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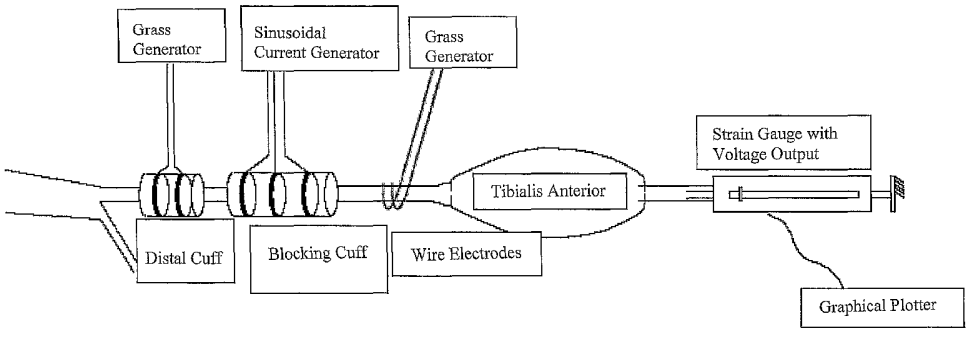

(57) Abstract: A device for pain relief, bowel and bladder control comprising a cyclical waveform, pulse generate, electrode system to block the propagation of action potentials in the axon only at that site, and a stimulus electrode system to generate action potentials in the axon. The stimulus electrode system is central and flanked on either side by a blocking electrode system. After applying stimulus electrical pulses to a first site on the nerve blocking cyclical waveform pulses are applied to a second site on the nerve. Then the blocking current amplitude is reduced so that the propagation of action potentials remains blocked in some axons but is no longer blocked in pre-selected axons.

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NERVE BLOCKING METHOD AND SYSTEM

The present invention relates to a method and system for blocking nerves.

The blocking of nerves is desirable for many conditions such as neuropathic pain and various clinical procedures, such as during operations. Anaesthetic nerve blocking agents can be injected directly around nerves to reduce pain for example. However, the injections are themselves painful and have time limited effect. Furthermore, they cannot be switched off at will and need to be administered by a healthcare professional. Thus a patient suffering from chronic pain can only receive intermittent pain relief from local anaesthetic and must use systemic drugs with undesirable side effects.

Alternative attempts to block nerves have involved applying alternating current (AC) to the nerve. However, this has produced mixed results. High frequency waveforms are applied to the nerve which induce action potentials. Each action potential is transmitted along a nerve axon to its terminal at the neuromuscular junction ("end plate") where it causes the release of a quanta of neurotransmitters from vesicles. The neurotransmitters cause the muscle to contract. However, the neurotransmitter stores in the vesicles become depleted and are not replenished in time to keep up with the action potentials. Accordingly, action potentials are generated in the nerves which do not result in muscle contractions. Studying the muscle activity, this would appear as though the nerve has been blocked. However, it is apparent this is a false conclusion as action potentials are still fired along the nerve. A nerve cell is only blocked locally when a part of the axon is in a state whereby it cannot propagate action potentials.

Another related phenomenon is collison block. An electrical stimulus pulse causes bidirectional action potentials (i.e. where one orthodromic action potential travels towards the neuromuscular junction and one antidromically towards the soma), the antidromic action potential will collide with any natural action potentials and effectively cancel them out so that they do not reach the muscle fibre. In certain tripolar electrode designs anodal blockade can be used to cancel the orthodromic action potential. However, this type of collision blockade requires regular antidromic action potentials in order to maintain the portion of the axon between the soma and the tripolar cuff blocked. The frequency of these antidromic pulses increases as the distance between the tripolar cuff and the soma decreases. There is an upper

limit, typically 30Hz beyond which the nerve may be damaged (Agnew, W.F., McCreery, D.B., Bullara. L.A., and Yuen, T.G.H. (1990), "Effects of prolonged electrical stimulation of peripheral nerve", Neural Prostheses: Fundamental Studies, Prentice Hall, Englewood Cliffs, NJ 07832). In contrast, AC block potentially offers a purely localised effect with no activity induced in the nerve. Canadian patent application No. 2171067 describes an implant that receives signals from sensors, such as accelerometers, that are attached external to the body, or implanted and used to determine when to switch on and off AC blocking to prevent uncontrollable reflex activity from producing unwanted movements. This document also describes unidirectional stimulation using an upstream AC blocking electrode. However, this is based on predictions of blocking from computer models using monopolar electrodes which produce inconsistent results.

Computer modelling and in-vivo studies (Richard Williamson PhD thesis, Department of Biomedical Enginering University of Alberta 2000) suggest that a sinusoidal waveform can be used to obtain localised block. Computer modeling of fibre diameter predictions were made using theoretical monopole electrodes, however the monopole electrodes induced unwanted action potentials. Thus this did not solve the problem of selectively blocking axons with alternating current according to their diameters.

The present invention seeks to overcome one or more of the above disadvantages.

According to a first aspect of the present invention, there is provided a device for controlling nerve activity in vivo comprising:
a current generator operable to produce current pulses having a cyclical waveform,
a plurality of blocking electrode systems electrically connectable to the current generator, each blocking electrode system being operable to deliver a current to the axon of a nerve at a site on the axon and to block the propagation of action potentials in the axon only at that site,
a stimulus electrode system for delivering a stimulus pulse to the axon to generate action potentials in the axon, the stimulus electrode being connectable to the current generator,
wherein the electrodes being arranged so that the stimulus electrode system is central and flanked on either side by a blocking electrode system.

Each blocking electrode system may have its own current generator circuit.

One or more of the blocking electrode systems or the stimulus electrode system may comprise a ring electrode.

Preferably at least one blocking electrode system is provided on a cuff. This arrangement is easy to apply to the nerve.

The blocking electrode systems and stimulus electrode system may be provided on a single cuff. This means that only a single cuff has to be applied to the nerve at a single time which speeds up the procedure and reduces the chance of damaging the nerve.

