Title: MICROCURRENT DEVICE AND THERAPY

Abstract: The present invention discloses devices and methods for the alleviation of medical fatigue. With these methods and devices, microcurrents with a preset current and frequency are delivered, and are used for the treatment of an individual suffering from fatigue.

Figure 6
MICROCURRENT DEVICE AND THERAPY

FIELD OF THE INVENTION

The invention relates to methods and tools for treating fatigue, more particularly fatigue associated with disease and therapeutic regimes. More particularly the invention relates to methods and tools based on the application of specific microcurrents.

BACKGROUND

Electric current has been used for decades to alleviate or cure different disorders. Most applications of electrotherapy focus on wound healing and on the stimulation of nerves. The medical use of electric currents in wound healing is reviewed for example in Ojingwa et al. (2002) Prog. Dermatol. 36, 1-12. Nerve stimulation can be performed by insertion of needle electrodes in the skin. Nerve stimulation through unbroken skin is performed using so-called Transcutaneous Electrical Nerve Stimulation (TENS) wherein two or more electrodes are placed in contact with the skin. TENS generally uses currents in the milliAmpere range. A typical battery-operated TENS unit consists of a pulse generator, a transformer, frequency and intensity controls, and a number of electrodes. US6,445,955 describes miniaturized, wireless TENS devices with remote controlled configurations with pre-programmable waveform modes and a detachable electrode-battery assembly.

Another electrotherapy, Microcurrent Electrical Neuromuscular Stimulation (MENS) uses electrodes placed on the skin to apply currents below 1000 microAmpere to nerves. Applications of MENS include treatments for age-related macular degeneration, wound healing, tendon repair, and ruptured ligament recovery.

Microcurrent electrotherapy (MET) is often used to alleviate pain, sleeping dysfunction and depression. Such devices are for example available from Electromedical Products (Mineral Wells, TX, USA). One of these devices (Alpha Stim 100) generates a current between 10 to 600 µA, which is continuously adjustable. The device works with a 9 Volt battery. The apparatus
can apply a frequency of 0.5, 1.5 or 100 Hz for e.g. 10, 20 or 60 minutes. The waves, which are generated, are bipolar asymmetric rectangular waves with a 50% duty cycle and a zero net current. A study on the use of such device for the treatment of fibromyalgia with preset values of a frequency of 0.5 Hz with daily treatments of one hour is published in Lichtbroun et al. (2001) J. Clin. Rheumatol. 7, 72-78.

The use of electric currents to stimulate ATP production, as well as to enhance protein synthesis, was initially described in Cheng et al. (1982) Clin. Orthop. Relat. Res. 171, 264-272. US6,275,735 refers to the same mode of action in the treatment of macular degeneration, and suggests that restoring the ATP level with microcurrent can reverse the phenomenon of dying retinal cells. Apart from this disorder also the treatment of retinitis pigmentosa, sciatica, pain disorders, fatigue disorders, myofascial pain syndrome, fibromyalgia, neuralgia, and cancer is suggested. The device described in US6,275,735 allows the generation of different types of unipolar, bipolar and bi-phasic waveforms. Frequencies in the range of 0 to 400 Hz are mentioned with embodiments referring to rectangular waves of 6 Hz upon application of 6 V.

US 5,658,322 describes a device which generates square waves having a 50 % duty cycle, for the treatment of a wide range of disorders including fatigue. While no clinical data are presented, suitable frequencies suggested for the treatment of fatigue which range from 2720 to 20 Hz and include 2720, 1800, 428, 660, 465, 125, 95, 72, 27.5, 20 and 2309 Hz.

**SUMMARY OF THE INVENTION**

The present invention provides devices and methods for treating fatigue, more particularly medical fatigue in a patient in need thereof.

In a first aspect, the invention provides electrotherapy devices configured so as to generate a pulsed current suitable for ensuring alleviation of fatigue when applied to the body. More particular embodiments of the invention relate to electrotherapy devices wherein the current is preset at values particularly suitable for the treatment of fatigue, i.e. the device will ensure that the current is ensured only with the pre-determined features. In particular embodiments
devices (1) are provided comprising a power supply (60), a microprocessor (32), a waveform generator (40) and a set of two electrodes for application to the skin (50), configured so as to generate a pulsed current of between 100 and 900 µA with a fixed frequency of between 50 and 150 Hz in the electrodes.

More particularly, the devices are configured with a current preset at one value between 100 and 900 µA, more particularly between 300 and 600 µA, most particularly about 430 or 450 µA.

In alternative embodiments, devices are provided wherein the current can be manipulated to discrete values between 100 and 900 µA, more particularly between 300 and 600 µA, most particularly including about 430 or 450 µA.

Additionally or alternatively, devices are provided wherein the frequency of the current is preset at a value of between 80 and 120 Hz, more particularly between 90 and 110 Hz, most particularly about 100 Hz.

According to particular embodiments, devices are provided wherein the waveform generator (40) generates a monophasic wave, more particularly a monophasic rectangular wave, most particularly the waveform generator generates a monophasic rectangular wave with decay.

In further particular embodiments of the invention, the current generated by devices described herein is characterized in that it has a pulse width of between 600 and 2000 µseconds, more particularly between 900 and 1700 µseconds, especially between 1100 and 1500 µseconds. In most particular embodiments, devices according to the invention are provided wherein the current is applied with a pulse width of 1300 µseconds.

In particular embodiments, devices are provided wherein the time-period of application of the current can be regulated with a timer. Most particularly, devices are provided comprising a timer for the current adjustable to discrete time points between 10 and 120 minutes, most particularly said time points are 30 and 60 minutes.

The electrodes envisaged in devices of the present invention are suitable for application to the skin, most particularly on the body surface (torso, arms or legs). Most particularly, electrodes are envisaged which are applicable to a flat
skin surface, i.e. electrodes in the form of patches having at least 2 cm², most particularly about 10 cm² in size.

