 10/674,324 (published September 2, 2004 as US Patent Application Publication No. 2004/0172085 A1). These patent applications describe, in a preferred embodiment, the application of neural conduction block therapy to a vagus nerve alone or in combination with a stimulation of the nerve.

The conduction block therapy includes application of an electrical signal with parameters selected to down-regulate vagal activity by creating conditions in which normal nerve propagation potentials are blocked at the

application of the signal on both afferent and efferent nerves fibers of the vagus. A number of different disorders are identified for treatment through the technique. These disorders include obesity, pancreatitis and other gastrointestinal disorders such as irritable bowel syndrome and functional disorders.

Electrodes may be placed directly on the vagus (for example as cuff electrodes) or may be placed on bands surrounding the vagus at the esophagus or placed on an intraluminal device within the esophagus for transmitting the energy from the device across the tissue of the esophagus to the vagus nerves in the region of the esophagus. These embodiments are disclosed with greater particularity in the Assignee's US Patent Application Serial Nos. 10/752,994 and 10/752,940 both filed January 6, 2004 with respective publication dates of August 26, 2004 and September 2, 2004, Publication Nos. US 2004/0167583 A1 and 2004/0172088 A1.

b. <u>Blocking Signal Parameters and Duty Cycle</u>

On June 30, 2004 the Assignee of the present application filed Serial No. 10/881,045 (published February 17, 2005 as Publication No. US 2005/0038484 A1) noting that a duty cycle of electrical impulses to the nerve to block neural conduction on the nerve can be adjusted between periods of blocking and no blocking in order to vary the amount of down regulation of the vagus nerve as well as preventing accommodation by the enteric nervous system.

On January 21, 2005 the Assignee filed Serial No. 11/040767 describing with greater particularity parameters for controlling block and to avoid accommodation. That application notes that a representative blocking signal is preferably greater than 500 Hz and that such conduction block is preferably within the parameters disclosed in Solomonow, et al. "control of muscle contractile force through indirect high-frequency stimulation", American Journal of Physical Medicine, Volume 62, No. 2, pages 71-82 (1983). Particularly, the nerve conduction block is applied with electrical signals selected to block the entire cross-section of the nerve (for example, both afferent, efferent, myelinated and non-myelinated fibers) at the site of applying the blocking signal (as opposed to selected sub-groups of nerve fibers or just afferent and not efferent or vice versa).

Preferably, the frequency of the blocking signal is selected to exceed a 200 Hz threshold frequency described in Solomonow, et al. More preferred

parameters are a frequency in excess of 500 Hz (with other parameters as non-limiting examples, being an amplitude of 1 – 8 mA, pulse width of 100 microseconds, and a duty cycle of 5 minutes on and 5 minutes off. A more preferred blocking signal has a frequency of 3,000 Hz to 5,000 Hz or greater applied by either by bi-polar or mono-polar electrodes. Such a signal has a preferred pulse width of 100 micro-seconds (associated with a frequency of 5,000 Hz).

It is believed this frequency and pulse width best avoid neural recovery from blocking and avoid re-polarization of a nerve. A "short-off" time in the pulse cycle (for example, between cycles or within a cycle) can be acceptable as long as it is short enough to avoid nerve re-polarization. The waveform may be a square, triangular or sinusoidal waveform or other shape. The higher frequencies of 5,000 Hz or more have been found, in porcine studies, to result in more consistent neural conduction block. Kilgore, et al., "Nerve Conduction Block Utilizing High-Frequency Alternating Current", Medical and Biological Engineering and Computing, Vol. 24, pp. 394 – 406 (2004). Applicants have determined that a signal amplitude of .5 mA to 8 mA is adequate for blocking. However, other amplitudes may suffice.

While a duty cycle can be a predetermined time period, it is currently preferred that the duty cycle be less fixed to reduce the likelihood of patient accommodation whereby the autonomic (parasympathetic, sympathetic and enteric) and / or the central nervous systems accommodates for the loss of signals on the vagus or other nerve. While the periods of off and on can be stable or random, they can be set at any fixed or non-fixed sequence (for example, 5 minutes on followed by 5 minutes off repeated for the duration of the therapy or, alternatively, 5 minutes on followed by 10 minutes off as a first cycle with a following cycle meaning a different set of time - such as 10 minutes on and 2 minutes off, with a non-repeating duty cycle continuing over a 24 hour period). Other signal attributes can be varied to reduce the likelihood of accommodation by the nerve or an organ. These include altering the power, waveform or pulse width.

II.

SUMMARY OF THE INVENTION

According to a preferred embodiment of the present invention, an apparatus is disclosed for applying a signal to a nerve for the treatment of a disorder. The apparatus includes a first electrode and a second electrode. Each of the electrodes is adapted to be secured to a nerve of a patient. A signal generator is electrically connected to each of the first and second electrodes. The signal generator is adapted to create a signal having a first waveform at the first electrode and a second waveform at the second electrode. The waveforms have parameters selected to block propagation of neural action potentials. The waveforms have a repeating pattern of cycles of pulses with a delay period between at least selected ones of said pulses. In one embodiment, the first and second waveforms are out of phase for a cycle of one of the waveforms to occur during a delay period of the other of the waveforms.

III.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic representation of electrodes on anterior and posterior vagus nerves on an esophagus;

FIG. 2 is a view similar to FIG. 1 showing additional anodic electrodes on nerves;

FIG. 3 is a view similar to FIG. 2 showing the anodic electrodes off of the nerves;

FIG. 4 is a graphical presentation of a waveform applied to a nerve with no delay between pulse cycles;

FIG. 5 is a graphical presentation of a waveform applied to a nerve with a delay between pulse cycles;

FIG. 6 is a graphical presentation of waveforms applied to two nerves with a delay between pulse cycles and with the timing of the waveforms offset;

FIG. 7 is a graphical presentation of a waveform applied to a nerve with a delay between pulse cycles and with a long period of no signal to illustrate a duty cycle over time;

FIG. 8 is an electrical schematic of an electrode on a nerve showing an idealized arrangement for sensing impulses on the nerve;

FIG. 9 is the view of FIG. 8 showing a practical arrangement for sensing impulses on the nerve;

FIG. 10 is a graphical representation of a pulse cycle waveform modified to illustrate an effect of a capacitance associated with a charge buildup on the surface of an electrode;

FIG. 11 is a perspective view of an electrode surface;

FIG. 12 is an end elevation view of the electrode of FIG. 11;

FIG. 13 is a perspective view of an electrode surface modified with nano-particles on the surface;

FIG. 14 is an end elevation view of the electrode of FIG. 13;

FIG. 15 is a circuit schematic view of an electrode on a nerve with a nerve pulse detection circuit;

FIG. 16 is the view of FIG. 15 showing two detection circuits on the nerve;

FIG. 17 is a circuit schematic view of the functional equivalent of FIG. 16 but with simplified circuitry;

FIG. 18 is a strength-duration curve illustrating a threshold curve for effective neural blockage;

FIG. 19 is a graph illustrating the cumulative amount of charge applied to a nerve under various signal parameters;

FIG. 20 is a decision tree to determine nerve capture parameters for a particular patient; and

FIG. 21 is a decision tree for setting a programmable controller to therapeutic signal parameters.

IV.

DESCRIPTION OF THE PREFERRED EMBODIMENT

With reference now to the various drawing figures in which identical elements are numbered identically throughout, a description of the preferred embodiment of the present invention will now be provided. The present invention will be described with reference to placing electrodes contacts on both the anterior

and posterior vagus nerves overlying the esophagus between a diaphragm and a stomach of a patient for the treatment of obesity. It will be appreciated this is a currently preferred embodiment and the present invention has wider applications as will be apparent to those skilled in the art and can be applied to other cranial nerves (such as the vagus) or peripheral nerves. Further, while the preferred embodiment illustrates application of a signal to block the propagation of action potentials along a nerve, the present invention is applicable to signals to stimulate a nerve, inhibit nerve function or only partially block a nerve.

1. Alternative Electrode Configurations

FIGS. 1 – 3 illustrate alternative applications for applying a neural conduction block signal to vagus nerves in a preferred embodiment for the treatment of obesity. Such a signal down-regulates a level of vagal activity and simulates, at least partially, a vagotomy that is reversible.

In FIGS. 1 – 3, the posterior vagus nerve PVN and the anterior vagus nerve AVN are shown extending along a length of the esophagus E and generally on diametrically opposite sides of the esophagus E just below the patient's diaphragm (not shown).

In each of FIGS. 1 – 3, a first electrode E_1 is placed on the posterior vagus nerve PVN. A second electrode E_2 is shown placed on the anterior vagus nerve AVN. The electrodes E_1, E_2 may be any suitable electrode for applying an electrical signal to a nerve. The electrodes E_1, E_2 could be cuff electrodes, patch electrodes, band electrodes or transluminal electrodes. The prior art contains numerous examples of electrodes for placement on nerves and treatments for applying electrical signals to such nerves. For example, U.S. Pat. No. 4,979,511 to Terry, Jr. dated December 25, 1990 teaches an electrode on a helical silicone rubber coil for placement on a cervical vagus nerve for treatment of epilepsy. Also, U.S. Pat. No. 5,215,089 to Baker, Jr. issued June 1, 1993 teaches an electrode for placement on a vagus and U.S. Pat. No. 5,251,634 to Weinberg issued October 12, 1993 and U.S. Pat. No. 5,531,778 to Maschino et al. issued July 2, 1996 and U.S. Pat. No. 6,600,956 to Maschino et al. issued July 29, 2003 teach vagal electrodes.

Other techniques are known for applying signals directly to a nerve. These include patches placed over the nerve with electrodes on the patch positioned

to overly the nerves. In so-called cuff electrodes, a portion of a nerve is dissected to permit a cuff to completely or partially encircle the nerve. An additional optional electrode format is such as that shown in a product brochure called "ATROSTIM Phrenic Nerve Stimulator", AtroTech Oy, P.O. Box 28, Fin-33721,Tampere, Finland (June 2004). The ATROSTIM nerve stimulator includes electrodes on opposite sides of PTFE strips for placement on opposite sides of a phrenic nerve for quad-polar stimulation. Another phrenic nerve electrode is sold by Avery Laboratories, Inc., 61 Mall Drive, Commack, New York, USA. The use of the Avery electrode is described in the website of Avery Laboratories, Inc. at www.breathingpacemakers.com.