Preferably the blocking electrode system on at least one side of the stimulus electrode system is a tripolar electrode and most preferably the blocking electrode systems on both sides of the stimulus electrode system are tripolar. Tripolar electrodes provide a uniform field distribution which is important for localised block. This is not achieved with monopolar electrodes.

The stimulus electrode system may be bipolar or tripolar (to ensure that all stimulating current is contained within the rings). The return electrode ring(s) of the stimulus ring electrode system may be shared with a neighbouring blocking electrode ring system.

It is preferred that the stimulus electrode system is connected to a current generator circuit which is separate from the blocking current generator circuit.

Preferably the device further comprises a signal amplifier and an electroneurogram cuff electrically connectable thereto.

The device may further comprise a control device operable to control the outputs of the current generator.

According to a second aspect of the present invention there is provided a method of controlling nerve activity in a mammal comprising the steps of:
applying stimulus electrical pulses to a first site on the nerve to generate action potentials in the nerve,
applying blocking current pulses to a second site on the nerve, the pulses having a cyclical waveform so that application of the pulses blocks the propagation of action potentials in the nerve only at that site,
reducing the blocking current amplitude so that the propagation of action potentials remains blocked in some axons but is no longer blocked in pre-selected axons.

The block is first removed in smaller diameter axons.

The blocking current may be from 0.5 to 50 mA, preferably from 5 to 20mA and most preferably about 10mA.

The blocking current may be reduced by up to 70%, preferably by up to 50%, and most preferably by up to 30%.

The frequency of the blocking current may be from 5 to 30 Hz, preferably from 11 to 20 Hz.

The blocking current is applied distal to the site where the stimulus pulses are applied. Alternatively, the blocking current is applied proximal to the stimulus pulses so that propagation back to the spinal cord is blocked.

The blocking current may also be applied distal to the stimulus pulses, whereby the proximal current is maintained to block the propagation of action potentials at that site and the distal current is reduced so that the propagation of action potentials remains blocked in some axons but is no longer blocked in pre-selected axons.

The frequency of the stimulus pulses may be from 5 to 30 Hz, and preferably about 15 Hz.

The blocking and stimulus pulses may be applied to the pudendal, S2, S3, tibial and / or a trigeminal nerve.

The method may further comprise the step of subsequently increasing the frequency of stimulus pulses to at least 30 Hz to induce cell death. This can be used to selectively kill pain fibres.

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 shows an embodiment of experimental set-up;

Figure 2 a typical force muscle block;

Figure 3 shows twitches generated by proximal stimuli;

Figure 4 shows possible stimulus/block combinations;

Figure 5 shows an example of blocking sequence; and

Figure 6 shows an embodiment of block stimulation electrode system.

Figure 7 shows the reduction in muscle force from decreased sinusoidal current amplitude.

Experimental Method

Five female rats (307 +/- 40 g) were tested. Each rat was anaesthetised with an intraperitoneal injection of 45 mg/kg pentobarbital sodium (Somnotol). After initial anaesthesia, pentobarbital sodium (45 mg/kg ip) was administered in a 1:5 dilution to maintain general anaesthesia. The trachea of each rat was cannulated and mechanical

ventilation assistance was applied for one animal. The body of each rat was warmed during the tests by radiant heat from above and a heating pad beneath.

The left sciatic nerve was exposed in each rat. The ipsilateral knee was held in place using a stereotaxic frame. Each ipsilateral muscle group, other than the tibialis anterior, was denervated. The tendon from the tibialis anterior was cut and tied to a strain gauge. Force was amplified and viewed on a Tektronix dual time base storage oscilloscope (model 5441), and monitored continuously on a Gould 1200S pen recorder. The force from the muscle was recorded under different stimulus conditions.

A schematic of the arrangement is shown in Figure 1.

A bipolar cuff electrode, constructed of silastic tubing (inside diameter 1.98 mm outside diameter 3.18 mm, length 6 mm, contacts of 15 strand Cooner wire symmetrically and longitudinally spaced by 4 mm) was placed around the sciatic nerve at the most distal site from the muscle. An intramuscular electrode, made by bared ends of Teflon™ coated fine silver wires (75 μm), was inserted near the motor point of the tibialis anterior in a position most proximal to the muscle. A symmetrical tripolar cuff electrode (inside diameter 1.98 mm outside diameter 3.18 mm, length 6 mm, contacts of 15 strand Cooner wire symmetrically spaced by 2 mm) was placed around the common peroneal nerve approximately halfway between the other two electrodes. The tripolar cuff has a central cathode flanked by a pair of anodes.

Action potentials and muscle firings were produced using unipolar 50 μs pulses produced by a Grass stimulus generator and connected to the bipolar and intramuscular electrodes. The amplitude of the pulses (typically 5 to 10 Volts) was set to cause the maximal force single muscle twitch from the muscle. Pulses could be generated independently from the bipolar and intramuscular electrode, or the timing of the pulses could be synchronised. In tests to demonstrate the localised nerve block, the muscle twitch produced by the intramuscular electrode typically preceded the muscle twitch from the cuff electrode by one second. In some tests, only the bipolar electrode was used to generate action potentials.

The centre contact of the cuff was connected to a variable frequency, variable amplitude alternating current sinusoidal waveform generator. The two outer contacts of the tripolar cuff electrode were connected to the common (ground) of a sinusoidal stimulator. The waveform generator used an analogue control to vary the frequency between 3 and 20 kHz block could typically be established with frequencies above 7kHz.. The magnitude of the first harmonic of the sine waveform, the largest frequency domain component of noise, was attenuated by 38 dB, measured on a Hewlett Packard digital storage oscilloscope, Model 54600A.

Experimental Results

The blocking current, typically 3 mA was applied in 15s bursts. Conduction was blocked in 4 out of 5 animals from the first burst and after the twelfth burst in the 5th rat.