In devices according to the invention, a current is generated between at least one set of two electrodes. In particular embodiments, more than one set of electrodes is provided. Accordingly, particular embodiments of the invention encompass devices comprising two channels with two microprocessors (32 and 132), two waveform generators (40) and (140) and two sets of electrodes (50) and (150) for application to the skin. More particularly, devices are provided which comprise two channels with a single microprocessor (32), two waveform generators (40) and (140) and two set of electrodes (50) and (150) for application to the skin.

Different methods of control are envisaged for manipulating devices described herein. In particular embodiments devices are provided which comprise a capacitive keyboard mechanism with a transparent front plate. In further particular embodiments devices are provided wherein input signals are sent to the microprocessor of the device via remote control.

A further aspect of the invention provides methods of treating fatigue, more particularly medical fatigue in a person in need thereof, which comprise applying a pulsed current to the skin surface of said person, the current being particularly suited for treating fatigue.

Methods of the present invention are particularly suitable for the treatment of fatigue which occurs as a symptom of a disorder selected from the group consisting of poliomyelitis, fibromyalgia, multiple sclerosis, Parkinson's disorder, chronic fatigue syndrome and cancer.

Methods of the present invention comprise applying electrodes to the skin surface of the body of said person, most particularly on the torso, arms or legs (including hands and feet). Most particularly the electrodes are applied on an area of flat skin surface using electrodes in the form of patches of at least 2 cm²; methods of the invention further comprise delivering to the skin surface a pulsed current particularly suitable for treating fatigue. More particularly, in methods of the invention a pulsed current of between 100 and 900 µA with a
preset frequency of between 50 and 150 Hz is applied. In further particular embodiments, the current is characterized in that it is applied with a frequency preset at a value of between 80-120 Hz, more particularly between 90-110 Hz, most particularly with a frequency preset at a value of 100 Hz and/or in that the current is applied with an amplitude preset at a value between 300 and 600 µA, preferably between 400 and 500 µA, most particularly preset at a value of about 430 or 450 µA.

Alternatively, methods are provided wherein the current is, depending on the patient and/or the position of the electrodes, manipulated to a discrete value between 100 and 900 µA, more particularly between 300 and 600 µA.

In further particular embodiments, methods are provided which are further characterized in that the current is applied with a pulse width of between 600 and 2000 µseconds, more particularly with a pulse width of between 900 and 1700, especially between 1100 and 1500 µseconds. Particular embodiments of the methods of the invention involve the application of a current with a pulse width of 1300 µseconds.

In particular embodiments of methods of the present invention, the current applied to the skin surface is further characterized in that the current is a monophasic current and/or the current has a rectangular waveform and/or the current is a current with decay. Most particularly, the current is characterized by all of these features.

Optimal results of methods of the present invention are envisaged application times of the current of one or more periods of between 10 and 120 minutes. Most particularly, it is envisaged that the current is applied for one or more periods of 30 or 60 minutes. In particular embodiments methods are envisaged wherein a current characterized by one or more of the features described herein is applied at least once a week during a period of at least 6 weeks.

Methods of the invention can be ensured by suitable electrotherapy devices capable of ensuring one or more, most particularly all of the features envisaged to ensure a suitable current for the treatment of fatigue. In particular embodiments however, methods of the present invention are ensured by
making use of an electrotherapy device comprising one or more sets of electrodes, such as the devices described herein, wherein the values of the device are pre-set (current, frequency etc.) to ensure optimal treatment of fatigue upon application of the electrodes. This ensures easy handling and optimal result.

**Brief description of the Figures**

**Figure 1**: shows a schematic overview of a single channel microcurrent device according to an embodiment of the invention; (22) = on/off switch, (26) = input, (27) = electrode port, (32) = microprocessor, (34) = optional LEDs, (36) = optional beeper, (40) = waveform generator, (50) = electrodes, (60) = power supply.

**Figures 2a and 2b**: show a schematic overview of a dual channel microcurrent device according to particular embodiments of the invention: (22) = on/off switch, (26) = input, (27/1 27) = electrode port, (30/1 30) = channels, (32/1 32) = microprocessor, (34/1 34) = optional LEDs, (36/1 36) = optional beeper, (40/1 40) = waveform generator, (50/1 50) = electrodes, (60) = power supply.

**Figure 3**: shows a schematic overview of a waveform generator of a microcurrent device according to an embodiment of the invention: (27) = electrode port, (32) = microprocessor, (36) = optional beeper, (41 ) = voltage multiplier, (42) = optional current modulator, (43) = integrator, (44) = switched bridge.

**Figure 4**: shows a schematic overview of a remotely controlled microcurrent device according to particular embodiments of the invention: (22) = on/off switch, (26) = input, (27) = electrode port, (32a/32b) = microprocessor, (34) = optional LEDs, (36) = optional beeper, (40) = waveform generator, (50) = electrodes, (60/60b) = power supply.
**Figure 5:** shows a schematic overview of the operational controls of a microcurrent device according to a particular embodiment of the invention: (A) = indicator low battery, (B) = indicator timer, (C) = power indicator, (D) = switches channels 1 and 2, (E) = disconnect alarm channels 1 and 2, (F) = on/off switch.

**Figure 6:** shows the results for 'total fatigue score' of microcurrent therapy according to an embodiment of the invention. The 'total fatigue' score was monitored over a period of 12 weeks on a group of 22 patients with post-poliomyelitis syndrome.

**Figure 7:** shows the results for 'interference with life (fatigue) score' of microcurrent therapy according to an embodiment of the invention. The 'interference with life (fatigue)' score was monitored over a period of 12 weeks on a group of 22 patients with post-poliomyelitis syndrome.

**Figure 8:** shows the results for 'endurance' of microcurrent therapy according to an embodiment of the invention. 'Endurance' was monitored over a period of 12 weeks on a group of 22 patients with post-poliomyelitis syndrome.

