PATENT SPECIFICATION (11) 1 596 512

(21) Application No. 47085/77 (22) Filed 11 Nov. 1977
(31) Convention Application No. 742706 (32) Filed 17 Nov. 1976 in
(33) United States of America (US)
(44) Complete Specification Published 26 Aug. 1981
(51) INT. CL.[3] A61N 1/40
(52) Index at Acceptance
A5R 85D8 85F2

(19)



(54) MODIFICATION OF THE GROWTH, REPAIR AND MAINTENANCE BEHAVIOUR OF LIVING TISSUES AND CELLS BY A SPECIFIC AND SELECTIVE CHANGE IN ELECTRICAL ENVIRONMENT

(71) We, ELECTRO-BIOLOGY INC, a corporation organized and existing under the laws of the State of New Jersey and having its principal place of business at 38 Wall Street, Passaic, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:-

Divisional application No. 80 20555 Serial No. 1596513 describes and claims subject-matter described herein.

This invention relates to the treatment of living tissues and/or cells by altering their interaction with the charged species in their environment. In particular, the invention relates to a controlled modification of cellular and/or tissue growth, repair and maintenance behaviour by the application of encoded electrical information. Still more particularly, this invention provides for the application, by a surgically non-invasive direct inductive coupling, of one or more electrical voltage and concomitant current signals conforming to a highly specific pattern.

Several attempts have been made in the past to elicit a response of living tissue to electrical signals.

Investigations have been conducted involving the use of direct current, alternating current, and pulsed signals of single and double polarity. Invasive treatments involving the use of implanted electrodes have been followed, as well as non-invasive techniques utilizing electrostatic and electromagnetic fields. Much of the prior work that has been done is described in Volume 238 of the *Annals of the New York Academy of Sciences* published 11 October 1974 and entitled "Electrically Mediated Growth Mechanisms in Living Systems" (Editors A.R. Liboff and R.A. Rinaldi). See also "Augmentation of Bone Repair by Inductively Coupled Electromagnetic Fields" by C. Andrew L. Bassett, Robert J. Pawluk and Arthur A. Pilla published in Volume 184, pages 575-577 of *Science* (3 May 1974).

The invention herein is based upon basic cellular studies and analyses which involve a detailed consideration of the interactions of charged species, such as divalent cations and hormones at a cell's interfaces and junctions.

Basically it has been established that, by changing the electrical and/or electrochemical environment of a living cell and/or tissue, a modification, often a beneficial therapeutic effect, of the growth, repair and maintenance behaviour of said tissue and/or cells can be achieved. This modification or effect is carried out by subjecting the desired area of tissues and/or cells to a specifically encoded electrical voltage and concomitant current, whereby the interactions of charged species at the cells' surfaces are modified. Such modifications engender a change in the state or function of the cell or tissue which may result in a beneficial influence on the treated site. For example, in the specific case of bone growth and repair, it is possible with one electrical code, hereinafter referred to as Mode 1, to change the interaction of the ion such as Ca^{2+} with a cell's membranes. Whereas, with another electrical code, hereinafter referred to as Mode 2, a modification in the same cell's protein synthesis capabilities can be affected. The present application is directed primarily to Mode 1 but for the sake of completeness Mode 2 is also fully described herein, since the two modes may be combined as will be explained.

Tissue culture experiments involving the study of embryonic chick limb rudiments show that the use of a Mode 1 code signal elicits enhanced Ca^{+2} release of up to 50% from the competent osteogenic cell. This effect is highly specific to the parameters of the electrical

code of Mode 1. Thus this code influences one major step of ossification, i.e., the mineralization of a bone growth site. Similar tissue culture studies using Mode 2 code signals have demonstrated that this code is responsible for enhanced protein production from similar competent osteogenic cells. This latter effect is also highly specific to the parameters of the electrical code of Mode 2. In other words, this code affects certain metabolic processes for these types of cells such as those involved in calcium uptake or release from mitochondria as well as the synthesis of collagen, a basic structural protein of bone.