Figure 2 is a typical muscle force record for block above 10 kHz. To the left of the graph, the larger series of muscle twitches was due to the bipolar cuff electrode and the second twitch the intramuscular electrode. A larger twitch is observed on turning on the block sine current which is applied in the region of the tripolar electrode. The tripolar cuff electrode is located downstream of the proximal bipolar cuff electrode and upstream of the intramuscular electrode. The blocking effect is localised to the tripolar cuff region; the current path is entirely contained within the length of the cuff. After applying the block, only twitches due to the intramuscular electrode are seen. This indicates that the neuromuscular endplate has not been depleted since the muscle receives the signals from the nerve. The block prevents pulses from the proximal bipolar cuff reaching the muscle. After the block has been switched off both stimulus twitches immediately resume. In other words, the block has a rapid onset and is immediately reversible.

Selective blockade and stimulation of axons

We have now determined that this method can be used to selectively stimulate populations of axons. In computer simulation, larger diameter axons are blocked first whereas smaller axons require larger currents to be blocked (Richard Williamson PhD thesis, University of Alberta 2000).

An example of selective stimulation is shown in Figure 3, in which muscle twitches were generated at 5s intervals by the proximal bipolar cuff stimuli. The sinusoidal current was applied at 2.4mA, a current found to produce complete blockade of the nerve. No muscle activity was observed indicating that all axons are blocked. The blocking current is then reduced and then increased to its original value over a period of 50 seconds. It is observed that single twitches were observed with amplitude inversely proportional to sine current. The smallest axons are first to unblock and can transmit signals to the muscle fibres, thus some twitching is seen. The sinusoidal current is then progressively increased again to maximum, so that all the axons are blocked, and held blocked at maximum until the sinusoidal blocking current is switched off.

This selective stimulation of axons is useful for example in bladder control. The S2 spinal nerve root innervates both the smooth muscle of the detrusor (bladder) and the external sphincter muscle (which is skeletal muscle). The bladder is innervated by axons with a smaller diameter than the axons that innervate the sphincter muscle. Thus if a supramaximal stimulus were applied to this spinal root both detrusor and sphincter would contract. However, is a blocking tripolar cuff is positioned distally with respect to this point of stimulation, the sinusoidal blocking current could be set a level which blocks signals to the external sphincter but not the detrusor muscle. Thus the detrusor would contract and the sphincter relax which would assist micturition. In this and the following arrangements, an intramuscular electrode is not required.

These results also show that a blockade can be established in a nerve which is localised (to the tripolar cuff region) and selectively applied to axons according to their diameter. The use of a tripolar electrode ensures that the electrical field is uniform which is important to generate a localised block. Furthermore, the onset of the block and recovery times are short.

Unidirectional stimulation

We have also determined that AC block can be combined with electrical stimulation as shown in Figure 4. In Figure 4(a), application of a stimulus results in uni-directional activation in larger axons, ie an action potential is propagated towards the nerve terminal and a further action potential is propagated towards the soma. The block current applied by the tripolar cuff is set to maximum, typically less than 10 mA . All propagation to the left i.e. back to the spinal cord is blocked (to avoid any undesirable sensation or reflex actions); propagation to the right is unaffected. The stimulus intensity can then be adjusted to activate the larger axons. In the case of the bladder sphincter, it is possible to monitor sphincter pressure and bladder pressure simultaneously. If the sphincter contracts and the sphincter pressure rises but the bladder pressure is unaffected, only the larger diameter axons are activated. This can be checked also by monitoring the compound action potential conduction times along the nerve. The conduction time is proportional to axon diameter.

In Figure 4(b) the stimulus generates action potentials in both directions in a population of axons determined by the stimulus intensity. The sinusoidal current can be adjusted to selectively block propagation in the larger axons to the right. For example, this could be used to activate the smaller axons of the detrusor whilst blocking the sphincter as described above. This arrangement would require both large and small axons to be activated and action potentials can travel back to the spinal cord which may cause unwanted sensation or reflex actions. This can be prevented in the following arrangement.

Figure 4(c) is used to establish uni-directional activation only in the smaller axons. It uses an arrangement with two tripolar cuffs to apply block in two regions either side of a point of stimulation (typically a biopolar electrode pair). The stimulus intensity is set to a sufficiently high level (such as up to 20mA) so that all axons are stimulated and action potentials travel bidirectionally. For action potentials propagating to the right, the right block current is set to level just sufficient to block the larger (sphincter) axons . The sinusoidal blocking current of the left blocking cuff is set sufficiently high so as to block all axons. Thus

all action potentials travelling to the left (towards the spinal cord) will be stopped, thus avoiding any unwanted sensation or reflex actions. The method can be applied vice versa for propagation to the left. Alternatively, this method could be carried out using a single cuff with up to eight electrodes (two tripolar blocks with a central bipolar). The number of electrodes can be reduced to six (to produce a shorter cuff length) with the two central electrodes could apply the stimulus pulse and the other electrodes apply a blocking current.

As the block is highly localised to the region of the tripolar electrode applying it, the block and stimulus electrodes may be in close proximity. This means the arrangement is very compact and less of the nerve must be exposed to put it in position.

Figure 7 shows a reduction in muscle force from decreased simusoidal current amplitude. Major divisions of the ordinate axis are 0.5 V recorded from the strain gauge transducer. Single muscle twitches are generated from pulses delivered to the bipolar cuff electrode. 3mA of 15-kHz sinusoidal current was applied at time T0. After the transient contraction, the muscle twitches due to bipolar cuff electrode pulses ceased, indicating a complete conduction block through the area of the sinusoidal current. The amplitude of the sinusoidal current was reduced between times T1 and T2 to 1.5mA. Initially, the decrease in amplitude did not permit any of the compound action potential to propagate. At time T2 muscle twitches were observed, indicating that part of the compound action potential was able to conduct through the area of the sinusoidal current. The amplitude of current was slowly increased to 2.4mA at time T3. During this increase, the muscle twitches exhibited less and less force, indicating that less of the compound action potential was able to propagate through the area of the sinusoidal current. At T3, the current was increased to the initial level. The sinuosoidal current was removed entirely at T4.