The electrodes E_1, E_2 are connected by conductors to a pulse generator PG. The pulse generator PG may be a fully implanted unit containing a power source such as batteries or rechargeable batteries, or the like as well as processing controllers for maintaining a desired wave form and duty cycle on the electrodes E_1, E_2. Also, and as described in the Assignee's earlier described applications, the electrodes E_1, E_2 can be connected to an implanted antenna for receiving transdermal signals from an external controller transmitted across the patient's skin to the electrode through radio frequency signals. In this later embodiment, the pulse generator PG includes both implanted and external components.

FIG. 1 shows an arrangement for applying a uni-polar waveform to the nerves PVN, AVN. The current flow path between the electrodes E_1, E_2 flows through the esophagus. The arrangement of FIG. 1 is uni-polar meaning there is only one location on the nerve subject to the treatment. In the embodiment of FIG. 1, the electrical signal is applied across the anterior vagus AVN and the posterior vagus PVN at electrodes E_1 and E_2.

FIG. 2 illustrates an alternative embodiment where each of the electrodes E_1 and E_2 has an associated anode electrode A_1, A_2. The anode electrodes A_1, A_2 are shown in FIG. 2 as being applied to the anterior vagus AVN and the posterior vagus PVN and spaced from electrodes E_1 and E_2. This results in bi-polar pacing (two sites per nerve receiving an electrical treatment). Unlike FIG. 1, the arrangement of FIG. 2 reduces likelihood of current flow through the esophagus thereby minimizing likelihood of patient sensation to the treatment.

FIG. 3 shows electrodes A_1, A_2 placed on other structures in generally close proximity (for example, 5 cm) of the primary electrodes E_1, E_2. These electrodes A_1, A_2 could be placed on the stomach, on the esophagus or on other anatomical structures in the general vicinity of the electrodes E_1, E_2. This results in uni-polar pacing similar to FIG. 1 but with the benefit of FIG. 2 in that current flow is not through the esophagus. Further, placement of the anode electrodes on the stomach permits monitoring of stomach contractions (e.g., by strain receptors associated with the anode electrodes) which can be of further benefit as will be described.

With the arrangement of FIG. 3, the pulse generator PG can be programmed to cancel the effect of the anode electrodes such that even though the anode electrodes are physically present, the effective circuit on the esophagus is that of FIG. 1. This adds greater flexibility to function of the apparatus as will be described.

In a preferred embodiment for treating obesity, the electrode configuration is that of FIG. 3 with the pulse generator PG programmed to permit functionally shifting to the configuration of FIG. 1. In the mode of FIG. 3 (with functioning anode electrode), the current path on the posterior nerve PVN is between the posterior nerve PVN and the anode A_1. Similarly, in such mode, the current path on the anterior nerve AVN is between the posterior nerve PVN and the anode A_2. With the apparatus of FIG. 3 in the functional mode of FIG. 1, the current path is between the anterior vagus nerve AVN and the posterior vagus nerve PVN.

2. Nerve-to-Nerve Waveform

a. Continuous Waveform Without Delays Between Pulses

FIG. 4 shows a representative waveform W_1 of a signal applied across the electrodes E_1, E_2 of the arrangement of FIG. 1 (or in the arrangement of FIG. 3 controlled by the pulse generator to function in the mode of FIG. 1) showing current flow to the electrodes. The waveform W_1 is shown as a square waveform having an amplitude A and a pulse duration of D.

In a preferred embodiment, the amplitude A is preferably between 0.5 mA and 8 mA and more preferably about 4 – 6 mA. The duration D is, in a preferred embodiment, about 100 microseconds for the total cycle time C (i.e., the

time between the initial application of the cycle at t_1 and the end of the cycle t_3) resulting in a frequency for the cycle of 5,000 Hz. A 100-microsecond pulse duration D for a 5,000 Hz signal results in no time between pulses where there is no signal. Longer pulse durations can be associated with lower frequencies. For example, a 200-microsecond pulse duration and a 2500 Hz frequency signal are also effective blocking signals. Still lower frequency signals are possible for effective blocking. However, it is believed a maximum pulse duration of 1 millisecond with an associated frequency of 500 Hz represents an effective maximum pulse duration to avoid nerve recovery in most patients. A 200 Hz signal as suggested by Solomonow, et al., may still effect a blocking of a nerve.

The cycles of FIG. 4 are continuously repeating without substantial periods of dead time between cycles. Other than a potential for a few microseconds, there is no substantial period of time between the cycles where no current is applied to the electrodes. After some period of time (for example, 5 minutes), at time t_n, the signal may be stopped so that there is a period of off time in the duty cycle (for example 10 minutes).

b. Continuous Waveform With Delays Between Pulses

FIG. 5 shows an alternative waveform W_2. While similar to the waveform W_1 of FIG. 4, the waveform W_2 of FIG. 5 includes built-in delay periods DP (for example, the time period between time t_3 and t_4) between each cycle. By building into the waveform periods DP of no signal, power can be conserved. Where the duration of the delay period DP is 100 microseconds, in FIG. 5, the frequency of the cycle C (less the delay period DP) remains 5,000 Hz. Where the delay is 200 microseconds, the frequency of the cycle C is 2,500 Hz. The time delay DP (i.e., the time between t_3 and t_4) is selected to be shorter than a time delay which would otherwise permit recovery of the nerve.

3. Nerve to Anodic Electrodes Waveforms

FIG. 6 is a graphical representation of waveforms W_3, W_4 of signals applied to the electrodes E_1, E_2 in FIG. 3 in the mode of FIG. 3 with anodic electrodes. The upper waveform W_3 is the signal applied to electrode pairs E_1, A_1 and the lower waveform W_4 illustrates a signal applied to electrodes E_2, A_2.

Both waveforms W_3, W_4 are structurally identical having common amplitude A and pulse duration D with the same parameters, in a preferred embodiment, as described with reference to FIGS. 4 and 5. Also, the structure of both waveforms W_3, W_4 is similar to that of FIG. 5 in that the waveforms W_3, W_4 include a delay period DP between cycles in the waveforms W_3, W_4. In FIG. 6, the delay periods DP could be eliminated with both waveforms then resembling the waveform of FIG. 4.

It will be noted that the two waveforms W_3, W_4 are out of phase such that the pulse cycle C of one waveform is timed to be occurring during the delay period DP of the other waveform. Further, the delay period DP of a waveform is selected to equal the cycle time C of the other waveform (i.e., twice the pulse duration D). This length of delay period DP is the smallest preferred delay period DP since it results in avoiding an instance where both electrodes E_1, E_2 are energized which could result in a direct-current component between the electrodes E_1, E_2. A longer delay period DP could be applied when the delay period length is selected so that the two waveforms continue to avoid having periods of time where both electrodes E_1, E_2 are receiving a signal simultaneously. The maximum duration of the delay period DP is selected to be less than an amount of time which would otherwise permit the nerve to recover from the blocking signal.

The application of anode A_1, A_2 is similar to a so-called VDD lead used in cardiac pacing. An example of a VDD electrode is the Solox™ single-lead VDD electrode of Biotronik GmbH & Co., Woermannkehre 1, D-12359 Berlin, Germany. More information is provided at its website www.biotronik.com. The pacing tip of such electrode in placed in the right ventricle of a heart at the apex and the anode ring resides in the right ventricle.

4. Waveforms with Duty Cycles

FIG. 5 illustrates a waveform with very small delay periods. Substantially longer delay periods can be applied to a treatment. In such longer delay periods, a nerve may at least partially recover.

In rat studies performed for the assignee, applicants applied blocking signals as described to isolated sciatic nerves of rats. After an effective block was applied and turned off, the nerve recovered in about 10 minutes. In this context,

recovery means the nerve response to a stimulus was substantially the same as a baseline response before application of the blocking signal. After about 2.5 minutes, the nerve had recovered about 50% of baseline. Also, the duty cycle can be turned completely off for extended period of times. For example, duty cycle could be applied for a 12-hour period associated with daytime and be continually off with a 12-hour period associated with the evening or during sleep hours.

FIG. 7 illustrates a representative duty cycle applied to the waveform of FIG. 5 (i.e., a waveform with built-in small delay periods DP during which the nerve does not recover). It will be appreciated a similar duty cycle can be employed in the waveforms of FIG. 4 and 6.

In FIG. 7, a plurality of cycles C such as that shown in FIG. 5 are shown in sequence for a duration D_1 of pulse application (either a blocking signal as previously described or a neural stimulation signal). The period of time may be two to five minutes to ensure an effective application of the signal is applied to a nerve. For application of a blocking signal, an effective application of the signal is estimated as about one minute and preferably 2 to 5 minutes to ensure the nerve has been treated to block propagation of action potentials along the nerve (as well as achieving desired end-organ response).

Followed by the pulse duration D_1, a period D_2 of no treatment for "off" portion of a duty cycle is shown which may last for 5 to 10 minutes associated with an estimate for an amount of time for the nerve to recover. After the off period, a sequence can repeat in identical format. The times of the pulse signal and the off signal may be varied to avoid nerve accommodation. Also, as previously stated, the duty cycle may include extended periods of off-time associated with sleeping or other periods during the day. The "off" period of 5 to 10 minutes avoids nerve accommodation while avoiding complete nerve recovery thereby maintaining therapy efficacy.

5. Programmable Options

As previously noted, the programmable pulse generator PG of FIG. 3 can be altered so that the electrodes on the nerves AVN, PVN can function as the functional equivalent of either of FIGS. 1 or 3. Further, the pulse generator PG

permits selection of any of the waveforms described above as well as altering pulse duration D, amplitude, delay periods DP and duty cycle.

