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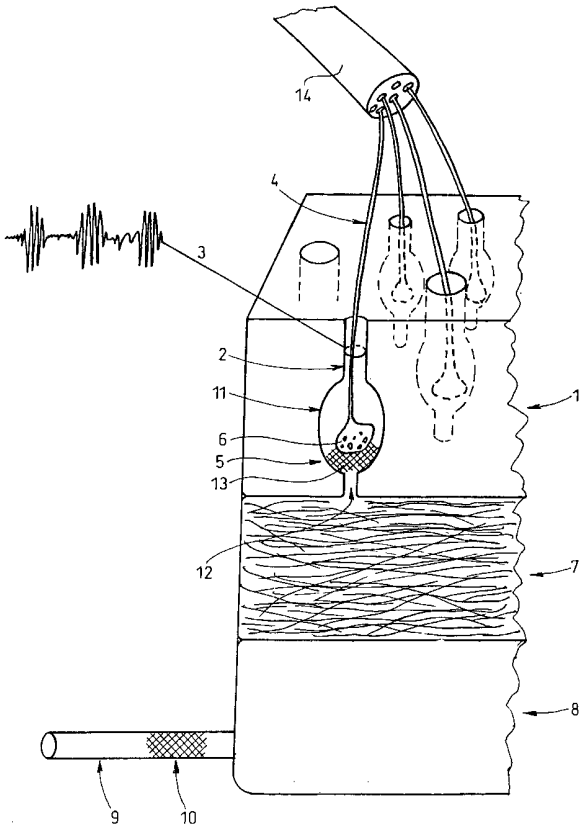
(54) Title: DEVICE FOR MEASURING THE ACTIVITY AND FOR STIMULATION OF NERVE FIBRES



(57) Abstract: The device has a body (1) provided with chambers (11) for growing intact or regenerating nerve fibres, wherein electrodes (3) are connected to said chambers (11) and a composition of extra cellular matrix materials containing molecules present on the surface of tactile cells or muscles as well as in the synaptic clefts are arranged at the bottom (5) of the chambers (11) and the surface of the body (1) and the chambers (11) is covered with chemical substrata allowing the adhesion and migration of axonal growth cones. The chambers (11) may open with tube-like neck-parts (2) on the surface of the body (1). Preferably, the chambers (11) are connected via channels (12) to a reservoir (8) containing compounds supplying the molecules needed for the long time survival and adequate physiological activity of the ingrown nerve fibres.

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DEVICE FOR MEASURING THE ACTIVITY AND FOR STIMULATION OF NERVE FIBRES

The present invention relates to a device which may be used for measuring, preferably simultaneous measuring the activity of individual peripheral motor nerve fibres or stimulation, preferably simultaneous stimulation of sensory nerve fibres and, moreover for simultaneous measuring and stimulation of a large number of individual peripheral motor and sensory nerve fibres, respectively, in people e.g. with lost limbs.

Experiments have been carried out since nineteen-thirties or forties in order to learn the electrical properties of neurons and the cell membrane and biochemical processes generating them. The first experiments were performed on giant axons of squids, but due to developing technical possibilities, by finer and finer methods, the measuring of smaller and smaller nerve fibres became possible. Basically three different techniques have been elaborated for measuring the activity of nerve fibres and/or for their stimulation:

In case of animals (usually monkeys) the nerve to be studied is exposed by surgical intervention, and after identifying an individual nerve fiber, mapping of its electrical properties is going on (Phillips et al. (1988): Spatial pattern representation and transformation in monkey somatosensory cortex, Proc. Natl. Acad. Sci., 85, 1317-1321).

In humans, the exposition of nerves by surgical methods is not admissible. Therefore, microelectrodes (needle electrodes) made of tungsten are inserted into the nerve by checking continuously until the tip of the electrode reaches a nerve fiber (Phillips et al. 1990: Representation of braille characters in human nerve fibres, Exp. Brain Res., 81, 589-592).

In the third approximation, prostheses have been designed for paralytic humans with intact neuromuscular system (e.g. after spinal cord injury) as well as for animals operated that way. These prostheses, implanted into the spinal

channel or around the spinal column, can not activate selectively the individual motor fibres, but a whole motor nerve, inducing thereby general contraction in a given muscle or muscle group. By using an optimal time sequence for the individual nerves, primitive sequences of movements (e.g. making some steps, changing the body position) can thus also be generated; see e.g. de Castro and Cliquet (2000): Artificial sensorimotor integration in spinal cord injured subjects through neuromuscular and electrotactile stimulation, Artif. Organs, 24, 710-717.