**Figure 9:** shows the results for 'total pain score' of microcurrent therapy according to an embodiment of the invention. The 'total pain score' was monitored over a period of 12 weeks on a group of 22 patients with post-poliomyelitis syndrome.

**Figure 10:** shows the results for 'interference with life (pain) score' of microcurrent therapy according to an embodiment of the invention. The 'interference with life (pain)' was monitored over a period of 12 weeks on a group of 22 patients with post-poliomyelitis syndrome.

**Figures 11 a, b and c:** show the results for 'total fatigue score' (a), 'interference with life (fatigue) score' (b) and 'endurance' (c) of microcurrent therapy according to an embodiment of the invention. The 'total fatigue' score, the 'interference with life (fatigue)' score and 'endurance' were monitored over an additional period of 12 weeks (total 24 weeks) on a group of 11 patients with post-poliomyelitis syndrome.
DETAILED DESCRIPTION OF THE INVENTION

The term "fatigue" as used herein relates to a feeling of weariness, tiredness or lack of energy. Fatigue has two known forms; one manifests as a local, muscle-specific incapacity to do work, and the other manifests as an overall, bodily or systemic, sense of energy deprivation.

The term "medical fatigue" as used herein relates to a feeling of weariness, tiredness or lack of energy which is correlated with a medical disorder or syndrome or which is correlated with the treatment of such a disorder or syndrome. Medical fatigue is notoriously difficult to treat and usually not alleviated by rest.

"Microcurrent" in the present invention relates to current below 1 milli-Ampere (mA) and is expressed in micro-Amperes (µA).

The present invention is based on the observation that mitochondrial ATP production is maximal at a current between 100 and 900 µA with a maximum at about 400-500 µA. Upon testing in the clinic it was observed that patient fatigue can be effectively alleviated by application of such a specific microcurrent to the skin of the patient. More particularly it was found that diseases and conditions characterized by mitochondrial exhaustion can be alleviated by applying a specific microcurrent to patients suffering from these diseases or conditions.

The present invention thus relates to methods wherein a therapeutic effect is obtained by influencing metabolic processes at the cellular level. Indeed the methods and tools of the present invention aim to create a current which promotes the dissociation of water into hydroxyl ions and protons. The protons which are generated upon application of the current have an influence on the cellular ATP production which comprises the transport of protons over the mitochondrial membrane. The chosen conditions of the methods and tools of the invention are expected to have no or little effect on the stimulation of nerves (see Mortimer (1981) in "American Handbook of Physiology", Vol. II, Section 1.1 55 - 187).

The methods of the invention are particularly suited for the alleviation and treatment of diseases characterized by mitochondrial exhaustion or
insufficiency. While many diseases challenge mitochondrial activity, prolonged challenge of the mitochondria can lead to disease. Mitochondrial exhaustion presents itself at the clinical level as medical fatigue. Medical fatigue often manifests itself as a chronic (meaning of six months or more duration) disorder. Typical diseases characterized by medical fatigue are fibromyalgia and chronic fatigue syndrome and medical fatigue is also commonly experienced by polio survivors. Further examples of disorders often associated with fatigue include but are not limited to Multiple Sclerosis, Parkinson's disorder, cancer and post-poliomyelitis syndrome. More generally, the methods and tools of the present invention are suitable for the treatment or alleviation of any disorder or syndrome characterized by mitochondrial insufficiency or exhaustion. Examples of such disorders include hereditary disorders which affect mitochondrial functioning, such as, but not limited to Progressive External Ophthalmoplegia (PEO), Diabetes Mellitus and Deafness (DAD), Leber Hereditary Optic Neuropathy (LHON), Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-Like Syndrome (MELAS), Myoclonic Epilepsy and Ragged-Red Fibers (MERRF), Leigh Syndrome, Neuropathy, Ataxia, Retinitis Pigmentosa, and Ptosis (NARP), Kearns-Sayre syndrome (KSS) and Myoneurogenic gastrointestinal encephalopathy (MNGIE). More particularly, the present invention alleviates or prevents the fatigue encountered by individuals suffering from one of the above conditions or disorders after a short intense physical effort or a longer physical effort.

Methods for determining fatigue are described in the art. More particularly, use can be made of the "Brief Fatigue Inventory" (BFI; Hann et al (1998) Quality of Life Research 7, 301 - 10).

In one aspect, the present invention provides methods for treating or alleviating fatigue, most particularly medical fatigue, in a person comprising the steps of applying electrodes to the skin surface on a part of the body of this person and delivering to the skin surface a micro-electrical current, more particularly a micro-electrical current characterized by a particular amperage, frequency, pulse-width and waveform. Accordingly, the present invention relates
to methods which involve applying, to a living body, more particularly to the skin thereof, a microcurrent with specified a pulsed monophasic or biphasic current between 100 and 900 µA with a preset frequency between 50 and 150 Hz. In particular embodiments the applied current is between 200 and 700 µA, more particularly between 300 and 600 µA, especially between 350 and 550 µA or between 300 and 500 µA, most particularly about 430 or 450 µA. In particular embodiments the current is applied with a preset frequency between 80 to 120 Hz, most particularly between 90 to 110 Hz. In further particular embodiments of these methods, the frequency of the current is preset at a value of about 100 Hz.

The applied current is generally monophasic (direct). The waveform of the applied current is generally rectangular, and typically rectangular with decay. The applied waves are typically constant in shape and/or pulse width.

In particular embodiments the pulsed current is a monophasic rectangular current of about 400 µA. In particular embodiments of methods of the invention, the current is applied with a fixed pulse width of between 600 and 2000 µseconds, more particularly between 900 and 1700 µseconds, especially between 1100 and 1500 µseconds, most particularly about 1300 µseconds.

In methods according to the invention it is envisaged that the current is applied for a timer period between 10 and 120 minutes, more particularly between 20 and 90 minutes (e.g., for a period of 30 or 60 minutes). In particular embodiments of these methods, the current is applied at least once a week during a period of at least 6 weeks.