The AC block may be used in combination with an ENG (electroneurogram) cuff and signal amplifier to selectively record from smaller axons by first blocking activity in the larger axons as shown in Figure 5. Without blocking the larger axons, it would be difficult to seperate the signals from the smaller axons since larger signals are produced by action potentials in the larger diameter axons and would dominate the reading.

These methods and systems have a wide range of applications, for example in patients with neuromuscular problems such as those with cerebral palsy, multiple sclerosis or stroke. In one embodiment it can be used for bladder and bowel control. Since the blockade does not induce activity in the nerve it is unlikely to cause discomfort and may thus be used where sensation is preserved. For example, a blocking cuff electrode could be positioned on the pudendal nerve (a branch of the S2 nerve) or on the S2 nerve itself to transiently block activity in the sphincters, which may be used assist micturition or defecation. This is useful where the sphincter does not relax when the bladder or bowel contracts. The same cuff could also double-up as a stimulating electrode to provide low-level neuromodulation during the filling phases to reduce hyperactivity in the detrusor or rectum.

With extradural sacral root AC blocking and stimulation, it is possible to restore control to the neurogenic bladder. The blocking cuff is positioned extradurally on the mixed sacral root (typically S3) as shown in Figure 6 following a similar surgical procedure to that used in the "Barcelona" technique [Sarrias M, Sarrias F, Borau A(1993) The Barcelona technique, Neurol & Urodyn, vol 12, p509-512.]. In Figure 6 the block/stimulation electrode system of Figure 4 (a) or (c) is positioned extradurally and bilaterally on the mixed sacral roots. The approximate location for S2 cuff electrode system is indicated. A stimulating electrode system is positioned distally. With the proximal block fully on, the stimulus is applied in bursts at typically 15Hz to provide post-stimulus voiding similar to that used in the FineTech-Brindley SARS system. The AC block would temporarily disrupt the reflex arc during micturition thus avoiding detrusor-sphincter-dyssynergia. During the filling phase the block is switched off and a low-level stimulation applied at typically 20Hz to provide neuromodulation to reduce detrusor hyperreflexia.

An additional refinement would be to use a combination that includes a second blocking electrode placed distally as shown schematically in figure 4(c). In this arrangement selective contraction of the detrusor with blockade of the sphincter provides low pressure voiding i.e. during micturition the proximal block would be set to maximum and the distal block set to block the larger efferents to the urethral sphincter.

In both arrangements the requirement for irreversible surgery in which the sensory spinal sacral roots are cut (posterior rhizotomy) may be avoided and the extradural surgery is less risky than intradural approaches. Furthermore, the method does not induce action potentials in sensory axons (which in some spinal cord injury patients can give rise to dangerous reflexs such as autonomic dysreflexia), it can also be used in patients to neurological disorders with some sensory sparing, such as incomplete spinal injuries or MS.

The system can also be used in cerebral palsy patients. Such patients suffer involuntary spasms. In addition, the calf muscle contracts so that the foot is plantar flexed during the terminal swing phase of the walking cycle. Thus the foot lands on the toes instead of the heel. This contraction leads to deformity. The system can be used by the patient to block the tibial nerve in key points in the walking cycle.

The system can also be used in pain control by blocking sensory rather than motor nerves. For example, the system could be used on the trigeminal nerves in the face to alleviate trigeminal neuralgia.

In use, the nerve to be blocked is exposed and a tripolar electrode cuff is placed around the nerve. A stimulus electrode cuff is put in place either upstream or downstream of the tripolar electrode. A neural prosthesis is implanted just below the skin and wires run from the prosthesis to the electrodes. The prosthesis has an RF receiver circuit and is powered by an external RF source. The prosthesis may have a rechargeable battery. Alternatively, the cuff electrode contains the RF receiver circuits. The patient then carries a control device which he can operate to transmit signals to the electrodes in order to block and/or stimulate the nerve activity. The current required to block a nerve depends on several factors such as the diameter of the axon and how slack the cuff is on the nerve. This may alter over time as fibrous tissue can begin to grow between the nerve and the cuff. The control device may monitor the impedance of the system and automatically adjust the current settings accordingly. The current required is also species dependent.

Another application of the method is to destroy signal sensory neurons involved in the pain pathway such as C fibres and Aδ fibres. Activity in the larger axons could be blocked and

then a high frequency stimulus (such as 50Hz or more) applied to the small axons to induce cell death by mechanisms similar to those described by Agnew & McCreary. This would be particularly advantageous for people suffering from chronic pain.

The method and system can be used in clinical and veterinary applications.

The tripolar cuff is a silicon rubber sheet with three electrodes embedded therein. Those commonly used are 'self-curl' or self-sizing'. The sheet is positioned by the nerve and it seals around the nerve forming a tube. Alternatively, a rubber tube is opened up, put in place around the nerve and then the tube is resealed. The cuff is oversized (compared to the nerve diameter) by about 20-50%. This is so the cuff does not compress the nerve and cause damage. The tripolar cuff may be a silicon rubber sheet with three electrodes embedded therein. Alternatively, the cuff may comprise a polyamide film with the electrodes printed thereon (Blocking of peripheral nerve conduction using AC signals: Which frequency is best? Schuettler, M [1], Andrews, BJ [2], Donaldson, NdeN [1]Proc 9th Ann Sci Conf IFESS, Bounemouth UK, Sept 2004)

Commonly used cuffs are 'self-curl' or self-sizing'. The sheet is positioned by the nerve and it seals around the nerve forming a tube. Alternatively, a rubber tube is opened up, put in place around the nerve and then the tube is resealed. The cuff is oversized (compared to the nerve diameter) by about 20-50%. This is so the cuff does not compress the nerve and cause damage.

The blocking electrode may have more than three electrodes in order to produce a uniform field distribution. However, using fewer than three electrodes, such as a bipolar arrangement does not produce a uniform electrical field and hence no localised block.