However, simultaneous measuring and/or stimulation of individual motor and sensory nerve fibres in a large number, respectively, are not solved up to now.

Neither is solved the problem how in people with lost limbs (accident, amputation) the artificial limbs could be moved by pulses originating from the brain in a "true to life" manner or, reversely, the results of sensing by artificial limbs, eyes (retina) or ears (Corti-organ) could be perceived by the brain.

Therefore, the object of the present invention is to provide a device which can be used for simultaneous, continuous and individual recording of the activity of many motoneurons as well as for generating action potential series (nerve pulses) on many individual sensory nerve fibres in the truncated nerves simultaneously.

Accordingly, the device according to the invention has a body provided with chambers for growing intact or regenerating nerve fibres, wherein electrodes are connected to said chambers and a composition of extra cellular matrix materials containing molecules present on the surface of tactile cells or muscles as well as in the synaptic clefts are arranged at the bottom of the chambers, and the surface of the body and the chambers is covered with chemical substrata allowing the adhesion and migration of axonal growth cones.

According to a preferred embodiment of the invention, the chambers are opening with tube-like neck-parts on the surface of the body and the electrodes are arranged around the neck-parts of the chambers.

According to further preferred embodiments of the invention, the chambers are connected to a reservoir containing compounds supplying the molecules needed for the long time survival and adequate physiological activity of the ingrown intact or regenerated nerve fibres and/or it is provided with a nutriment feeding tube, wherein channels are provided in the body between said reservoir or said nutriment tube and said chambers.

The device according to the invention may easily be manufactured, and it enables the measuring the activity of individual peripheral motor nerve fibres or stimulation of individual sensory nerve fibres and even for simultaneous measuring and stimulation of individual peripheral motor and sensory nerve fibres, respectively. This means that the measuring and stimulating device according to the invention may be used as an "artificial synapse", which enables sensing and moving with artificial limbs. In addition, vision and hearing can also be given back for many blind people and those of hearing defects, respectively, if in the artificial synapse the output of an artificial retina or sound detector is transformed to series of action potentials processable by the brain.

Further details of the invention will be described by referring to preferred embodiments, on the basis of the drawing included. In the drawing

Figure 1 is the cross-section of a possible embodiment of the device according to the invention and

Figure 2 shows a part of another embodiment.

In body 1 shown in Fig. 1, small chambers 11 are provided for the growing, regenerating nerve fibres. Each chamber 11 has a thin neck-part 2 and a ring-formed electrode 3 is arranged around each neck part 2. The surfaces of body 1 and the chambers 11 in the inside are covered by extra cellular chemical substrata (e.g. collagen, laminin, fibronectin, poly-L-Lysine etc.) allowing the adhesion and facilitating the migration of axonal growth cones of regenerating axons 4 protruding from a damaged (truncated) nerve 14. At the bottom 5 of

chambers 11 there is an extra cellular matrix material 13 of a composition corresponding to that of the synaptic clefts and the surface of tactile cells and muscles. In this matrix material 13 containing the molecules present in the synaptic clefts and on the surface of tactile cells and muscles, the growth cones of axons 4 are capable of forming "pseudo-synapses" in the absence of postsynaptic partners. The growing-in of sensory or motor axons 4 is going on in a way that the damaged nerve 14 is re-transected in close vicinity to its ending and the regenerating axons are than directly introduced into the chambers 11 of the body 1 according to the invention, wherein appropriate adhesion, migration, and nutrition of the axons 4 growing out of the nerve trunk are ensured. Regenerating axons 4 are not surrounded by thick myelin sheaths, thus there is no "isolation" between axons 4 and electrodes 3. Thus, ion flows and potential changes caused by them in the immediate neighbourhood of the cell membrane of any axon 4 can directly be measured. As only one axon 4 can penetrate into any chamber 11, the activity of a single motor nerve fiber becomes measurable, and the selective stimulation of a single sensory nerve fiber in each chamber 11 becomes also possible.

As body 1 comprises many chambers 11 and each of them is provided with electrode 3, the activity of all motor nerve fibres in a nerve can be measured simultaneously, and/or any sensory nerve fiber (or several, or even all) can be stimulated in distinct combinations as well.

Fig.1 also shows that a porous layer 7 is arranged on the surface of body 1 and chambers 11 are in connection with that via individual channels 12. Porous layer 7 can be of fibres or thin tubes of arbitrary spatial arrangement and pattern.