Settings as applied in methods of the invention typically result in an energy per pulse of maximally 35 µJoule (e.g., about 30 µJoule).

In methods according to the invention, a microcurrent is typically applied to the skin. The size of the load will depend on the nature of the skin and vary between 500 Ohm (for open wet skin) and 200 000 Ohm (for very dry skin). However, when applied to normal skin, as is the object in particular embodiments of the invention, the load is typically 1000 to 2000 Ohm. In particular embodiments, the maximal load is envisaged to be about 68000 Ohm.
The voltage obtained in the methods of the invention will accordingly be dependent on the current applied and the load of the skin. In particular embodiments of methods of the invention, a voltage of between 1 and 33 V, e.g., about 800 miliV, is obtained.

The methods of the invention comprise administering a micro-electrical current to all or part of the body. According to particular embodiments, methods of the present invention comprise applying the current to the whole body. According to further embodiments, methods of the invention encompass positioning two or more electrodes generating the current according to the methods of the invention simultaneously or sequentially to one or more, more particularly two or more different parts of the body. The electrodes can be placed at different locations on the user's body (i.e. excluding the head) including but not limited to the neck, wrist, shoulder, the elbow or forearm, the hand or a finger, scapula, abdomen, lower back, knee, hip, buttocks, thigh, ankle, or foot. Most particularly, the location of the electrode couple is selected such that the current has maximal coverage of the body. Most particularly, the electrodes are placed on an essentially flat continuous skin surface of at least 2 cm².

Particular embodiments of methods of the present invention have the advantage that the applied microcurrent is not felt by the user and has no side effects such as skin irritation. Moreover, methods of the present invention are not invasive. In particular embodiments of methods and devices of the present invention, electrodes can easily be applied on the skin and require no skills of the patient (contrary to e.g. subcutaneous electrodes).

A further aspect of the present invention provides microcurrent devices for use in methods of the present invention, more particularly for the treatment and alleviation of fatigue, more particularly medical fatigue. The microcurrent devices generally comprise a power source, elements for generating waves with a defined shape, frequency and amplitude.
This aspect of the present invention provides electrotherapy devices, such as illustrated by the Figures herein as (1) and (10) comprising a power supply (60) at least one waveform generator (40) and at least two electrodes for application to the skin (50), wherein a pulsed current between 100 and 900 µA with a preset frequency between 50 and 150 Hz is generated in the electrodes.

In particular embodiments the current is between 200 and 700 µA, between 300 and 600 µA, most particularly between 400 and 500 µA. The current can be direct or alternating. Typically the pulsed current is a direct current. Accordingly, in particular embodiments the pulsed current is about 400 µA. Accordingly, in particular embodiments devices are provided whereby the current can be manipulated only within the ranges provided above, more particularly the current can be manipulated only to discrete, preset values within the ranges described above, most particularly is preset at a value within the ranges provided above.

In particular embodiments of the invention devices are provided whereby the generated current has a fixed frequency of between 80 and 120 Hz, more particularly between 90 and 110 Hz, such as about 100 Hz. Accordingly, in particular embodiments devices are provided whereby the frequency of the current can be manipulated only within the ranges provided above, more particularly whereby the frequency is can be manipulated only to discrete, preset values within the ranges described above, most particularly the frequency is preset at one value within the ranges provided above.

Accordingly, in particular embodiments of the devices of the present invention, the settings for the current and/or the frequency are limited to a number of fixed values, which can be selected by the user. Typically, the frequency and the current are also preset to fixed values in the device and can not be adjusted by the user. In particular embodiments both the frequency and the current are preset to one fixed value.

According to most particular embodiments, this fixed frequency is 100 Hz. According to further particular embodiments, devices are provided comprising two waveform generators generating a monophasic rectangular wave, optionally with decay. According to particular embodiments of devices
according to the invention, the current is fixed such that it is applied with a fixed pulse width of between 600 and 2000 µseconds, more particularly between 900 and 1700 µseconds, especially between 1100 and 1500 µseconds, for example 1300 µseconds.

In particular embodiments of devices of the present invention the pulse width and waveform of the current are preset in the device at fixed values and can not be adjusted by the user.

Upon application of the above mentioned settings, namely a frequency between 50 and 150 Hz and a pulse between 600 and 2000 µseconds, a duty cycle between at least 3,0 % and at most 30 % is obtained. Accordingly, the duty cycle can be increased by increasing the frequency and or increasing the pulse width. In a particular embodiments wherein a current with a pulse width of 1300 µseconds is applied at a frequency of 100 Hz, a duty cycle of 13 % is obtained.

The above parameters of the device define the voltage which has to be provided to obtain the required current through the body of the patient, whereas the skin of the treated person will influence the resistance encountered by the current. Devices of the invention are typically configured such that a maximal voltage of about 33 V (e.g., typically an actual voltage of about 800 miliV) can be applied through the electrodes at a load of 1000 to 68000 Ohm (typically about 2000 Ohm).

In particular embodiments of the devices of the invention, a timer is provided which ensures the application of the current in the electrodes for a predetermined period. Typically, the timer can be used to preset the current at one or more discrete time limits between 10 and 120 minutes. In particular embodiments the timer can be set at a 30 and a 60 minute treatment period, whereby the device switches off automatically at the end of the indicated period.

Devices provided in accordance with the present invention typically include a housing, two or more electrodes attached to the housing, an electronics module located within the housing and comprise an electrical circuit which provides a pre-programmed monophasic sequence of pulses to the
electrodes, a means to regulate the intensity of the current, a means to set the time period of treatment and a means for supplying power to the electronics module. According to particular embodiments, devices according to the invention comprise two channels with two waveform generators (40) and (140) and two sets of electrodes ((50) and (150)) for application to the skin.