6. Selection of Waveform Parameters

Effective blocking of neural impulses requires treating the nerve with a signal to prevent the depolarization of the nerve that is associated with the conduction of nerve signals (nerve action potentials) past the point of application of the blocking signal. As noted in the assignee's earlier applications (referenced above and incorporated by reference), such depolarization can be achieved by a direct current signal. However, such a signal represents a significant burden to a battery. Low frequency alternating current signals (e.g., less than 20 Hz) permit the nerve to recover. As a result, such signals are useful for stimulating therapies where the nerve is used as a highway for directing the stimulation signal to an organ. Where, as in the present application, the desired therapy is to block the nerve and prevent transmission of neural impulses along the nerve, a higher frequency maintains the nerve in a polarized state. As mentioned above with respect to articles of Solomonow et al. and Kilgore, et al. such frequencies are in excess of 200 Hz and up to 5,000 Hz or more.

Effective blockage of a nerve is a function of both the strength of the signal applied to the nerve as well as the duration of such application. FIG. 18 illustrates such a relation. The curve of FIG. 18 is taken from Easton, "The Nerve Impulse Seen From Outside", Florida State University, Department of Biological Science, July, 2000 available on line at http://www.bio.fsu.edu/faculty-easton_actionpotential.htm. . The vertical axis of FIG. 18 represents the intensity of a signal applied to a nerve. In FIG. 18, this is represented by voltage but could be represented by charge or current. The horizontal axis represents the length of time during which the signal is applied. The curve represents a threshold curve. Below the curve, the nerve does not excite. Above the curve, the nerve excites. For signals having intensity and duration above the curve, the nerve remains in an excited state and cannot propagate neural impulses (i.e., is effectively blocked).

Using, as an example, a 5,000 Hz signal, such a signal will have a pulse duration (D in FIG. 4) of 100 microseconds assuming there is no time delay between negative and positive pulses. With reference to FIG. 18, such a short pulse

duration is associated with a steep-slope portion of the threshold curve requiring a fairly high intensity for an effective signal. In animal studies, applicants have found that signal intensities of 0.5 mA to 8 mA have been effective (recognizing subject-to-subject variability).

Since neural blockage is jointly dependent upon the amount of charge applied to the nerve and the pulse duration of such application, a blocking therapy can be adjusted for a particular patient. FIG. 19 is a graph illustrating the cumulative amount of charge applied to a nerve under various signal parameters. In FIG. 19, the duty cycle (as described above) is a five-minute "on" treatment followed by an "off" period (e.g., five to twenty minutes) during which the nerve may partially recover. The vertical axis is the cumulative amount of charge applied to a nerve during one "on" cycle of five minutes. The horizontal axis is the time point in the "on" cycle. The lines A – I represent the following representative signal parameter options:

A. 6 mA at 5 kHz
B. 5 mA at 5 kHz
C. 4 mA at 5 kHz
D. 6 mA at 2.5 kHz
E. 5 mA at 2.5 kHz
F. 4 mA at 2.5 kHz
G. 3 mA at 2.5 kHz
H. 2 mA at 2.5 kHz
I. 1 mA at 2.5 kHz

With the above, a patient being treated for 2.5 minutes at 6 mA at 5 kHz (line A) and who is tolerating the treatment (no associated discomfort) can have the programmable controller programmed to be treated at 5 mA at 5 kHz (line B). With the line B treatment, the amount charge applied to the nerve over the five minute "on" period is the same as the amount of charge which the patient tolerated for 2.5 minutes of the line A "on" period.

While only 5 kHz and 2.5 kHz options are illustrated in this application, any of the blocking frequencies over 200 Hz could be used. In the examples that follow, the following terms have the following meaning:

1. Electrode configuration No. 1 means the functional circuit of FIG. 1 with the waveforms of either FIG. 4 (with a 5 kHz frequency and a 100 microsecond

pulse width and no delay) or FIG. 5 (with a 2.5 kHz frequency and a 100 microsecond pulse width and a delay period DP of 200 microseconds).

2. Electrode configuration No. 2 means the functional circuit of FIG. 3 with the waveforms of either FIG. 6 with either signals on the nerves AVN, PVN being nested (i.e., a delay period on one nerve coincides with pulses on the other nerve) and with the following frequency options:

    1. a 5 kHz frequency with the signal of FIG. 6 having a pulse width of 100 microseconds and a delay period of 200 microseconds, or
    2. a 2.5 kHz frequency with the signal of FIG. 6 having a pulse width of 100 microseconds and a delay period of 400 microseconds.

FIGS. 20 and 21 illustrate how the foregoing can be used to treat a particular patient. FIG. 20 is a decision tree to assess a patient's responsiveness to certain key parameters.

In FIG. 20, after placement of the electrodes on the nerves AVN, PVN (step 201), the impedance across the electrodes can be measured to assure electrical coupling with the nerves (step 202). If such testing is done during the surgery, the placement may be altered in response to such impedance check.

After such impedance check, an initial stimulation signal can be applied to the electrodes (step 203). Preferably, the programmable controller is set to electrode configuration No. 1 (defined above). Unlike the blocking therapeutic signal, the stimulation signal is set at a low enough frequency to result in a signal applied to the electrodes to be propagated to remote sensing equipment or, more preferably, to an organ of the patient which can be monitored to observe a response to the signal. For example, the stomach can be visually observed to note contractions in response to an applied stimulation signal. Alternatively, the stomach contractions can be measured electronically by sensors on the anodic electrodes

placed on the stomach as described above. A representative stimulation signal has a frequency of about 12 Hz.

The stimulation testing of FIG. 20 is to identify values of key parameters (e.g., pulse width and amplitude) for with the particular patient is responsive. These values can then be used in combination with a therapeutic frequency (e.g. over 200 kHz) to treat the patient with a blocking signal. Initially, such parameters can be set at initial target values (e.g., pulse width of 100 microseconds and 2 mA amplitude (as described above for configuration No. 1).

The patient response is observed (step 204). If there is an observed response (e.g., a stomach contraction), the responsive values for the parameters are recorded (step 205). If predetermined ranges of values for such parameters remain to be tested (step 206), the parameters are varied (step 207). For example, amplitude can be increased in value by 1 mA increments while holding pulse duration constant or pulse width can be increased in 100 microsecond increments while holding amplitude constant). After a range of values has been tested (e.g., up to a maximum pulse width of 500 microseconds or a maximum amplitude of 6 mA), the patient is sent to post-operative recovery (step 208.

After any suitable period of post-operative recovery (e.g., fourteen days), the programmable controller can be set to a therapeutic signal parameter as illustrated in the decision tree of FIG. 21. Initial signal parameters are set (step 301). The amplitude and pulse width of the therapeutic signal are preferably selected from those noted as responsive during the testing of FIG. 20. By way of example, the therapeutic signal can be set at a pulse width of 100 microseconds and an amplitude of 4 mA. Blocking frequency and pulse width may be those expected to have greatest likelihood of complete blocking of the nerve (e.g., 5000 Hz and 100 microseconds) and "on" time may be selected to be short-term (e.g., 3 minutes) relative to an anticipated full-term signal application (e.g., 5 minutes).

Patient acceptance of the signal is noted (step 302). Acceptance may be any factor but may include pain or discomfort after a short-term application of the signal. A short-term discomfort is suggestive of discomfort due to signal flow through the esophagus in the configuration of FIG. 1. Also, amplitude may be a discomfort influencing parameter. If patient acceptance is noted in step 302, parameters may be altered to move the parameters to a more ideal setting (step 303

and 304). Ideal may mean a more aggressive treatment (e.g., higher amplitude), a treatment which conserves battery power or otherwise improves operation (e,g,. configuration No. 1, altered "on" time, lower frequency at extended "on" time, etc.). If such altered treatment continues to be acceptable (step 305), the parameters are set as the treatment algorithm. If not, the parameters can be further altered.

If discomfort is noted (step 302), such parameters may be altered in a manner anticipated to improve comfort (step 307). For example, the electrode configuration No. 2 may be selected or amplitude may be reduced. Patient acceptance is noted (step 308) and acceptance influence parameters are further altered until acceptance is noted. Once acceptance is achieved, remaining parameters are compared to ideal and altered (steps 309 – 311) in a manner as described above with reference to steps 303 – 305. For example, if the electrode configuration is altered from configuration No. 1 to configuration No. 2 and acceptance is noted, parameters such as amplitude and frequency may be altered as described above.

a. Circuit Schematic

U.S. Patent No. 6,895,278 (the "'278 patent") to Gordon issued May 17, 2005 teaches systems for measuring signals on neuromuscular tissue in the stomach. The '278 patent is incorporated herein by reference.

FIG. 8 is an electrical schematic of the electrode such as electrodes E_1 on a nerve with the electrode and nerve shown as circuit components including resistance R_F representing a resistance due to fibrous tissue which grows following application of the electrode to the nerve. It will be appreciated that circuit models such as FIG. 8 are simplifications of a complex physiologic contribution to a circuit.

The resistance R_F may be large after first placement of the electrode on the nerve with the resistance reducing in size or magnitude as fibrous growth occurs. Resistance R_N represents resistance which is a function of the size of the electrode in contact with the nerve. Resistance R_L represents the trans-membrane resistance associated with current leakage through the body of the patient. The capacitance C represents a capacitance associated with charge buildup on the surface of the electrode throughout the cycle of the signal application (also known as polarization of the nerve).

Measurement of impedance on the electrode represents conductivity with the nerve since a low impedance suggests an undesired alternative electrical pathway exists in the patient. A very high impedance suggests a broken electrode or other occurrence of non-conductivity.

The circuit of FIG. 8 also includes an amplification circuit AC which will be separately described as an alternative embodiment. Numerous such amplification circuits are known including charge amplification circuits and trans-impedance amplification circuits.

The amplifier AC amplifies a charge across resistance R_n of electrode E_1. If a amplifier AC is placed across the resistance of R_n, a change in the charge provides an indication of movement of potassium and sodium ions across the cell membranes of the nerve. This provides evidence of depolarization of the nerve.

Accordingly, monitoring of the nerve with a amplifier AC would permit recognizing that the particular set of signal parameters supplied for a particular patient are achieving the desired effect of blocking neural impulses on the nerve. In response to the presence or absence of a detected desired effect, the signal parameters can be modified for a particular patient to achieve the desired effect or to minimize power consumption.