The third element of the device is a reservoir 8 which is in contact with layer 7 and, in this way, it is in connection with chambers 11. Reservoir 8 contains fluid nutriments and substrata (e.g. ions, carbohydrates, amino acids, growth factors, cell-adhesion molecules, chemoattractants, extracellular matrix components) dissolved therein. The fluid can reach axonal endings 6 through porous layer 7 and channels 12. On the other hand, reservoir 8 may reinforce the thin body 1, if needed, by providing mechanical stability to it. If the distance between the

fibres constituting the layer 7, or the diameter of tubes in case of a tube network falls into the order of magnitude of the pore size of bacterium filters, it also hinders the infection of axonal endings 6 grown into body 1. Continuous supply of the nutrient liquid to reservoir 8 can be ensured through a nutrient introduction tube 9, which may be provided with a further bacterium filter 10.

In another preferred embodiment - a part of which is shown in Figure 2 – the device according to the invention consists only of body 1, without any porous layer or inner reservoir. In this case, the nutrient liquid is introduced through a feeding tube 9 directly from an auxiliary tank (not shown) into the lower part of chambers 11. Preferably, a bacterium filter 10 is arranged in the nutrient feeding tube 9 connecting the auxiliary tank with chambers 11, in order to protect the device (and thus also the human or animal organism) from bacterial infection originating from the artificial nutrient solution from outside.

In special cases, e.g. when transferring the input from an artificial retina to implanted sensory neurons in the eyes, the device may not have any connection with any tank or reservoir, as the implanted sensory neurons may receive nutriments from humor aquosus secreted by the ciliary body.

The body 1 of the device should be made of tissue-compatible materials (e.g. of methyl-methacrylate) which do not activate the immune system, but assist the growing-in, adhesion, and physiological activity of regenerating sensory and/or motor nerve fibres. The thickness of body 1 may be several 10 μms.

The material of electrodes 3 preferably resists to the "corrosion" originating from living tissues, and it should not induce immune reactions. Therefore, the electrodes are preferably made of gold.

As motor nerve fibres are in contact with muscle tissue, meanwhile sensory nerve fibres usually with some tactile cells, the extra cellular matrix molecules assisting the adhesion of regenerating nerve fibres in the chambers of the device as well as the nutriment containing the factors needed for the physiological operation of the nerve fibres and the molecules necessary to substitute the degrading matrix material are necessarily different for the two nerve fiber types. These two different types of nutriments and extra cellular

matrix molecules can most easily be provided, if the motor and sensory nerve fibres are handled separately in two devices, or in two, independently operable compartments of the same device (they can be overlapping in space), and two reservoirs containing the different nutriments are applied.

Accordingly, two devices or a device with two compartments should preferably be built in under the skin for each nerve trunk. The motor and sensory nerve fibres can be introduced into the two devices/compartments separately, by means of different cell-adhesion factors and chemoattractants.

One of the possible applications of the device according to the invention enables "life-like" movements of artificial limbs of people with lost limbs (accident, amputation) by means of the accurate reading off the motor programme originating from the brain, but stopped at the end of the injured nerve trunk, by measuring individually the activity of many, even several thousands of motor nerve fibres simultaneously. At the same time, tactile information originating from an "artificial skin" can be transferred to sensory nerve fibres in the injured nerve trunk (simultaneous, but individual stimulation of many, even several thousands of sensory nerve fibres), which fibres mediate the tactile information to the cerebral cortex (via several synapses), where pattern and shape recognition and their perception occur.

A further application of the device according to the invention is transferring visual signals from an artificial retina or sound signals from a sound detector to the brain of blind people or people with a hearing defect. In this case the device should operate only in one mode, as both the acoustic nerve and the optic nerve consist only of sensory nerve fibres, and do not contain motor nerve fibres. In case of such people it is therefore enough to implant only one of the device either into the eye (replacing the vitreous body with the device), or into the inner ear of the patients.

Claims

1. Device for measuring the activity of one or, simultaneously, more individual peripheral motor nerve fibres and/or for stimulation of one or, simultaneously, more individual sensory nerve fibres, **characterised in that** it has a body (1) provided with chambers (11) for growing intact or regenerating nerve fibres, wherein electrodes (3) are connected to said chambers (11) and a composition of extra cellular matrix materials containing molecules present on the surface of tactile cells or muscles as well as in the synaptic clefts are arranged at the bottom (5) of the chambers (11), and the surface of the body (1) and the chambers (11) is covered with chemical substrata allowing the adhesion and migration of axonal growth cones.