The means for supplying power are typically integrated within the housing. The device optionally displays readout means such as LCDs and/or lights (e.g. light emitting diodes LEDs), or audible signals to indicate time of application, intensity of the current, status of the power supply, and functioning of the device (on/off). Microcurrent devices of the present invention can have one or more channels. In a particular embodiment, two channels are provided which allow the treatment of two sites of the body at the same time.

Figure 1 shows the basic electronic operating configuration of a device with one channel, comprising a power supply (60), an on/off switch (22), an electrode port (27), a microprocessor (32), optional LEDs (34), an optional beeper (36), and a waveform generator (40).

Figures 2a and 2b shows the basic electronic operating configuration of a device with two channels (30) and (130). Both channels ((30) and (130)) either include (Figure 2a) or share (Figure 2b) a micro-processor (32 and 132), both channels include an electrode port ((27) and (127)), optional LEDs ((34) and (134)), an optional beeper ((36) and (136)), and a waveform generator ((40) and (140)). Connected to the device (10) are an on/off switch (22), a number of input switches (collectively 26), a first and second set of (two) electrodes ((50) and (150)), and a power supply (60). The electrodes (50) and (150) can be of any type known in the art of microcurrent electrotherapy.

Devices of the present invention make use of electrode couples. Accordingly, devices typically comprise or are configured to be used with 2, 4, 6, 8 or more electrodes.

As illustrated above, the devices of the present invention typically comprise a power source (60). Typically, power is supplied by one or more batteries either replaceable or rechargeable. Lithium or alkaline batteries are
suitable for the disposable applications. NiCd and NiMH are suitable for rechargeable applications. Generally a power supply (60) resides within the housing and supplies the microprocessor and the rest of the channels with power. The power supply can include 4 batteries (AA or LR6).

Turning on the devices of the invention via the on/off switch (22) activates the power supply (60).

The microprocessors control and/or monitor voltage, current, input switches, status LEDs, beepers, and the waveform generator(s). A waveform generator, e.g. generator (40) takes signals from the microprocessor, transforms them into waveforms, e.g. square waveforms, and supplies the waveforms to the primary electrode port (27). From the primary electrode port (27), the primary electrodes (50) carry the waveforms to the tissue to be treated.

According to particular embodiment, the waveform generator (40) includes a voltage multiplier (41), an optional current modulator (42), an integrator (43), and a switched bridge (44) (see Figure 3). The combined portions of the waveform generator (40) take power from the power supply (60) and generate a waveform under direction from the microprocessor (32).

The voltage multiplier (41) supplies a voltage pumped signal to the switched bridge (44). In particular embodiments, the voltage multiplier (41) includes a voltage feedback loop with the microprocessor (32). The switched bridge (44) supplies the generated microcurrent waveform to the primary electrode port (27). The switched bridge (44) comprises for example four opto-isolators in a bridge configuration. In addition to the voltage pumped signal from the voltage multiplier (41), the switched bridge (44) receives an output polarity control signal from the microprocessor (32) and optionally, a current modulation signal from the current modulator (42) to ensure a unipolar pulsed direct current. Integrator (43) manipulates the waveform signals received from the microprocessor (32) resulting in a preset square wave output. The microprocessor (32) controls the frequency of the generated signal which is typically a preset value of 100 Hz. Input switches (26) further instruct microprocessor (32) to provide a output current typically between 300 and 600
µA (e.g., 400 µA). The design of a waveform generator for the second channel is identical to the one for the first channel as described above.

Each channel output from the devices of the invention is to the electrodes. These electrodes are, for each channel, supplied with electrical signals from the waveform generator (40) via the electrode port (27). The status of the device is indicated by LEDs (34) which are controlled by a microprocessor (32). Also, particular embodiments of the devices according to the invention include a warning beeper (36) which is controlled by the microprocessor (32). The warning beeper (36) is activated when the device detects any break in the circuit between the electrodes of an electrode pair, indicating that the electrodes are not making proper contact to the portion of the body to be treated.

From an inactivated state, devices of the invention are activated via the on/off switch (22). These switches can be manual or digital switches. Once energized, the microprocessor (32) checks the other switches to determine which current level and time period has been selected. Based on the selected settings, the microprocessor (32) sends the appropriate signals to the waveform generator (40) to cause the appropriate signals to be sent to the electrodes (50). The microprocessor also instructs the LEDs (34) and the beeper (36) to indicate the appropriate status. Once the selected treatment is completed, the unit automatically returns to a ready state.

Devices of the invention with a second (and optionally further additional) channel(s) (130) within the same housing as the first channel (30) are suitable for a "whole body" treatment wherein for example the electrodes of one channel are applied to the left hand/arm and the left foot/leg, and wherein the electrodes of the other channel are applied to the right hand/arm and the right foot/leg.

In particular embodiments (see Figure 4), microcurrent devices of the invention optionally comprise a controller capable of being worn on a comfortable position on the user's body wherein a transmitting device comprised in the controller sends transmission signals by a communication means from the controller to the stimulation unit. At the stimulation unit a receiver is present capable of receiving and decoding the input signals from the
transmitting device. In one embodiment, the communication means is achieved by a physical connection (e.g., communication wire) between the controller and the stimulation unit. In another embodiment the communication means is achieved by wireless, over-the-air RF transmission comprised of a plurality of antennas with transmission signals between 40 kHz to 915 MHz or higher. In this embodiment the input signals can be sent to the microprocessor of the device via remote control.

In yet another embodiment, the communication means is achieved by a capacitive coupling comprising a plurality of conductive plates, transducers placed near or on the surface of the user's skin wherein one of the conductive plates or transducers resides in the controller means and another conductive plate or transducer resides in the wireless stimulation unit, using the user's body as a wireless, conductive medium to transmit the transmission signals. In yet another embodiment, the controller means transmits signals between 20 and 500 kHz from the controller means through the user's body to the microcurrent device stimulation unit. Typically the controller means is worn on the wrist or belt where it can be easily seen and manipulated.