As a practical matter, an amplifier AC cannot be placed solely on the R_n but must be placed across the entire electrode as illustrated with reference to the amplifier AC placed on electrode E_1 in FIG. 9. Unfortunately, very small changes in charge must be measured to demonstrate the efficacy of the particular signal to depolarize the nerve. The sensitivity of a amplifier AC increases as the capacitance C is decreased. Accordingly, increasing the surface area of the electrode (thereby increasing the capacitance C, decreasing impedance and reducing noise contribution of the electrode) increases a likelihood of reliable data being attained with a charge amplifier CA.

b. <u>Capacitance</u>

While the waveforms in Figures 4, 5 and 6 and 7 are shown as square waveforms, it will be appreciated that a true square shape is not achieved in a natural embodiment such as application of electrodes to a nerve. Figure 10 illustrates a truer representation of the shape of the waveform resulting from the capacitance C

associated with charge buildup on the surface of the electrode using a constant current output.

As shown in FIG. 10, the signal is initiated at time T_1. Between times T_1 and T_2, there is a sloped surface S associated with buildup of charge on the surface of the electrode. After the charge has achieved a maximum charge to permit discharge of the capacitance on the electrode (e.g., at T_2) the pulse reverses and a complimentary shaped slope S occurs on the second pulse.

The waveform includes a square area component A_1' and a component A_2' between the square component A_1' and bounded by the slope S. The square component A_1' represents the amount of energy that is being applied to the nerve by the electrode. The remainder of the area A_2' represents wasted energy which is consumed during the pulse but which is absorbed at the electrode-tissue interface and, therefore, not contributing energy to the nerve system.

The volume of the wasted energy component A_2' varies with the capacitance of the electrode. A small capacitance is associated with a large electrode surface area illustrated by the solid curve S. A small electrode surface area is associated with a larger capacitance illustrated by the surface area S_1. Therefore, as illustrated in FIG. 10, a large electrode surface area results in the smallest amount of wasted energy.

It is desirable to minimize the amount of wasted energy. Such waste unnecessarily consumes battery power. Accordingly, the amount of wasted energy can minimize by maximizing the surface area of the electrode.

FIG. 11 illustrates an electrode E having a contact surface area CS which is the product of the length L and the width W of the electrode. It will be appreciated that while the electrode E is shown in FIG. 11 as having a flat contact surface CS the electrode E can be curved to increase the amount of contact area between the electrode E and the nerve on which the electrode is placed. The contact surface CS of the electrode E in Figures 11, 12 is shown as a flat smooth surface which will have a characteristic capacitance.

FIGS. 13 and 14 illustrate a modification to the contact surface where the electrode E' of FIGS. 13 and 14 has identical length and width of the electrode E of FIGS. 11 and 12 but has a surface treatment to greatly increase the contact surface CS' of the electrode E'.

The surface CS' is formed by nano technology placement of nano-particles. Since the nano-particles appear on the surface CS' as beads having arcuate individual surfaces, the combined surface area is greatly increased over the flat smooth surface area of FIG. 11.

The surface area CS could be increased by any technique which roughens the surface CS. However, the spaces between the modules may be filled with fibrosis which presents a resistance between opposing surfaces. Through use of nano-application of nano-beads, very small separation occurs. The small separation is so small the surface appears smooth and presents an atraumatic surface to opposing tissue. The use of nano-technology to increase a surface area of an electrode to alter its capacitance is known for cochlear implants

c. Controlling Therapy in Response to Detected Neural Activity

FIG. 15 illustrates detecting neural impulses along the nerve and modifying an application to an electrode based on the detected impulses. In FIG. 15, the nerve is illustrated as N. A therapy application electrode is illustrated as E and a signal source (such as a pulse generator with logic and control circuits) is indicated as PG.

A first detection electrode DE_1 is positioned on the nerve as is a second detection electrode DE_2. The first detection electrode DE_1 is positioned between the therapy electrode E and the second detection electrode DE_2. The detection electrodes DE_1 and DE_2 are connected to an amplifier placed in close proximity to the electrodes DE_1 and DE_2. The amplifier has an output connected to the logic of the pulse generator PG.

Neural impulses are illustrated in FIG. 15 as a first neural impulse NE_1 which is propagating in a direction from the therapy electrode E to the first detection electrode DE_1. The direction of travel of the first propagation signal NS_1 is labeled A_1. The second neural signal NS_2 travels along the nerve in the opposite direction illustrated by arrow A_2.

In the event it is desirable to block neural impulses traveling along the direction of arrow A_2, as neural impulses pass electrode DE_2, they pass a signal to the amplifier A. After a very short period of time (representing the time for a neural impulse to travel the distance between electrodes DE_2 and DE_1), the pulse

NE_2 passes electrode DE_1 generating a further impulse which is amplified by the amplifier A. The output from the amplifier A is again sent to the pulse generator which can compare the signals indicating that a neural impulse NE_2 is traveling in the direction of arrow A_2. Recognizing such neural activity in the undesired direction, the pulse generator can then energize the electrode E with a blocking signal selected to block the nerve N and block the neural impulses from passing the electrode E.

The apparatus of FIG. 15 can also be used to control a blocking signal. Namely, the specific parameters of the blocking signal to the electrode E can be modified by the pulse generator PG in response to detection of neural impulses NS_1 traveling in the direction of arrow A_1. The presence of such neural impulses indicates that the blocking signal for the particular patient is not optimized and the blocking parameters can be adjusted as desired to optimize the blocking effect at therapeutic electrode E.

Since neural impulses pass along a nerve at known speeds, preferably, the amplifier A is positioned in very close proximity to the electrodes DE_1 and DE_2 so that the amplifier A can detect the signals and provide an amplified signal to the pulse generator in time to present an appropriate blocking signal (or stimulation signal) to the therapeutic electrode E.

FIG. 16 illustrates two circuits of FIG. 15 placed on a nerve. The elements of the second circuit are identical to the first with the addition of an asterisk to distinguish the circuits. Two circuits on a nerve permit detection and control on both afferent and efferent nerve fibers. FIG. 17 is the functional equivalent of FIG. 16 but with simplified circuitry. Unlike previously described embodiments which block the nerve at all times during application of the blocking signal (and during a neural recovery period), the embodiments of FIGS. 15 – 17 are impulse targeted blocking.

The polarity of the amplified signal provides a determination of the nerve signal. By applying a polarity discriminator, the direction of the signal can be determined with a single amplifier system and appropriate action of programmable direction blocking can be taken.

With the foregoing detailed description of the present invention, it has been shown how the objects of the invention have been attained in a preferred

manner. Modifications and equivalents of disclosed concepts such as those which might readily occur to one skilled in the art, are intended to be included in the scope of the claims which are appended hereto.

What is claimed is:

1. An apparatus for applying a signal to a nerve for the treatment of a disorder, said apparatus comprising:

a first electrode and a second electrode, each adapted to be secured to a nerve of a patient;

a signal generator electrically connected to each of said first and second electrodes;

said signal generator adapted to create a signal having a first waveform at said first electrode and a second waveform at said second electrode, said waveforms having parameters selected to block propagation of neural action potentials; said waveforms having a repeating pattern of cycles of pulses with a delay period between at least selected ones of said pulses.

2. An apparatus according to claim 1 wherein said delay period is at least equal to a time interval of one complete cycle.

3. An apparatus according to claim 2 wherein said delay period is less than a time period identified as sufficient for a recovery of a nerve from a neural block induced by said cycle.

4. An apparatus according to claim 2 wherein said first and second waveforms are out of phase for a cycle of one of said waveforms to occur during a delay period of the other of said waveforms.

5. An apparatus according to claim 1 further comprising at least a first anodic electrode and a second anodic electrode connected to said first electrode and said second electrode respectively.

6. An apparatus according to claim 1 wherein said waveforms have an amplitude between 0.5 mA and 8 mA.

7. An apparatus according to claim 1 wherein said waveforms have a cycle frequency in excess of 250 Hz.

8. An apparatus according to claim 7 wherein said waveforms have a cycle frequency in excess of 3000 Hz.

9. An apparatus according to claim 1 wherein said electrodes include a contact surface area enhance by a surface treatment selected to increase said surface area by creating a plurality of protuberances with opposing surfaces of protuberances sized to present an atraumatic surface to opposing tissue.

10. An apparatus according to claim 1 further comprising a signal amplifier connected across at least one of said electrodes and selected to identify a depolarization of a nerve.

11. A method for the treatment of a disorder susceptible to down-regulation of neural activity, said method comprising:

identifying a first nerve and a second nerve for down-regulation to advance said treatment;

placing a first electrode on said first nerve and a second electrode on said second nerve;

electrically connecting a signal generator to each of said first and second electrodes; said signal generator adapted to create a signal having a first waveform at said first electrode and a second waveform at said second electrode, said waveforms having parameters selected to block propagation of neural action potentials; said waveforms having a repeating pattern of cycles of pulses with a delay period between at least selected ones of said pulses;

activating said signal generator to apply said waveforms to said first and second nerves.

12. An apparatus for applying a signal to a nerve for the treatment of a disorder, said apparatus comprising:

a first electrode and a second electrode, each adapted to be secured to a nerve of a patient;

a signal generator electrically connected to each of said first and second electrodes;

said signal generator adapted to create a signal having a first waveform at said first electrode and a second waveform at said second electrode:

said waveforms having a repeating pattern of cycles of pulses with a delay period between at least selected ones of said pulses;

said waveforms synchronized for a delay period of one of said waveforms to occur during a pulse of the other of said waveforms.

13. An apparatus according to claim 12 wherein said delay period is at least equal to a time interval of one complete cycle.

14. An apparatus according to claim 13 wherein said cycle is selected to induce a neural block and said delay period is less than a time period identified as sufficient for a recovery of a nerve from said neural block.

15. An apparatus according to claim 12 further comprising at least a first anodic electrode and a second anodic electrode connected to said first electrode and said second electrode respectively.