2. Device according to claim 1, **characterised in that** the chambers (11) are opening with tube-like neck-parts (2) on the surface of the body (1).

3. Device according to claim 2, **characterised in that** the electrodes (3) are arranged around the neck-parts (2) of the chambers (11).

4. Device according to any of claims 1 to 3, **characterised in that** the chambers (11) are connected to a reservoir (8) containing compounds supplying the molecules needed for the long time survival and adequate physiological activity of the ingrown intact or regenerated nerve fibres.

5. Device according to any of claims 1 to 4, **characterised in that** it is provided with a nutriment feeding tube (9).

6. Device according to claim 4 or 5, **characterised in that** channels (12) are provided in the body (1) between said reservoir (8) or said nutriment tube (9) and said chambers (11).

7. Device according to any of claims 4 to 6, **characterised in that** a porous layer (7) is arranged between reservoir (8) and body (1).

8. Device according to claim 7, **characterised in that** the porous layer (7) is a bacterium filter.

9. Device according to claim 8, **characterised in that** the porous layer (7) consists of fibres with distances from each other, or tubes of diameters and with distances from each other falling into the order of magnitude of bacterium filters.

10. Device according to claim 5, **characterised in that** a bacterium filter (10) is in the feeding tube (9).

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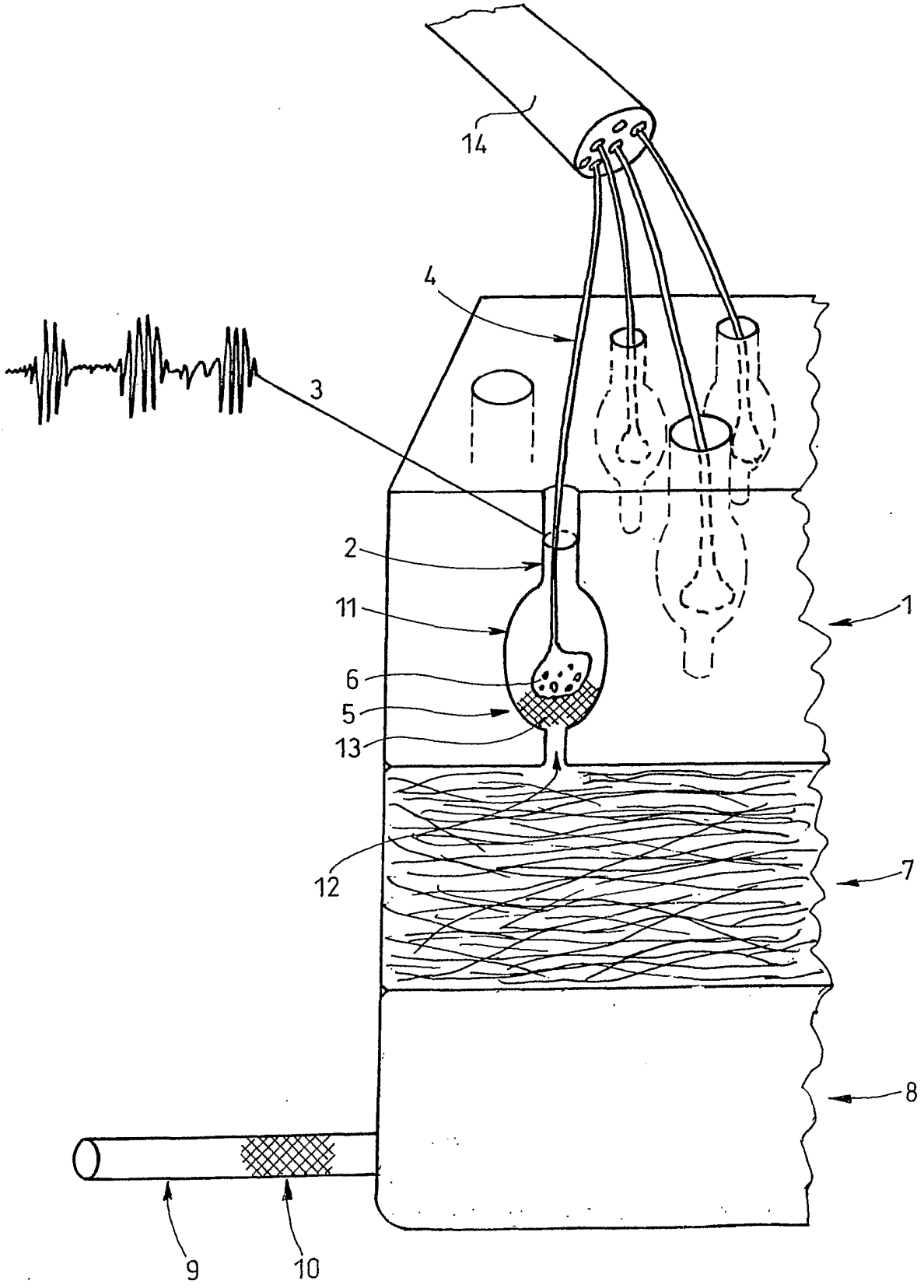