In particular embodiments, the electronic microprocessor module of devices of the present invention is a miniature remote module residing in or on one electrode and with display means which allows the remote module to be identified by the controller means and which sets a software address thereby allowing the controller means to send transmissions signals to an identifiable remote module. Also for these embodiments, typically the controller means is worn on the wrist or belt where it can be easily seen and manipulated.

The electrodes can vary in shape size and composition and can be disconnected from the device. Electrodes can be made of metal (e.g. a flexible silver alloy film), impregnated gauze or felt, foam or elastomer, hydrogels or any other conductive material. In a particular embodiment the electrode is a patch, i.e. suitable for application to a (relatively) flat skin surface. For example, the electrode can comprise a hydrogel which ensures a good contact with the between electrode and skin. In particular embodiments, the patch comprises multiple layers of different material (adhesive layer, conductive layer, insulating
layer). Depending on the part of the body where the electrodes are to be placed, electrodes have a surface of at least 2cm², more particularly between about 4 to 100 cm², more particularly about 14 cm².

According to particular embodiments of the invention, the microcurrent devices comprise fixed settings for frequency, current and waveform and adjustable settings for time. Consequently, the devices contain a minimal number of components which makes it possible to create a lightweight device which is operated by alkaline batteries or the like. In addition, the limited number of dials and switches ensure an easy and error-proof operation of the device.

In particular embodiments of the invention the manipulation of the microcurrent device is performed via a capacitive keyboard mechanism with a transparent front plate, such as described for example in DE1 0224537.

The features of devices according to particular embodiments of the invention suitable for use in the treatment and/or alleviation of fatigue, more particularly medical fatigue, are illustrated in Table 1 below. Table 2 and Figure 5 provide an example of the operational control provided in the devices of the present invention.

Table 1: features of a microcurrent device according to a particular embodiment of the invention

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specification</th>
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<tbody>
<tr>
<td>Power Supply</td>
<td>6V (4 AA batteries)</td>
</tr>
<tr>
<td>Channels</td>
<td>2 separate channels, dual output</td>
</tr>
<tr>
<td>Type</td>
<td>Constant Current</td>
</tr>
<tr>
<td>Current</td>
<td>About 400 µA</td>
</tr>
<tr>
<td>Frequency</td>
<td>About 100Hz</td>
</tr>
<tr>
<td>Waveform</td>
<td>Monophasic, rectangular with decay</td>
</tr>
<tr>
<td>Pulse Width</td>
<td>1,300 microseconds</td>
</tr>
<tr>
<td>Voltage</td>
<td>Variable up to 33 V</td>
</tr>
<tr>
<td>Energy per pulse</td>
<td>About 35 micro Joule maximum</td>
</tr>
</tbody>
</table>
Table 2: Operation details of a microcurrent device according to a particular embodiment of the invention.

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<tr>
<th>LEDs</th>
<th>Timer</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>6 (Green), in vertical row, indicating 10 minute intervals</td>
</tr>
<tr>
<td></td>
<td>Low Battery</td>
</tr>
<tr>
<td></td>
<td>1 (Orange), usually off, comes on when battery output &lt; 3.7V</td>
</tr>
<tr>
<td></td>
<td>Channel 1</td>
</tr>
<tr>
<td></td>
<td>1 (Green)</td>
</tr>
<tr>
<td></td>
<td>a. Channel off: Green LED off</td>
</tr>
<tr>
<td></td>
<td>b. 400 μA : Green LED on</td>
</tr>
<tr>
<td></td>
<td>Channel 2</td>
</tr>
<tr>
<td></td>
<td>1 (Green)</td>
</tr>
<tr>
<td></td>
<td>a. Channel off : Green LED off</td>
</tr>
<tr>
<td></td>
<td>b. 400 μA : Green LED on</td>
</tr>
<tr>
<td></td>
<td>Power (On /Off switch)</td>
</tr>
<tr>
<td></td>
<td>1 (Green)</td>
</tr>
<tr>
<td></td>
<td>activated with finger audible signal (beep) to confirm On or Off</td>
</tr>
<tr>
<td></td>
<td>Timer</td>
</tr>
<tr>
<td></td>
<td>60 or 30 minutes treatment period, device switches off automatically at end of period</td>
</tr>
<tr>
<td></td>
<td>Disconnect Alarm</td>
</tr>
<tr>
<td></td>
<td>Green LEDs flash on/off every second for the affected channel only</td>
</tr>
<tr>
<td></td>
<td>Manipulation</td>
</tr>
<tr>
<td></td>
<td>capacitive keyboard mechanism with transparent front plate.</td>
</tr>
</tbody>
</table>

5 EXAMPLES

Example 1. : Alleviation of fatigue using microcurrent therapy in post-polio patients.

The efficacy of Bio-Electric Stimulation Therapy (BEST) on fatigue, endurance and pain relief was determined in 22 "post-polio" (PP) patients who had not previously received BEST treatment and had no contra-indications for BEST treatment (cancer, pregnancy, cardiac disease, pacemaker implant). All 22 PP patients received daily BEST treatment (1 hour BEST treatment during weekdays) for 12 weeks. BEST treatments were in accordance with the present invention, using the device and settings described in Figure 5 and Tables 1 and 2.
The fatigue score was documented with the Brief Fatigue Inventory (BFI) Hann et al. (1998) Quality of Life Research 7, 301-10, which is a validated questionnaire for this purpose (see e.g. Mendoza et al. (1999) Cancer 85, 1186-1 196). At the end of the 12 week BEST treatment, a positive response in total fatigue score was observed in 86% of all persons undergoing the treatment: 50% of all subjects showed a major response (> 30% improvement in total fatigue score; range 32-74%), 36% of all subjects had a modest response (10-30% improvement in total fatigue score) and only 14% showed no response. Statistical analysis (paired student t-test and ANOVA) demonstrated a significant (P < 0.0001) reduction in the average total fatigue score after 12 weeks of BEST treatment from about 52 to about 37, which is a decrease of 29%. (see Figure 6). These results were closely mirrored for the other aspects of fatigue that were recorded: the average 'worst level of fatigue' and the 'average level of interference with daily life'. When compared to the baseline score, the score for the average 'level of interference with daily life' had decreased with 25% (P < 0.0001) after 12 weeks of BEST treatment (see Figure 7). After 12 weeks of BEST treatment significant improvements were also observed for both endurance and pain relief.