These studies show that the electrical codes of Mode 1 and Mode 2 elicit individual tissue and cellular responses, indicating that each code contains a highly specific informational content therein. Based upon these and other studies, it has been possible to utilize Mode 1 or Mode 2 signals or a particular combination of Mode 1 and Mode 2 signals to achieve a specific response required to enable the functional healing of a bone disorder. These electrical modes have been applied successfully to human and animal patients for non-healing fractures such as congenital pseudarthrosis and non-unions as well as fresh fractures. Successes achieved in the congenital pseudarthrosis cases are particularly noteworthy, since normally 80% of children thus afflicted require amputation, since conventional treatments such as bone grafting and internal fixation are unsuccessful.

While there have been many investigations in the past of the response of living tissues and/or cells to electrical signals, clinical results to date using prior techniques have not been uniformly successful or generally accepted within the appropriate professional community. Several reasons contribute to this state. First, it has not been realized heretofore that electrical signals of very specific informational content are required to achieve a specifically desired beneficial clinical effect on tissue and/or cells. Second, most of the prior techniques utilize implanted electrodes, which by virtue of unavoidable faradaic (electrolysis) effects are often more toxic than beneficial in the treated site. Furthermore, the cells and/or tissues are subjected to a highly uncontrolled current and/or voltage distribution, thereby compromising the ability of the cells to respond, should they do so, to the applied signal. This highly uncontrolled current and/or voltage distribution also applies in the case of capacitively coupled signals.

In contrast, the surgically non-invasive direct inductive coupling of electrical informational content of specific electrical codes as involved in the present invention produces within living tissue and/or cells a *controlled* response.

In brief, the present invention involves the recognition that the growth, repair and maintenance behavior of living tissues and/or cells can be modified beneficially by the application thereto of specific electrical information. This is achieved by applying pulse waveforms of voltage and concomitant current of specific time-frequency-amplitude relations to tissue and/or cells by a surgically non-invasive means through use of a varying electromagnetic field which is inductively coupled through direct induction into or upon the tissue and/or cells under treatment. The information furnished to the cells and/or tissues by these signals is designed to influence the behaviour of non-excitable cells such as those involved in tissue growth, repair, and maintenance. These growth, repair and maintenance phenomena are substantially different from those involved in excitable cellular activity (e.g. nerves, muscles, etc.), particularly with respect to the type of perturbation required. Thus, the voltages and concomitant currents impressed on the cells and/or tissues are typically at least three orders of magnitude lower than those required to affect cellular activities such as cardiac pacing, bladder control, etc.

According to the invention there is provided apparatus for treating living tissues and/or cells, by electromagnetically inducing voltage and current pulses within said tissue and/or cells, said apparatus comprising coil means adapted to be positioned in proximity to the tissue and/or cells to be treated, and pulse-generator means connected to said coil means and adapted to excite the same to create when in use within said tissue and/or cells therapeutic pulses of electrical energy that satisfy the following criteria:

(a) each pulse is composed of a first pulse-signal portion of a first polarity and greater magnitude and lesser time duration, followed by a second pulse-signal portion of opposite polarity and lesser magnitude and greater time duration;

(b) the peak magnitude of said second pulse-signal portions is no greater than one third the peak magnitude of said first pulse-signal portions; and

(c) the time duration of each of said first pulse-signal portions is no greater than one ninth the time duration of an adjacent one of said second pulse-signal portions;

(d) each of said first pulse-signal portions has an average amplitude of between about 0.0001 and 0.01 volts per centimeter of treated tissue and/or cells corresponding to between about 0.1 and 10 microamperes per square centimeter of treated tissue and/or cells.

The invention will be more completely understood by reference to the following detailed description:

Fig. 1 is a simplified view showing the treatment of a bone by apparatus in accordance with the invention.

Fig. 2 is a perspective view of the treatment unit shown in Fig. 1.

Fig. 3 is a view (from the rear) of the unit shown in Fig. 2, showing the positioning of a coil therein used for treatment purposes.

Fig. 4 is a block diagram of an electrical system for energizing the coil shown in Fig. 3 for Mode 1 treatment.

Fig. 5 is a block diagram of an electrical system for energizing the coil shown in Fig. 3 for Mode 2 treatment.