16. An apparatus according to claim 1 wherein said waveforms have an amplitude between 0.5 mA and 8 mA.

17. An apparatus according to claim 1 wherein said waveforms have a cycle frequency in excess of 250 Hz.

18. An apparatus according to claim 7 wherein said waveforms have a cycle frequency in excess of 3000 Hz.

19. An apparatus according to claim 1 wherein said electrodes include a contact surface area enhance by a surface treatment selected to increase said surface area by creating a plurality of protuberances with opposing surfaces of protuberances sized to present an atraumatic surface to opposing tissue.

5

20. An apparatus according to claim 1 further comprising a charge amplifier connected across at least one of said electrodes and selected to identify a depolarization of a nerve.

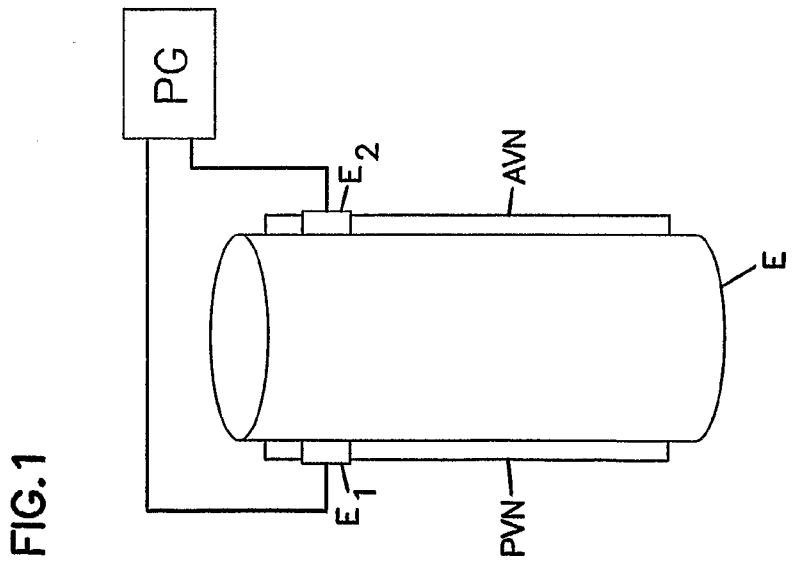