The electrodes may be stainless steel. However, platinum iridium electrodes are preferred as stainless steel will eventually pit with higher current levels. The electrodes in the tripolar cuff are about 2mm apart in a cuff having an internal diameter of approximately 2mm. The cuff diameter is dependent on the nerve diameter. The larger the diameter of the nerve, the larger

the internal diameter of the cuff. Details including examples are provided in Richard P. Williamson and Brian J. Andrews, IEEE transactions on Biomedical Engineering Vol. 52, No. 3, March 2005, and BJ Andrews and R. Williamson, AC Nerve Blocking: in-viro tests and potential applications, 9th Annual Conference of the International FES Society, pages 11-13, September 2004, Bournemouth, UK.

It is not essential that the blocking current is sinusoidal, merely that it is cyclical. Other waveforms could be used such as square or rectangular waves.

CLAIMS

1. A device for controlling nerve activity in vivo comprising:
a current generator operable to produce current pulses having a cyclical waveform,
a plurality of blocking electrode systems electrically connectable to the current generator, each blocking electrode system being operable to deliver a current to the axon of a nerve at a site on the axon and to block the propagation of action potentials in the axon only at that site,
a stimulus electrode system for delivering a stimulus pulse to the axon to generate action potentials in the axon, the stimulus electrode system being connectable to the current generator, wherein the electrode systems are arranged so that the stimulus electrode system is central and flanked on either side by a blocking electrode system.

2. A device as claimed in claim 1 wherein at least one of the blocking electrode systems and/or the stimulus electrode system comprises a ring electrode.

3. A device as claimed in any preceding claim wherein at least one blocking electrode system is provided on a cuff.

4. A device as claimed in any preceding claim wherein two blocking electrode systems and the stimulus electrode system are provided on a single cuff.

5. A device as claimed in any preceding claim wherein the blocking electrode system on at least one side of the stimulus electrode system is a tripolar electrode.

6. A device as claimed in any preceding claim wherein the blocking electrode system on both sides of the stimulus electrode system are tripolar electrodes.

7. A device as claimed in claim 3 wherein the blocking electrode systems are bipolar.

8. A device as claimed in any preceding claim wherein the stimulus electrode system is a bipolar electrode.

9. A device as claimed in any preceding claim further comprising a signal amplifier and an electroneurogram cuff electrically connectable thereto.

10. A device as claimed in any preceding claim further comprising a control device operable to control the outputs of the current generator.

11. A method of controlling nerve activity in a mammal comprising the steps of:
applying stimulus electrical pulses to a first site on the nerve to generate action potentials in the nerve,
applying blocking current pulses to a second site on the nerve, the pulses having a cyclical waveform so that application of the pulses blocks the propagation of action potentials in the nerve only at that site,
reducing the blocking current amplitude so that the propagation of action potentials remains blocked in some axons but is no longer blocked in pre-selected axons.

12. A method as claimed in claim 11 wherein the blocking current is from 1 to 50 mA.

13. A method as claimed in claim 11 wherein the blocking current is from 5 to 20mA.

14. A method as claimed in claim11 wherein the blocking current is about 10mA.

15. A method as claimed in any preceding claim wherein the blocking current is reduced by up to 70%.

16. A method as claimed in any preceding claim wherein the blocking current is reduced by up to 50%.

17. A method as claimed in any preceding claim wherein the blocking current is reduced by up to 30%.

18. A method as claimed in any preceding claim wherein the frequency of the blocking current is from 7 to 20 Hz.

19. A method as claimed in any preceding claim wherein the blocking current is applied distal to the site where the stimulus pulses are applied.

20. A method as claimed in any of claims 11 to 18 wherein the blocking current is applied proximal to the stimulus pulses so that propagation back to the spinal cord is blocked.

21. A method as claimed in claim 20 wherein the blocking current is also applied distal to the stimulus pulses, whereby the proximal current is maintained to block the propagation of action potentials at that site and the distal current is reduced so that the propagation of action potentials remains blocked in some axons but is no longer blocked in pre-selected axons.

22. A method as claimed in any preceding claim wherein the frequency of the stimulus pulses is from 5 to 30 Hz.

23. A method as claimed in any of claims 11 to 21 wherein the frequency of the stimulus pulses is about 15 Hz.

24. A method as claimed in any preceding claim wherein the blocking and stimulus pulses are applied to the pudendal, S2, S3, tibial and / or a trigeminal nerve.

23. A method as claimed in any preceding claim further comprising the step of subsequently increasing the frequency of stimulus pulses to at least 30 Hz to induce cell death.

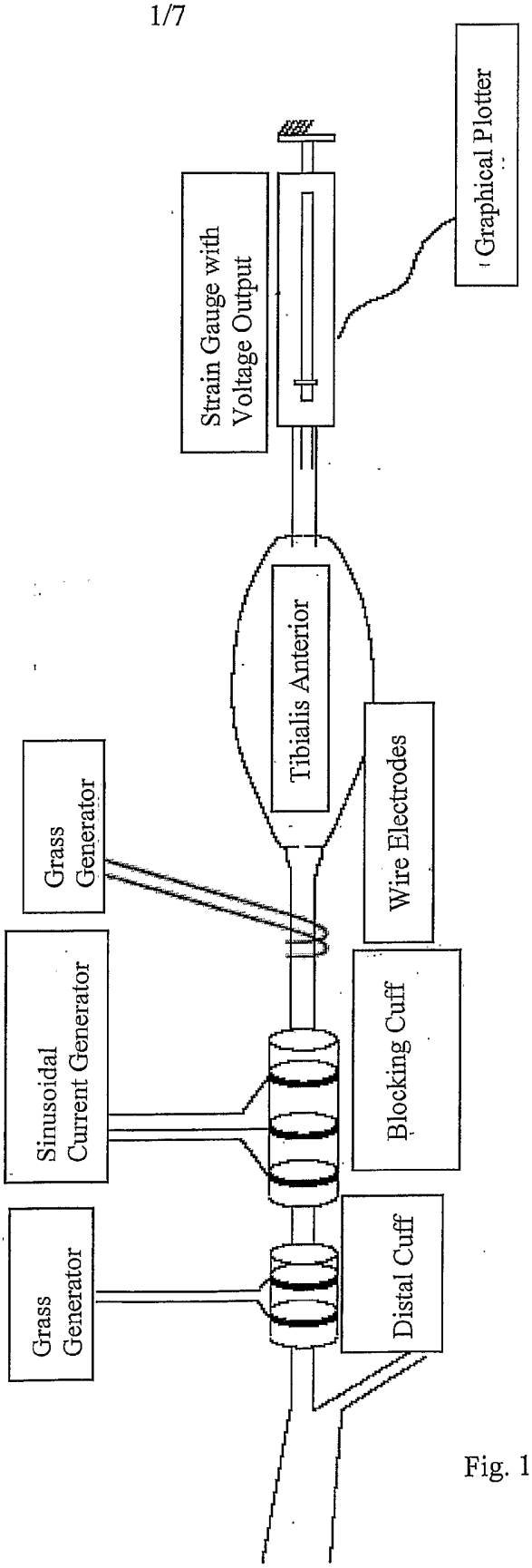
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Fig. 1