Endurance was measured using the Borg CR10 scale, which is a number between 0 and 10 indicating the Rate of Perceived Exertion (RPE) that is reported by the patient at the completion of the 6-minute walk test (see e.g. Chen et al. (2002) J. Sports Sci. 20, 873-899). The improvement of endurance and stamina is illustrated in Figure 8, showing a decrease of the average Borg RPE score from about 8.5 to about 5.3 over the 12 week BEST treatment period, which corresponds to an improvement of about 38% (P < 0.005). A positive response in endurance was observed in 79% of all persons undergoing the treatment: 53% of all subjects showed a major response (> 40% reduction in Borg CR10 score; range 41-88%), 26% of all subjects had a modest response (10-40% reduction in Borg CR10 score) and only 21% showed no response.

Pain relief was assessed using the Brief Pain Inventory (BPI) (Cleeland et al. (1988) Journal Pain Symptom Management 3, 23-27), which is a validated and
frequently used multidimensional pain assessment tool including both pain intensity and pain's interference with functions (see e.g., Holen et al. (2008) Clinical Journal of Pain 24, 219-225). At the end of the 12 week BEST treatment, a positive response in total pain score was observed in 72% of all persons undergoing the treatment: 50% of all subjects showed a major response (> 30% improvement in total pain score; range 34-92%), 22% of all subjects had a modest response (10-30% improvement in total pain score) and 28% showed no response. Statistical analysis (paired student t-test and ANOVA) demonstrated a significant (P < 0.0001) reduction in the average total pain score after 12 weeks of BEST treatment from about 55 to about 33, which is a decrease of 40%. (see Figure 9). These results were closely mirrored for the other aspects of fatigue that were recorded: the average 'worst level of pain' and the 'average level of interference with daily life'. When compared to the baseline score, the score for the average' level of interference with daily life' had decreased with 40% (P < 0.001) after 12 weeks of BEST treatment (see Figure 10).

A total of 11 PP patients completed another 12 weeks of extended BEST therapy. As earlier, the BEST treatments were in accordance with the present invention, using the device and settings described in Figure 5 and Tables 1 and 2. Most patients treated themselves for 1 hour in (on average) twice weekly BEST sessions. Figure 11 demonstrates that the favorable effect of BEST treatment on fatigue, endurance and pain relief observed during the first 12 weeks in this patient group were maintained throughout the second 12 week period by a on average twice a week BEST maintenance treatment.

Example 2: Alleviation of fatigue using microcurrent therapy in Multiple Sclerosis patients.

To determine the efficacy of Bio-Electric Stimulation Therapy (BEST) on muscle strength, functional mobility and fatigue in Multiple Sclerosis (MS) patients, 17 MS patients with mild to moderate disability (rating between 1.5 and 6.5 on the Expanded Disability Status Scale (EDSS) (see Kurtzke (1983), Neurology 33, 1444-1452) and who had not received any steroid drug treatment
to alleviate MS disability during at least 28 days prior to the start of the study were included in a randomized, controlled design study (stratification by age, gender and EDSS scores) with 9 patients receiving daily BEST treatment (1 hour BEST treatment during weekdays) and 8 control patients receiving no such BEST treatment. BEST treatments were in accordance with the present invention, using the device and settings described in Figure 5 and Tables 1 and 2. All patients were evaluated vis-a-vis their initial baseline ability for muscle strength, functional ability and fatigue levels after 10 weeks of BEST treatment.

After 10 weeks of treatment (see Table 3) two-factor ANOVA analysis demonstrated significant (P < 0.05) improvements in walking capacity (average of 16% increase versus baseline in BEST treated subjects vis-a-vis average of 1% decrease versus baseline in control subjects), fatigue scores after performing short, intense physical effort (average of 18% reduction versus baseline in BEST treated subjects vis-a-vis average of 5% increase versus baseline in control subjects) and fatigue scores after performing long physical effort (average of 18% reduction versus baseline in BEST treated subjects vis-a-vis average of 22% increase versus baseline in control subjects). In these clinical experiments the walking capacity was evaluated using the '2-minute walking test', which measures distance covered in 2 minutes (see Butland et al (1982) British Medical Journal 284,1607-1608) and fatigue levels were assessed using the Brief Fatigue Inventory (BFI; Hann et al (1998) Quality of Life Research 7, 301 -10). Short, intense physical effort and long physical effort consisted of respectively the 2-minute walking test and 1 hour muscle strength testing on gym equipment.

Table 3: Effect of 10 weeks microcurrent therapy on muscle strength, functional mobility and fatigue on a group of 17 MS patients

<table>
<thead>
<tr>
<th>BEST Group</th>
<th>Parameter</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 % increase</td>
<td>1. Walking capacity</td>
<td>1% decrease</td>
</tr>
<tr>
<td>no change</td>
<td>2. Other functional ability tests</td>
<td>no change</td>
</tr>
<tr>
<td>no change</td>
<td>3. Muscle strength</td>
<td>no change</td>
</tr>
</tbody>
</table>
These results demonstrate that, although no direct improvement of muscle strength was observed after 10 weeks of BEST treatment, BEST treated MS patients could walk further and were less tired, indicating that the BEST treatment did significantly increase their endurance.