FIG.1

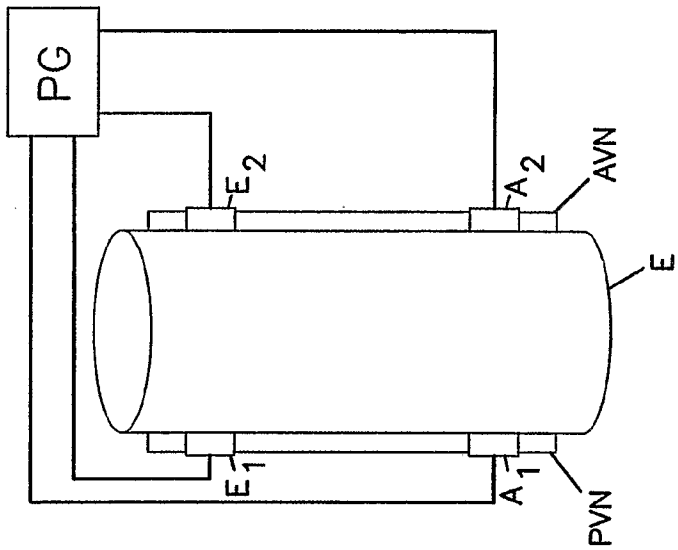


FIG.2

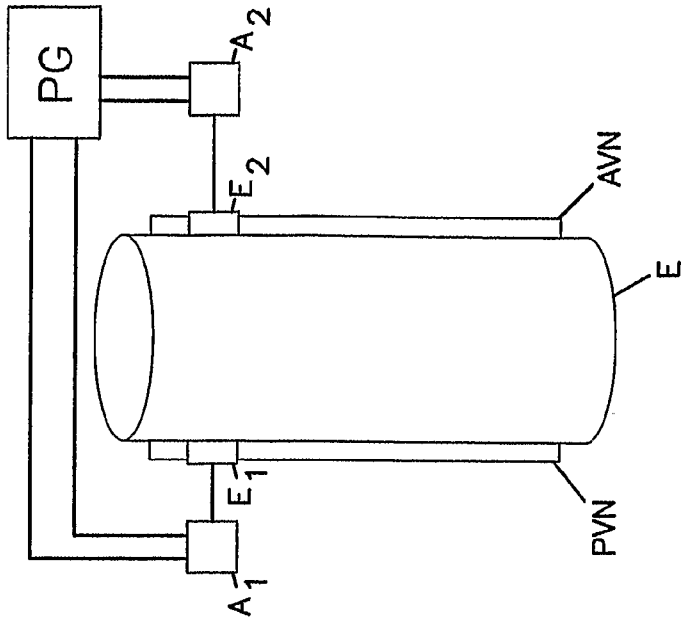


FIG.3

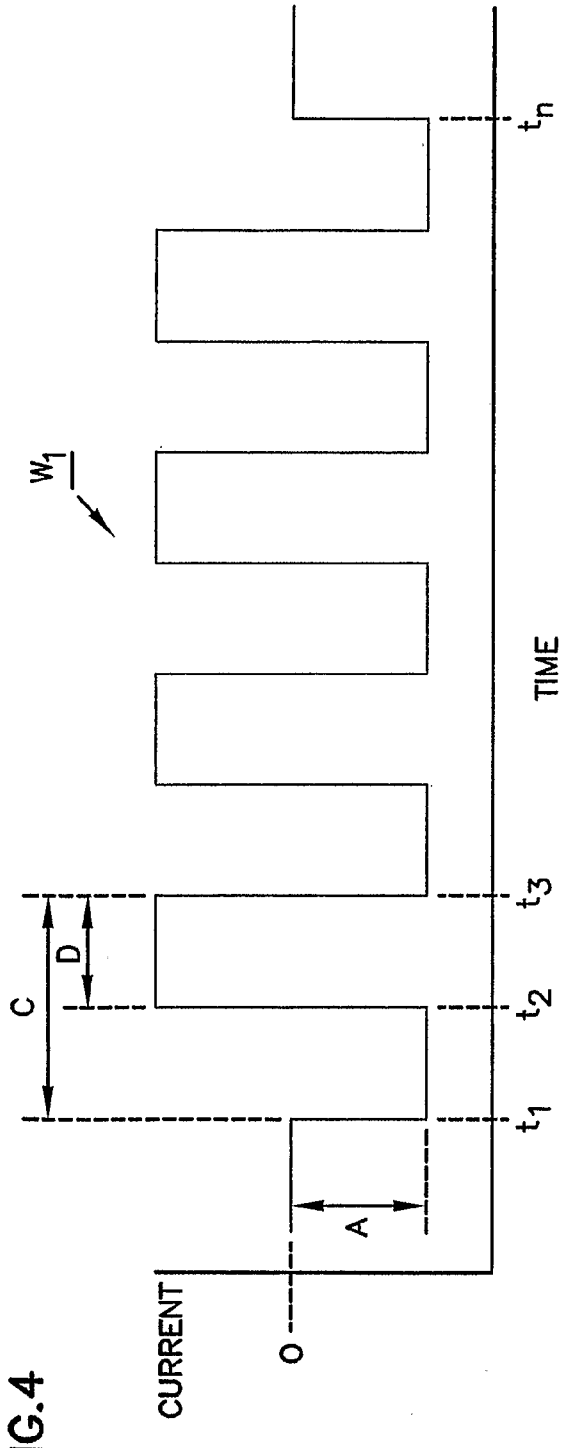

W1
CURRENT
TIME
O
A
C
D
t1
t2
t3
tn

FIG.4

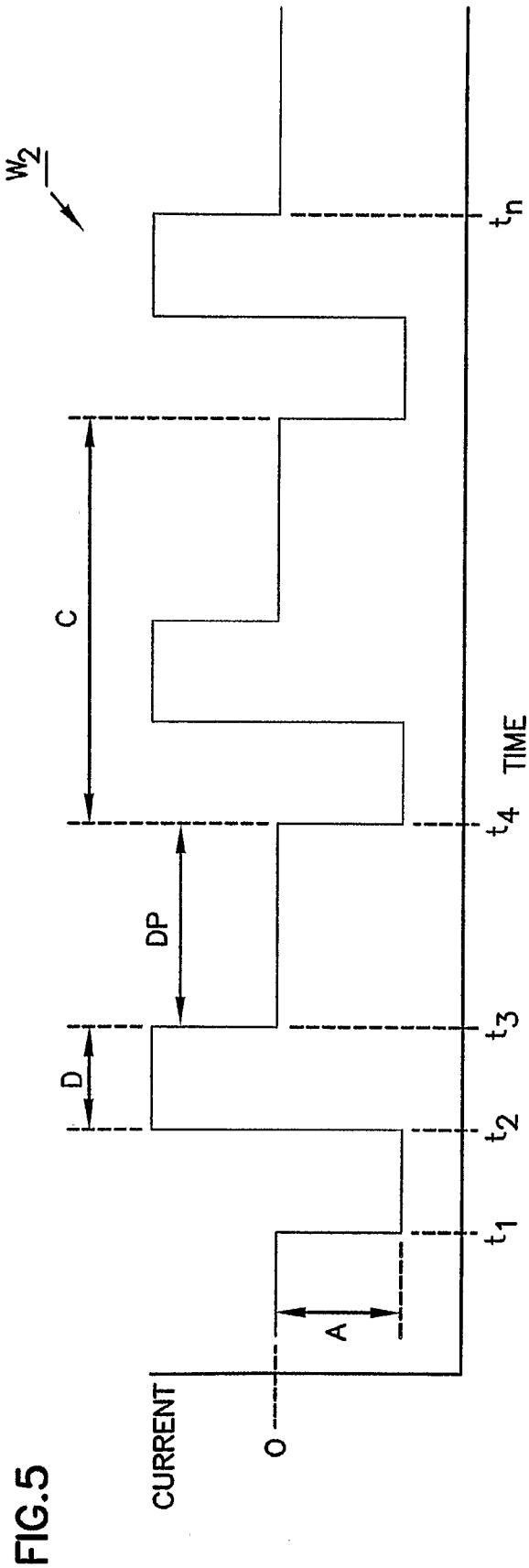

W2
CURRENT
TIME
O
A
C
D
DP
t1
t2
t3
t4
tn

FIG.5

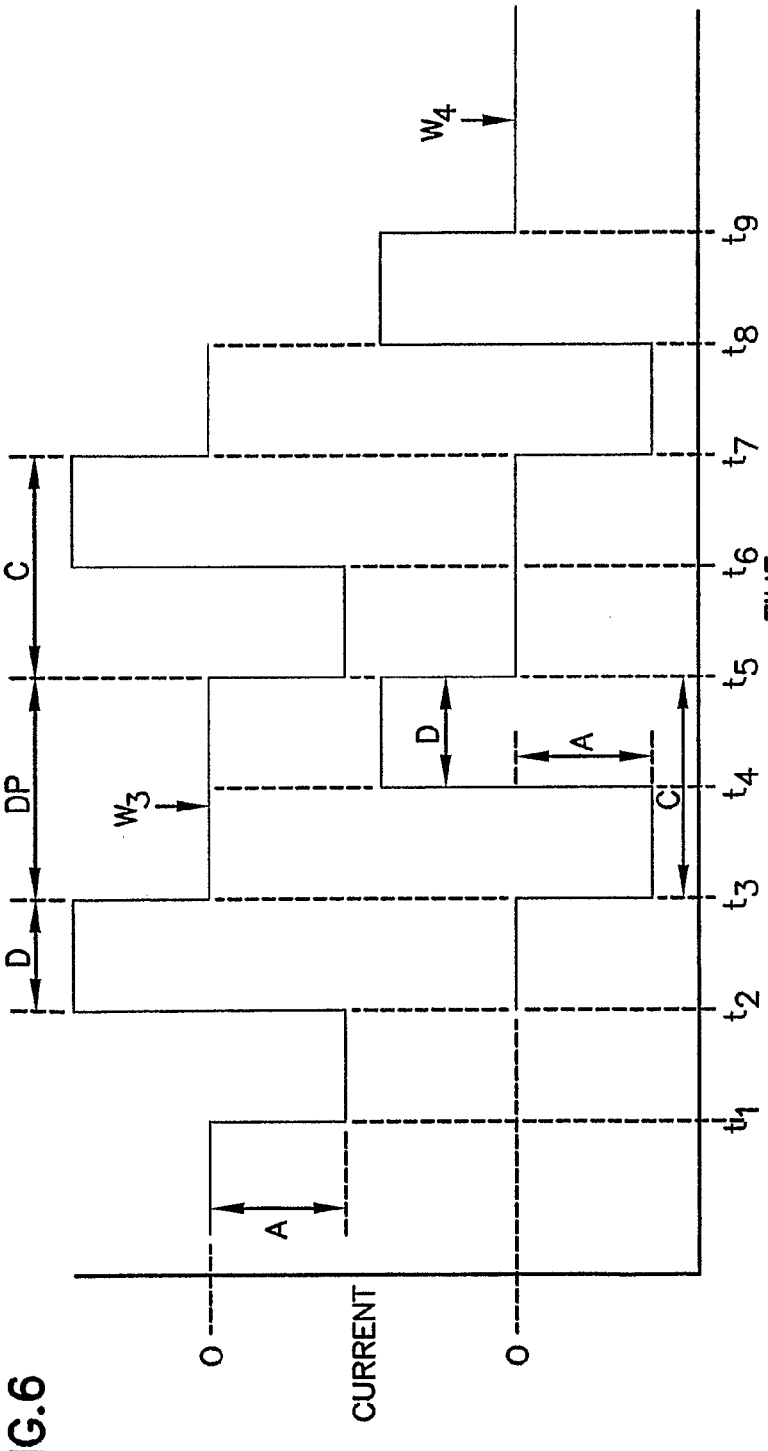

w_4
t_9
t_8
t_7
C
t_6
TIME
t_5
D
A
DP
w_3
C
t_4
t_3
D
t_2
t_1
A
0
CURRENT
0

FIG.6

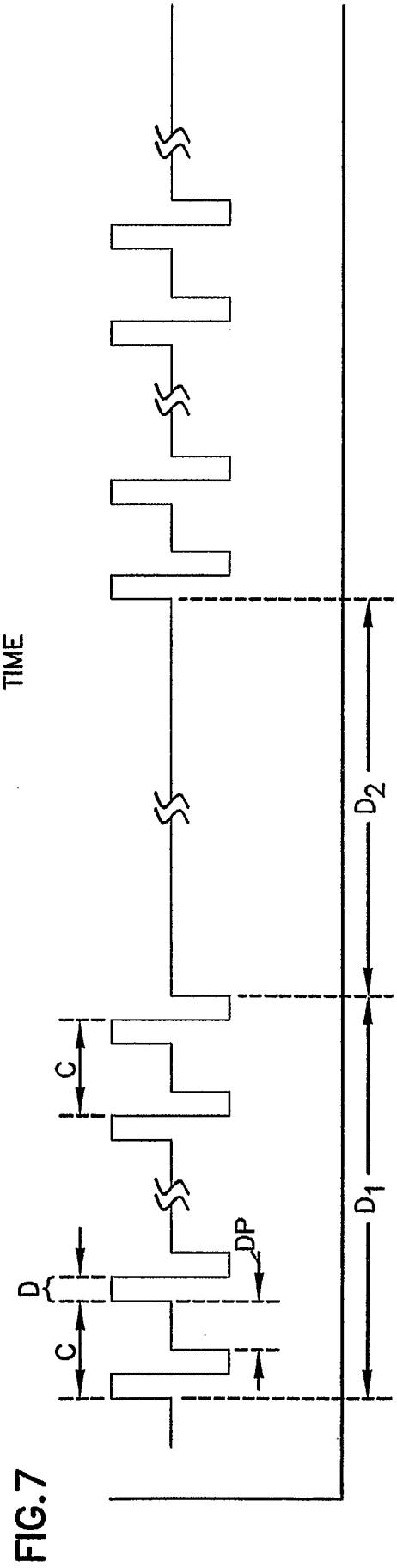

D_2
C
D_1
D
DP
C

FIG.7

FIG.8

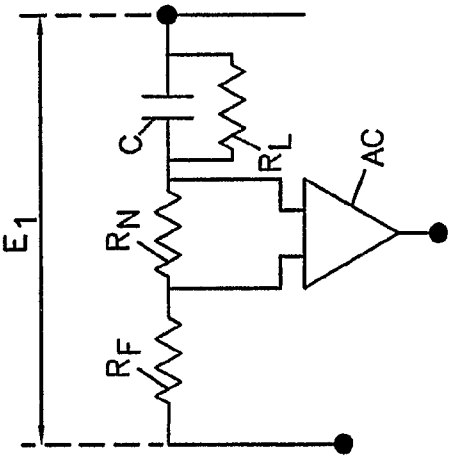


FIG.9

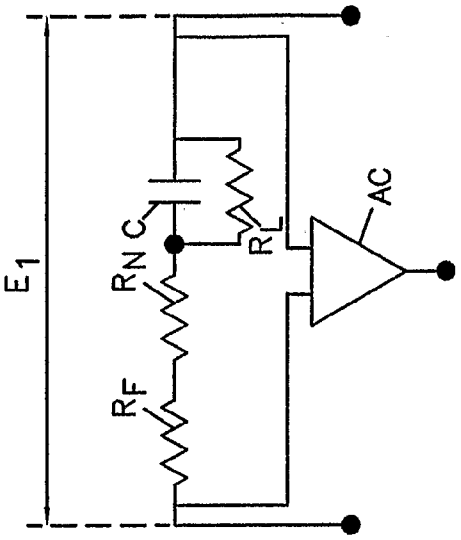


FIG.10

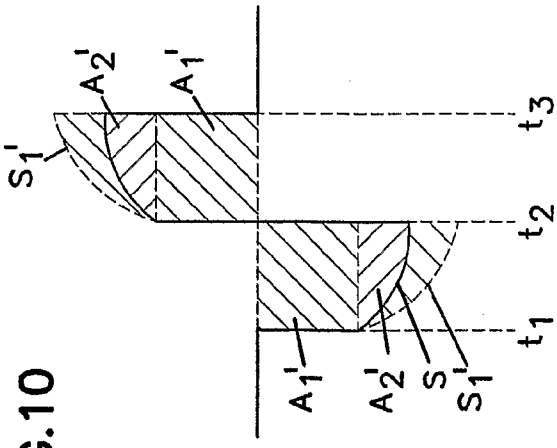


FIG.11

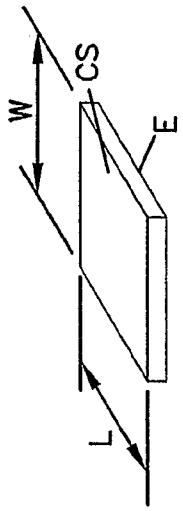


FIG.12

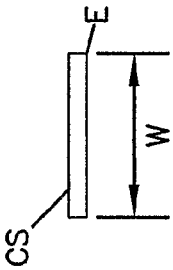


FIG.13

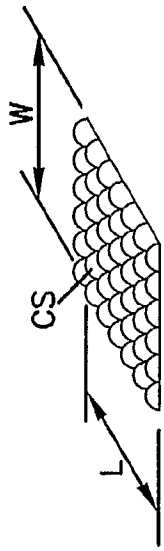
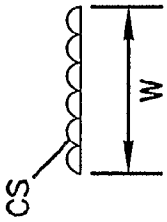