Fig. 1

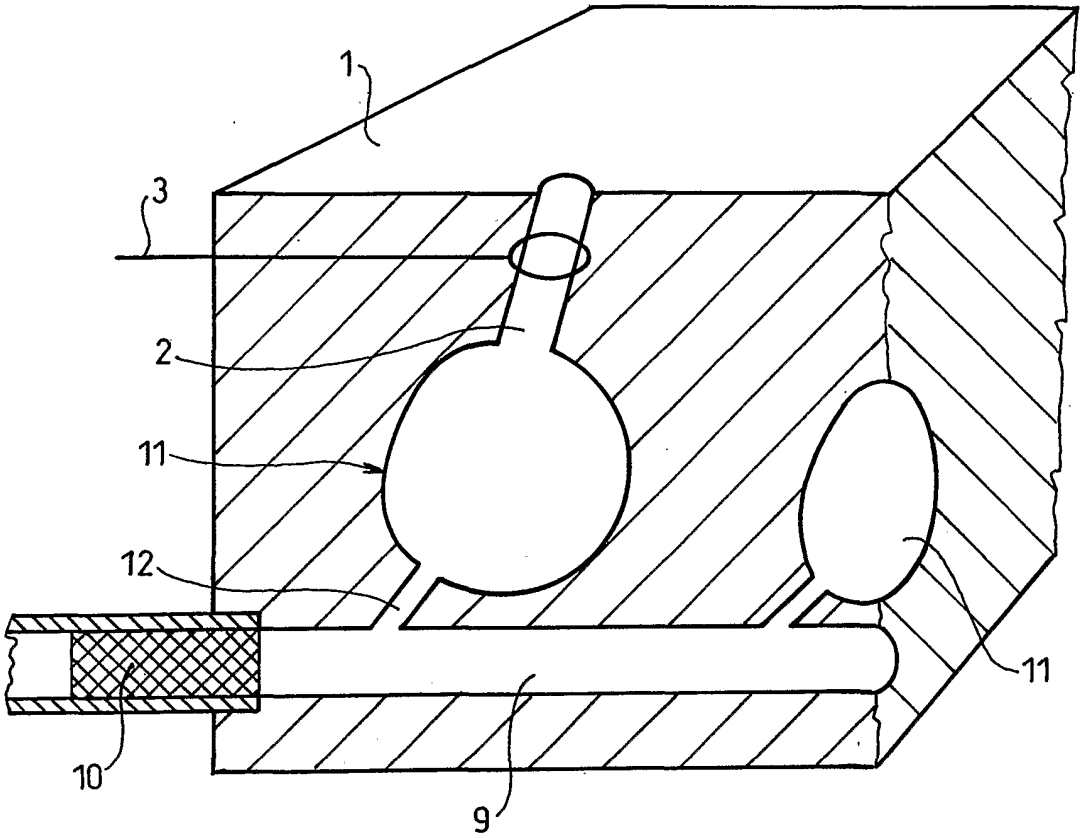

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 02/00009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/04 A61N1/05

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 A61B 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.
A	US 3 955 560 A (R. B. STEIN ET AL) 11 May 1976 (1976-05-11) column 1, line 34 -column 2, line 20 column 3, line 23 - line 45	1-10
A	EP 0 306 187 A (PFIZER HOSPITAL PRODUCTS GROUP, INC.) 8 March 1989 (1989-03-08) column 2, line 43 -column 6, line 47	1-10
A	EP 0 261 833 A (AMERICAN BIOINTERFACE CORPORATION) 30 March 1988 (1988-03-30) column 1, line 1 -column 4, line 30	1-10
A	US 4 778 467 A (L. J. STENSAAS ET AL) 18 October 1988 (1988-10-18) abstract	1-10

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

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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