<table>
<thead>
<tr>
<th>BEST Group</th>
<th>Parameter</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 % reduction</td>
<td>4. After short, intense physical effort (2 minutes walking)</td>
<td>5 % increase</td>
</tr>
<tr>
<td>18 % reduction</td>
<td>5. After long physical effort (1 hour muscle strength on gym equipment)</td>
<td>22 % increase</td>
</tr>
</tbody>
</table>
CLAIMS

1. An electrotherapy device (1) comprising a power supply (60), a microprocessor (32), a waveform generator (40) and a set of two electrodes for application to the skin (50), configured so as to generate a pulsed current in said electrodes of between 100 and 900 µA with a fixed frequency of between 50 and 150 Hz in the electrodes.

2. A device according to claim 1, further characterized in that said set of two electrodes comprise electrode patches for application to the skin surface, having a size of at least 2 cm².

3. The device according to claim 1, wherein the current is preset at a value between 100 and 900 µA, more particularly between 300 and 600 µA, most particularly about 430 or 450 µA.

4. The device according to claim 1, wherein the current can be manipulated to discrete values between 100 and 900 µA, more particularly between 300 and 600 µA, most particularly including about 430 or 450 µA.

5. The device according to any one of claims 1 to 4, wherein the frequency is preset at a value of between 80 and 120 Hz, more particularly between 90 and 110 Hz, most particularly about 100 Hz.

6. The device according to any of claims 1 to 5, wherein the waveform generator (40) generates a monophasic wave.

7. The device according to claim 6, wherein the waveform generator (40) generates a monophasic rectangular wave.

8. The device according to claim 7, wherein the waveform generator generates a monophasic rectangular wave with decay.
9. The device according to any of claims 1 to 8, wherein the current is applied with a pulse width of between 600 and 2000 µseconds, more particularly between 900 and 1700 µseconds, especially between 1100 and 1500 µseconds.

10. The device according to claim 9, wherein the current is applied with a pulse width of 1300 µseconds.

11. The device according to any one of claims 1 to 10, comprising a timer for the current adjustable to discrete time points between 10 and 120 minutes.

12. The device according to claim 11, wherein said time points are 30 and 60 minutes.

13. The device according to any one of claims 1 to 12, which comprises two channels with two microprocessors (32 and 132), two waveform generators (40) and (140) and two sets of electrodes (50) and (150) for application to the skin.

14. The device according to any one of claims 1 to 12, which comprises two channels with a single microprocessor (32), two waveform generators (40) and (140) and two set of electrodes (50) and (150) for application to the skin.

15. The device according to any of claims 1 to 14, which comprises a capacitive keyboard mechanism with a transparent front plate.

16. The device according to any of claims 1 to 15, wherein input signals are sent to the microprocessor of the device via remote control.

17. A method for treating or alleviating fatigue in a person comprising:
- applying electrodes to the skin surface of the body of said person; and
- delivering to said skin surface a pulsed current of between 100 and 900 µA with a preset frequency of between 50 and 150 Hz, thereby alleviating or treating said fatigue.

18. The method according to claim 17, wherein said fatigue is medical fatigue.

19. The method according to claim 17 or 18, wherein said fatigue is a symptom of a disorder selected from the group consisting of poliomyelitis, fibromyalgia, multiple sclerosis, Parkinson's disorder, chronic fatigue syndrome and cancer.

20. The method according to any of claims 17 to 19, wherein the frequency is preset at a value of between 80-120 Hz, more particularly between 90-110 Hz.

21. The method according to claim 20, wherein the frequency is preset at a value of 100 Hz.

22. The method according to any of claims 17 to 21, wherein the current is preset at a value between 300 and 600 µA, preferably between 400 and 500 µA.

23. The method according to claim 22, wherein the current is preset at a value of about 430 or 450 µA.

24. The method according to any one of claims 17 to 21, wherein the current can be manipulated to discrete values between 100 and 900 µA, more particularly between 300 and 600 µA, most particularly including 430 or 450 µA.

25. The method according to any of claims 17 to 24, wherein said current is applied with a pulse width of between 600 and 2000 µseconds, more
particularly with a pulse width of between 900 and 1700, especially between 1100 and 1500 µseconds.

26. The method according to claim 25, wherein said current is applied with a pulse width of 1300 µseconds.

27. The method according to any of claims 17 to 26, wherein said current is applied for a period of between 10 and 120 minutes.

28. The method according to claim 27, wherein said current is applied for a period of 30 or 60 minutes.

29. The method according to any one of claims 17 to 28, wherein said current is applied at least once a week during a period of at least 6 weeks.

30. The method according to any of claims 17 to 29, wherein the current is further characterized by one or more of the following features:
- the current is a monophasic current,
- the current has a rectangular waveform,
- the current is a current with decay.
Figure 11

(a) BAR Score

(b) Borg CR10 Scale

(c) BPI Score

weeks treatment

baseline

weeks treatment

baseline
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61N1/34 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

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>X</td>
<td>US 3 911 930 A (HAGFORS NORMAN R ET AL) 14 October 1975 (1975-10-14) the whole document</td>
<td>1-12,14</td>
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<tr>
<td>Y</td>
<td>Y1 5 395 398 A (ROGOZINSKI WALLACE J [US]) 7 March 1995 (1995-03-07) column 4, lines 3-64, figure 4</td>
<td>13,15,16</td>
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<td>Y</td>
<td>US 2006/052844 A1 (NEWMAN TOM [US]) 9 March 2006 (2006-03-09) paragraphs [0031], [0060], [0063]</td>
<td>16</td>
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</table>

D 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 for 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

Date of the actual completion of the international search

12 September 2008

Date of mailing of the International search report

06/10/2008

Name and mailing address of the ISA/

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

Schöffmann

Authorized officer

Form PCT/ISA/210 (second sheet) (April 2005)
INTERNATIONAL SEARCH REPORT

Box No. 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:

   because they relate to subject matter not required to be searched by this Authority, namely:
   Rule 39.1(lv) 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 No. 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 fees, this Authority did not invite payment of additional fees.

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 applicants' protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicants' protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
<table>
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<th>Publication date</th>
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<tr>
<td>US 3911930</td>
<td>A 14-10-1975</td>
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