FIG.14



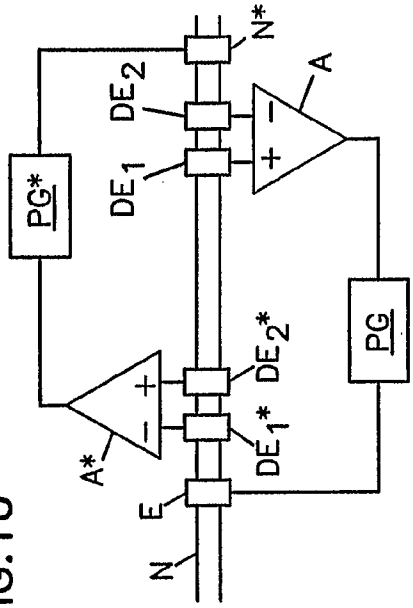


FIG.16

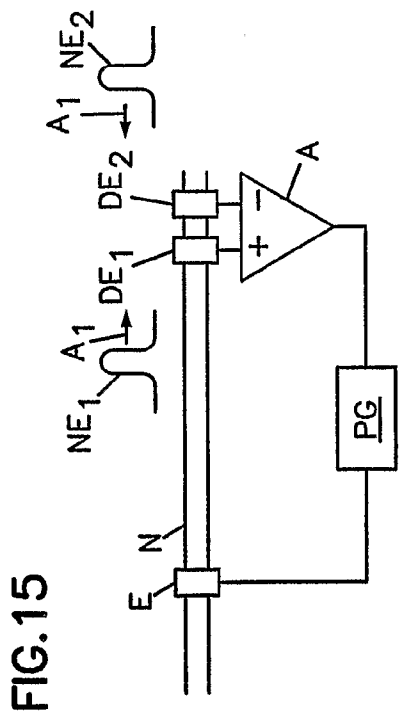


FIG.15

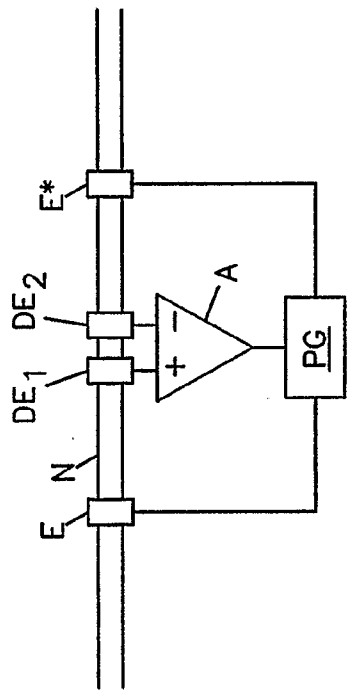


FIG.17

FIG.18

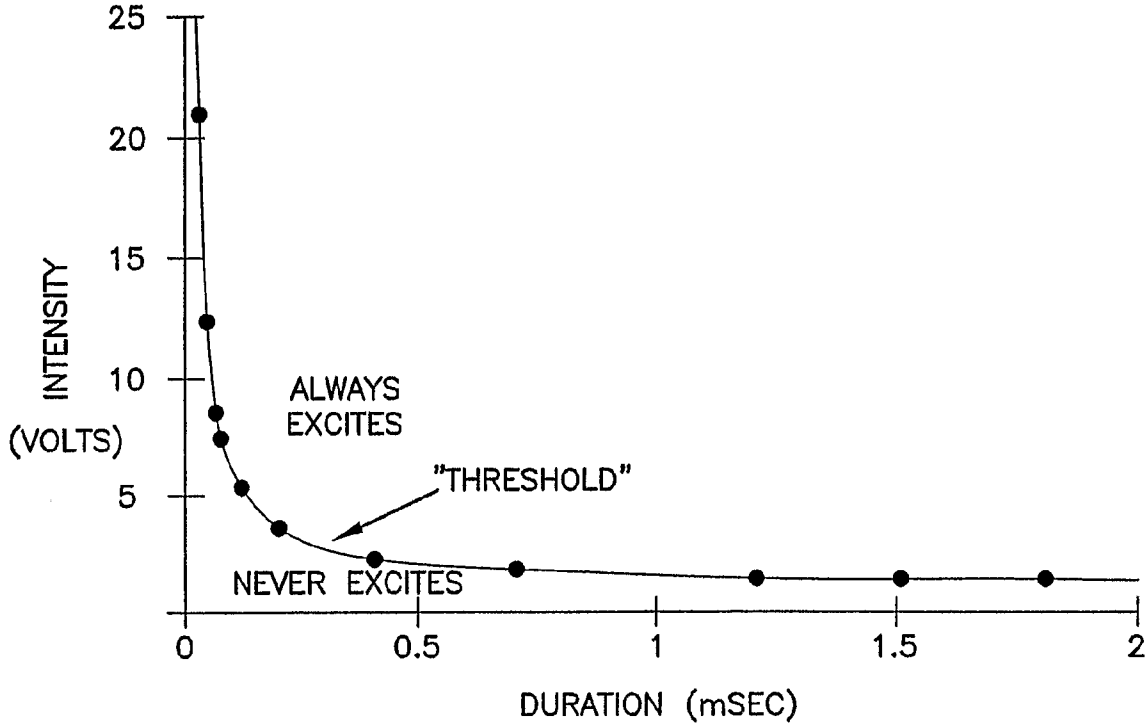

25
20
15
10
5
INTENSITY
(VOLTS)
ALWAYS
EXCITES
"THRESHOLD"
NEVER EXCITES
0
0.5
1
1.5
2
DURATION (mSEC)

FIG.19

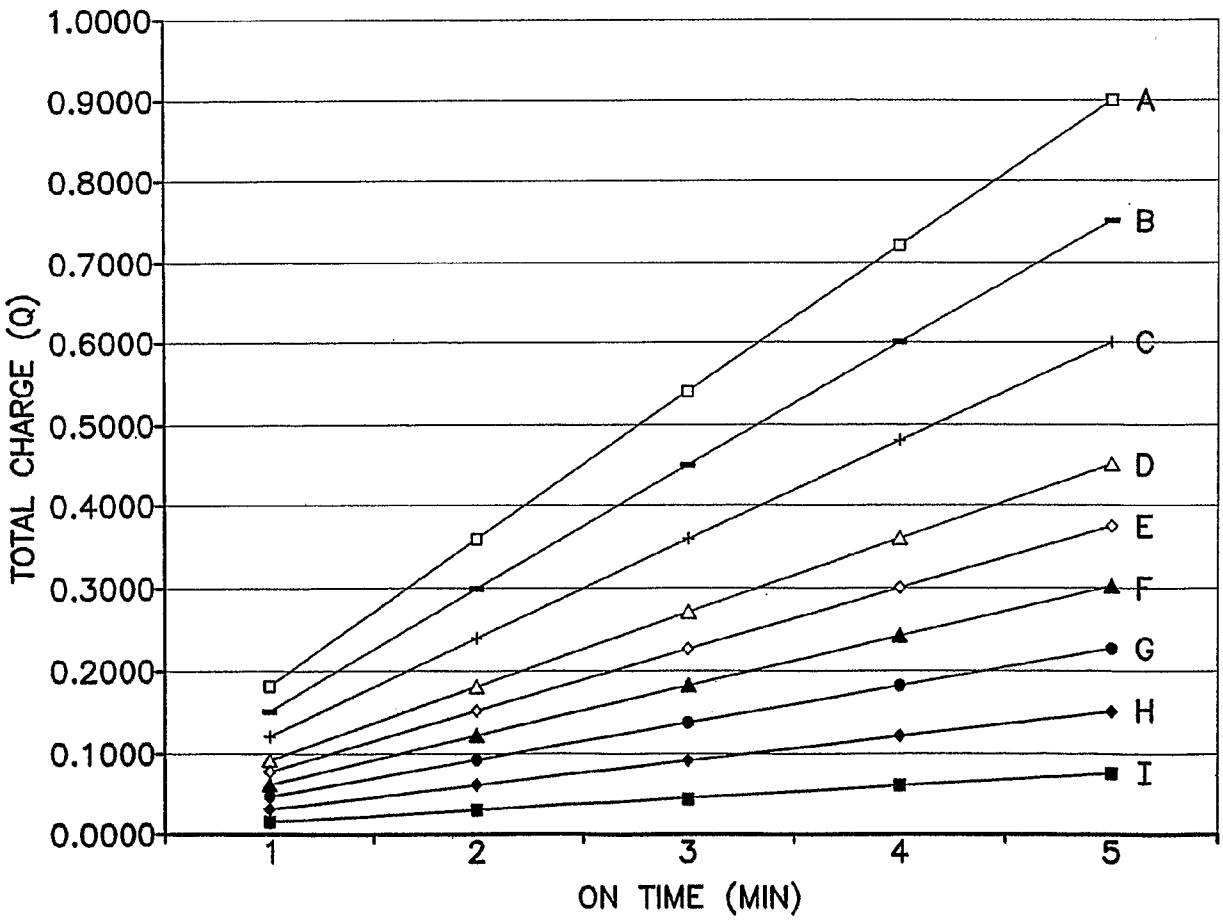
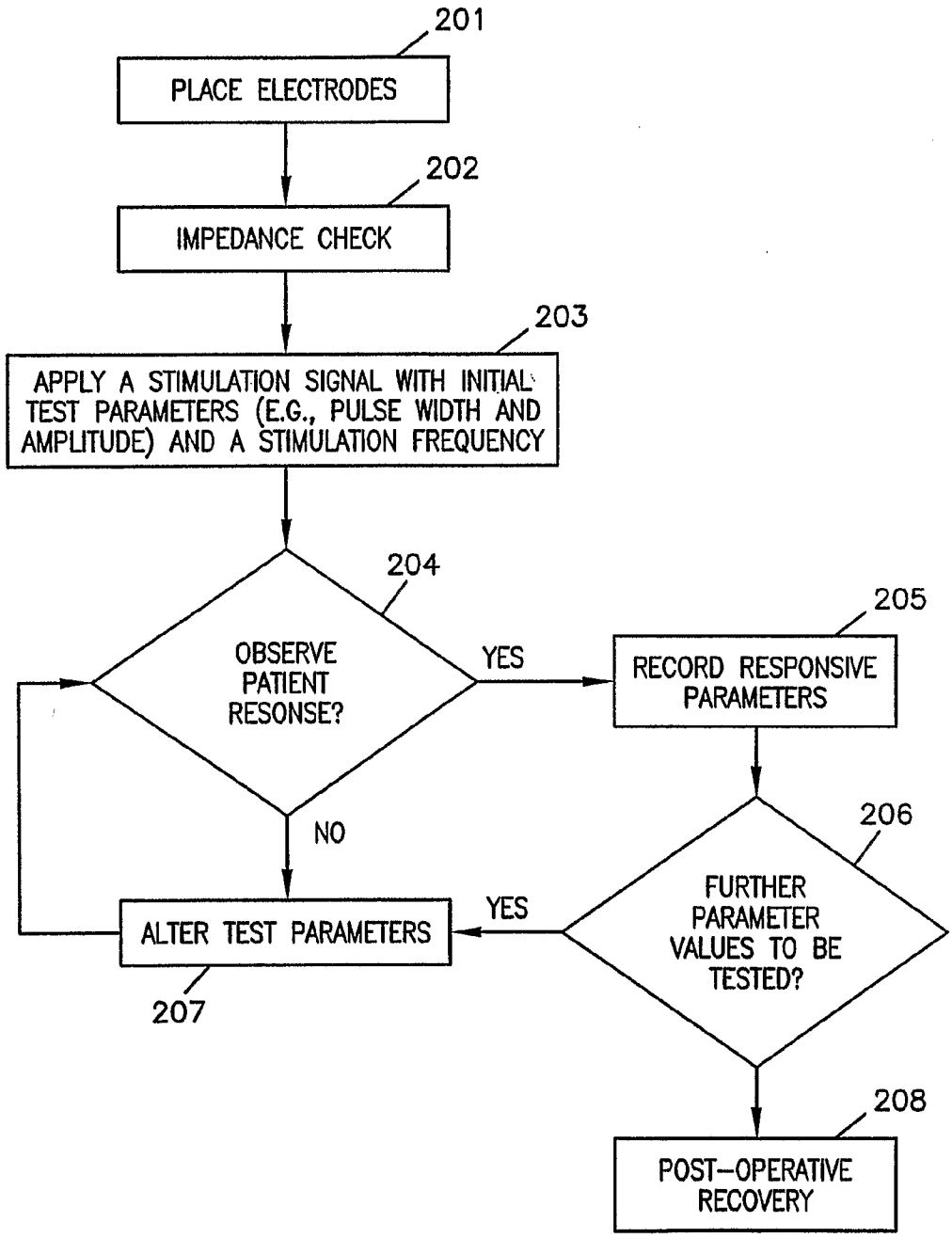