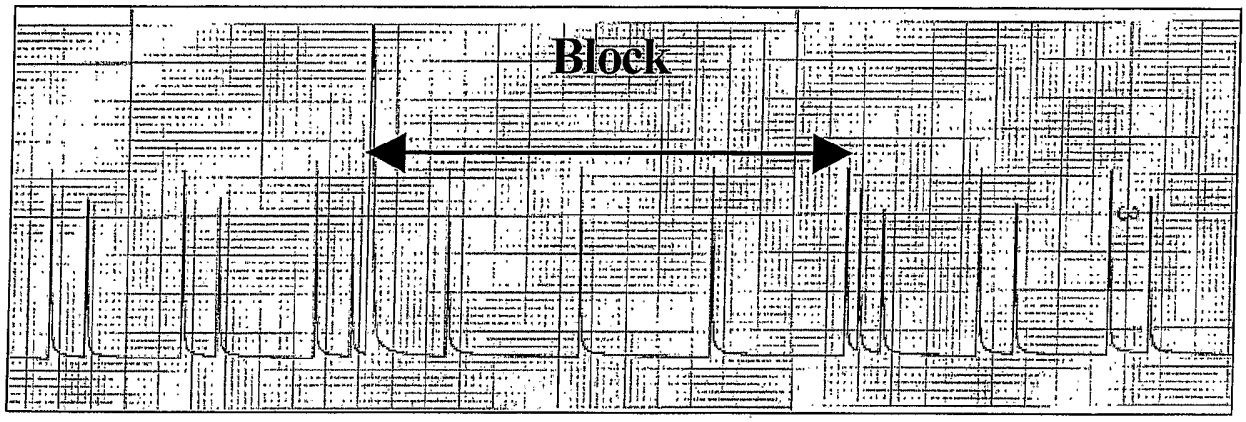

Fig. 2

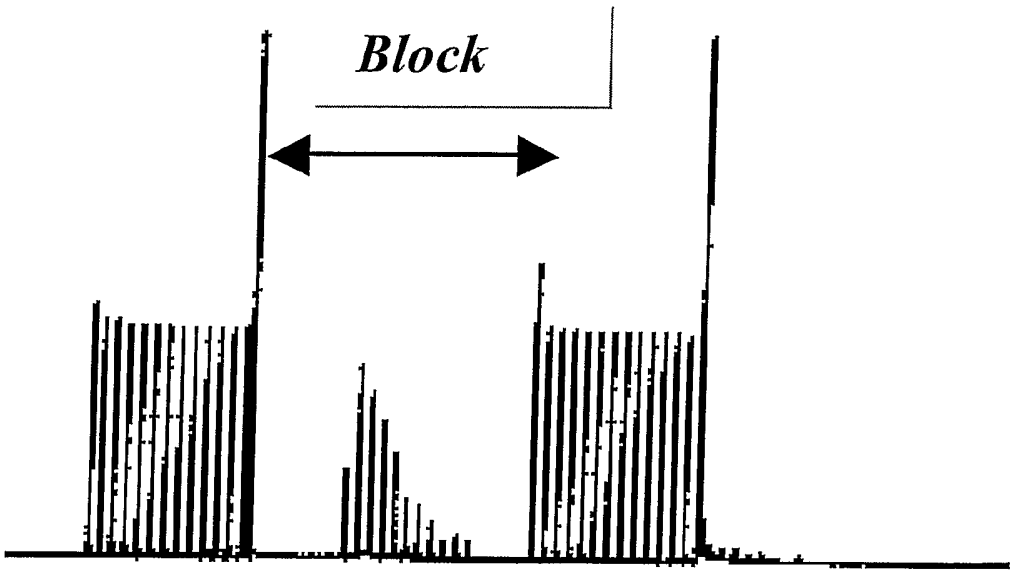

Fig. 3

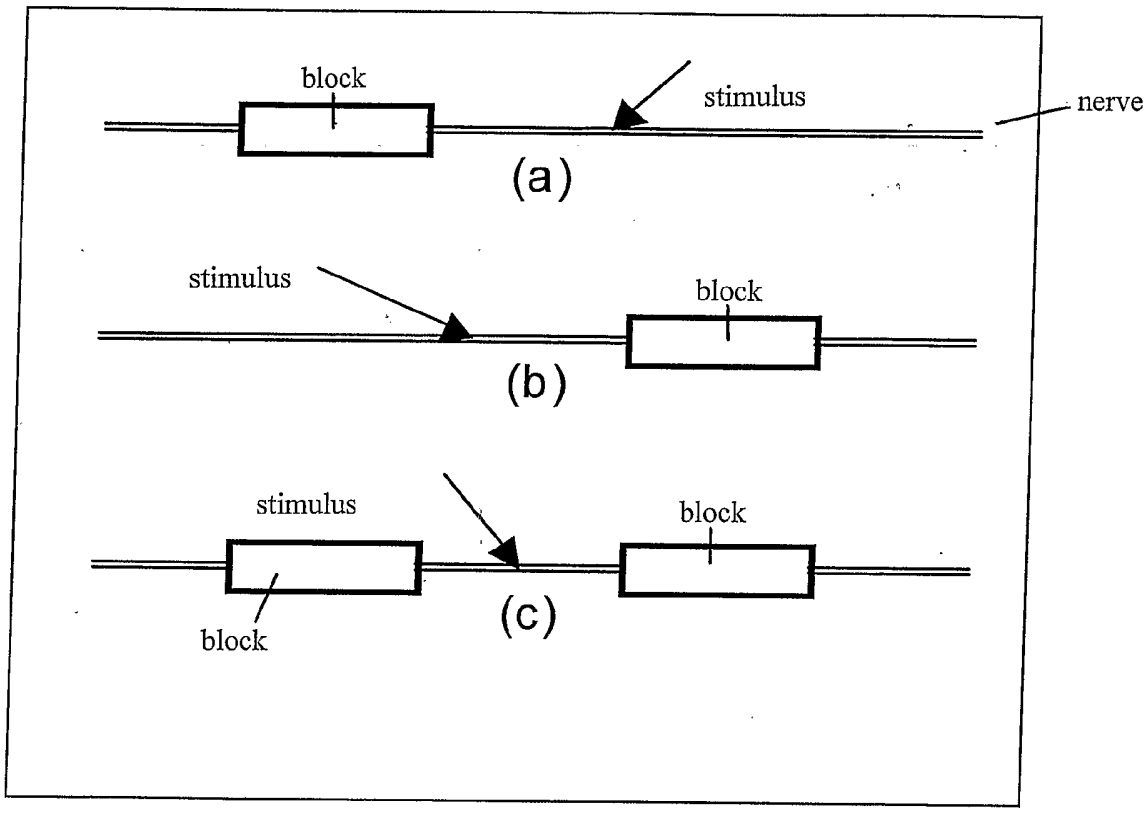
block
stimulus
nerve
(a)
stimulus
block
(b)
stimulus
block
block
(c)