1.0000
0.9000
0.8000
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
TOTAL CHARGE (Q)
A
B
C
D
E
F
G
H
I
1
2
3
4
5
ON TIME (MIN)

FIG.20


201
PLACE ELECTRODES
202
IMPEDANCE CHECK
203
APPLY A STIMULATION SIGNAL WITH INITIAL TEST PARAMETERS (E.G., PULSE WIDTH AND AMPLITUDE) AND A STIMULATION FREQUENCY
204
OBSERVE PATIENT RESONSE?
YES
205
RECORD RESPONSIVE PARAMETERS
NO
206
FURTHER PARAMETER VALUES TO BE TESTED?
YES
ALTER TEST PARAMETERS
207
208
POST-OPERATIVE RECOVERY

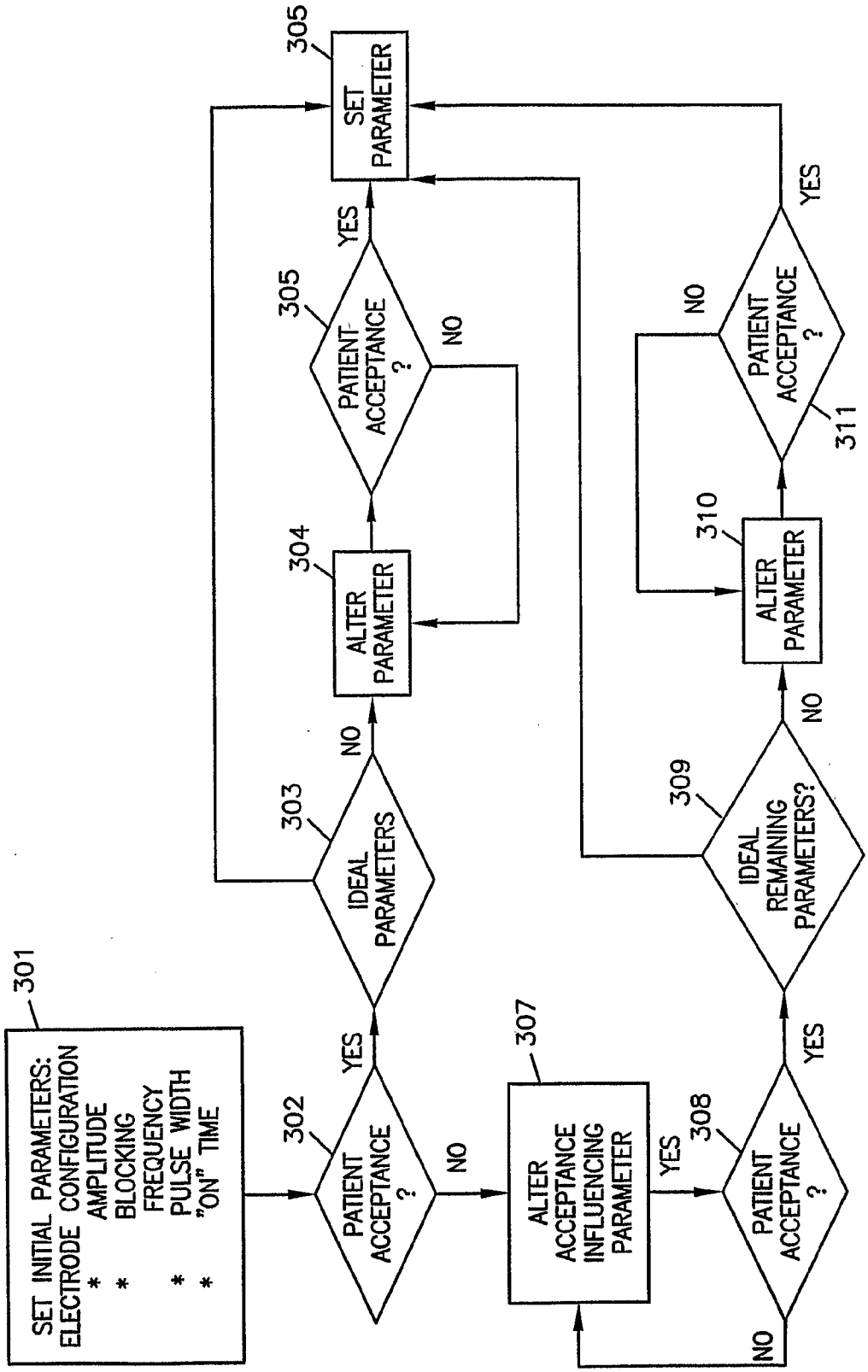

SET INITIAL PARAMETERS:
ELECTRODE CONFIGURATION
* AMPLITUDE
* BLOCKING FREQUENCY
* PULSE WIDTH
* "ON" TIME
301
PATIENT ACCEPTANCE ?
302
YES
NO
IDEAL PARAMETERS
303
NO
YES
ALTER PARAMETER
304
PATIENT ACCEPTANCE ?
305
NO
YES
SET PARAMETER
305
ALTER ACCEPTANCE INFLUENCING PARAMETER
307
YES
PATIENT ACCEPTANCE ?
308
NO
YES
IDEAL REMAINING PARAMETERS?
309
NO
YES
ALTER PARAMETER
310
PATIENT ACCEPTANCE ?
311
NO
YES

FIG.21

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/029926

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2004/254616 A1 (ROSSING MARTIN A [US] ET AL) 16 December 2004 (2004-12-16) paragraphs [0087] - [0093]; figure 5	1-5,10, 12-15,20 6-9, 16-19
X	WO 2004/093981 A (KERNFORSCHUNGSANLAGE JUELICH [DE]; TASS PETER [DE]) 4 November 2004 (2004-11-04) page 16, line 8 - page 20, line 7; figure 5 page 28, line 9 - page 29, line 4	1-3,7,10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2006	29/11/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Loveniers, Kris

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/029926

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KILGORE K ET AL: "NERVE CONDUCTION BLOCK UTILISING HIGH-FREQUENCY ALTERNATING CURRENT" MEDICAL AND BIOLOGICAL ENGINEERING AND COMPUTING, SPRINGER, HEILDELBERG, DE, vol. 42, no. 3, May 2004 (2004-05), pages 394-406, XP001221013 ISSN: 0140-0118 cited in the application the whole document	6-8, 16-18
Y	US 2003/195601 A1 (HUNG ANDY [US] ET AL) 16 October 2003 (2003-10-16) paragraph [0009]; figures 1,2	9,19
A	US 2005/038484 A1 (KNUDSON MARK B [US] ET AL) 17 February 2005 (2005-02-17) cited in the application abstract paragraph [0044]	6,7,16, 17
A	US 2003/135245 A1 (CAMPOS JAMES M [US]) 17 July 2003 (2003-07-17) paragraphs [0090], [0091]; figure 8	1-10, 12-20
A	US 2002/016617 A1 (OLDHAM JACQUELINE A [GB]) 7 February 2002 (2002-02-07) paragraph [0047]; figure 8	1-10, 12-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/029926

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgeryRule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/029926

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004254616 A1	16-12-2004	AU 9479901 A	08-04-2002
		EP 1330288 A1	30-07-2003
		JP 2004526471 T	02-09-2004
		WO 0226314 A1	04-04-2002
WO 2004093981 A	04-11-2004	CN 1774279 A	17-05-2006
		DE 10318071 A1	25-11-2004
		EP 1613394 A1	11-01-2006
		KR 20060003025 A	09-01-2006
		US 2006212089 A1	21-09-2006
US 2003195601 A1	16-10-2003	NONE	
US 2005038484 A1	17-02-2005	NONE	
US 2003135245 A1	17-07-2003	US 2004236386 A1	25-11-2004
		US 2004243196 A1	02-12-2004
US 2002016617 A1	07-02-2002	NONE	