Fig. 4

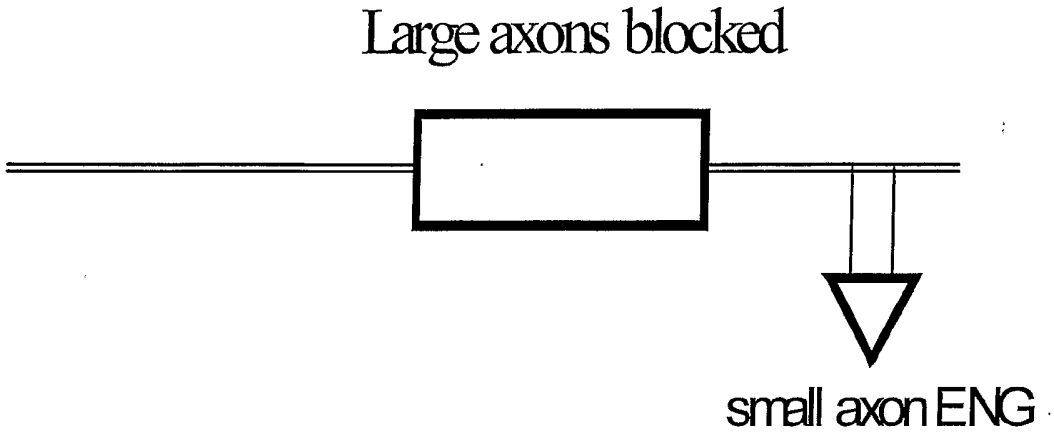

Fig. 5

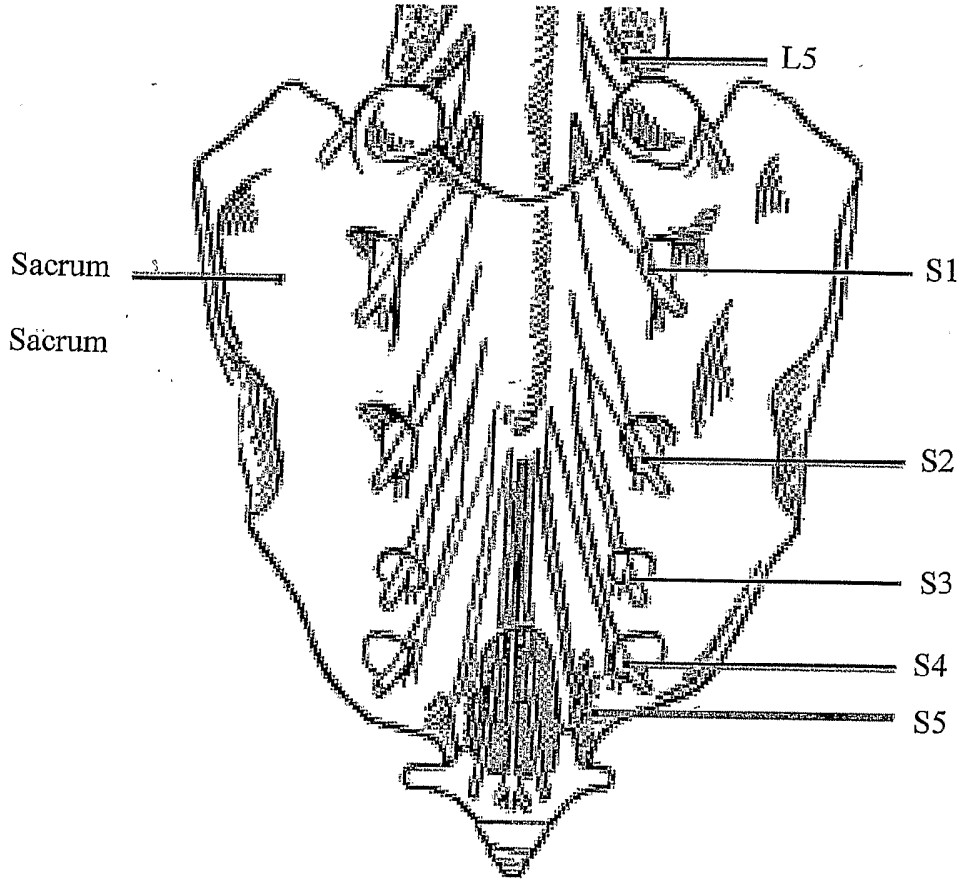

Fig. 6

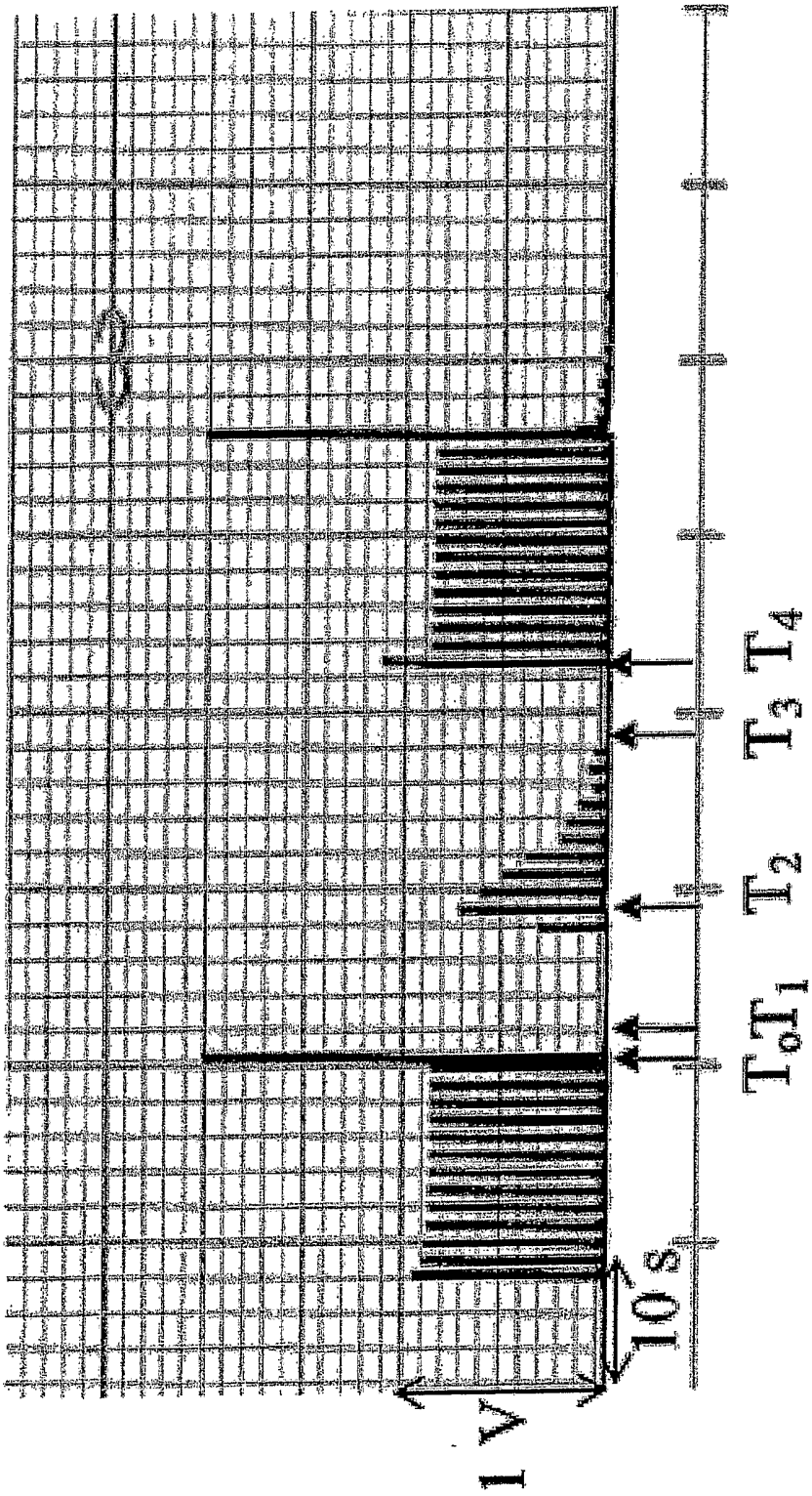

Fig. 7

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PC I/GB2005/001682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 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)
IPC 7 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, WPI Data

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 2002/055779 A1 (ANDREWS BRIAN J) 9 May 2002 (2002-05-09) paragraphs '0018!, '0049!; figures 3,6	1 2-10
Y	WO 2004/000416 A (ADVANCED BIONICS CORPORATION) 31 December 2003 (2003-12-31) paragraph '0069!	2-10
A	US 2003/004553 A1 (GRILL WARREN M ET AL) 2 January 2003 (2003-01-02) the whole document	1-10
A	EP 1 004 330 A (MEDTRONIC, INC) 31 May 2000 (2000-05-31) the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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
8 August 2005	16/08/2005

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	Edward, V

INTERNATIONAL SEARCH REPORT

ıtional application No.
PCT/GB2005/001682

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.: 11-23
because they relate to subject matter not required to be searched by this Authority, namely:

Due to the step of applying a stimulus electric pulse to a first site on a nerve, independent claim 11 relates to a method for treatment of the human or animal body by therapy (Rule 39.1(iv) PCT).

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

ormation on patent family members

Inter al Application No
PCT/GB2005/001682

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		EP 1004330 A1	31-05-2000