Figs. 5a and 5b are pulse waveform diagrams for Mode 1 and Mode 2 treatments, respectively, showing presently preferred pulses as induced in living tissues and cells.

Fig. 6 shows alternative forms of negative pulse portions for Mode 2 treatment.

Referring to Figs. 1 to 3, the leg 10 of a person having a broken bone as indicated as at 12 is shown as representative of the application of apparatus embodying the invention to the stimulation of bone growth for healing purposes. A treatment head 14 is positioned outside the skin of the person, and is held in place by use of a strap 16 (secured to head 14 by fasteners 16a) which may include Velcro (Registered Trade Mark) material 18 thereon so that the strap may be wrapped about the leg and about the treatment head to maintain the treatment head in position against the leg. The treatment head 14 may include a foam material 20 on the inside surface thereof for the purpose of cushioning and ventilating the treatment head against the leg. It will be noted that the treatment head 14 is generally curved on the interior surface thereof so that it conforms to the shape of the leg under treatment.

The treatment head 14 includes therein a coil 22 which may be of any suitable shape. As shown in Fig. 3 the coil 22 is generally rectangular in shape so as to define a "window" within the interior portion of the turns of the coil. The coil 22 may lie in a plane or it may generally be curved to conform to the curvature of the treatment head 14. The coil 22 includes terminals 24 which extend away from the treatment head 14 to be coupled to a cable 26 for connection to a suitable energizing circuit, as will be explained below in more detail. A diode 27 may be included within the cable 26 for connection across the coil 22, as will also be explained below.

The treatment head 14 is positioned on the patient so that the "window" formed by the coil 22 is adjacent the break 12, i.e., adjacent the tissue under treatment. The coil 22 is energized, as will be explained in more detail below, and induces an electrical potential within the tissue under treatment. It has been found that a particular type of signal should be induced within the tissue and this is achieved by energizing the coil 22 by a circuit such as shown in Fig. 4 or Fig. 5 to produce the pulse signal shown in Fig. 5a or Fig. 5b.

Referring to Fig. 4, a variable dc supply 30 is coupled through a gate 32 to the treatment coil 22 (or coils as the case may be and as will be explained in more detail below). The gate 32 is under the control of control units 34 and 36 which cause a pulse signal consisting of repetitive pulses of electrical potential to be applied to the treatment coil 22. Each pulse, as shown in Fig. 5a, is composed of a "positive" pulse portion P1 followed by "negative" pulse portion P2 because of the stored electrical energy within the treatment coil. In the circuit of Fig. 4, a diode clamping unit 38 may be employed to limit the peak potential of that negative pulse portion. The diode clamping unit 38 may be one or more diodes connected across the coil 22, and may be advantageously located within the cable 26. The diode 27 shown in Fig. 1 constitutes such a clamping unit 38.

In Fig. 5a, the signals at the treatment coil 22 and hence the induced signal within the tissue to be treated are shown. At time t1, it is assumed that gate 32 is gated on by an appropriate signal from control unit 36 (designated a pulse width control unit) so that the electrical potential across the treatment coil 22 is raised from about zero volts along pulse segment 39 to a potential designated v1 in Fig. 5a. The signal across the treatment coil decays in a second pulse segment along the portion of the curve designated 40 in Fig. 5a. The slope of that curve is determined by the L/R time constant of the circuit of Fig. 4, i.e., the inductance of the treatment coil and the effective resistance of the circuit, including distributed factors of capacitance, inductance and resistance. For treatment of many tissues and cells, it is believed desirable to adjust the circuit parameters so that the portion 40 of the curve is as flat as possible, rendering the signal applied to the treatment coil 22 as rectangular in shape as possible. At the time t2, the gate 32 is gated off by the control unit 36. Just prior to being gated off, the signal across the treatment coil is at the potential v2 shown in Fig. 5a. The potential across the treatment coil drops from the level v2 in a third pulse segment 41 to a potential of opposite polarity designated v3 in Fig. 5a. The magnitude of the opposite polarity potential v3 may be limited by the diode clamping unit 38 to a relatively small value as compared with value v1. The signal across the treatment coil 22 then decays exponentially from the potential level v3 to the zero or reference potential

level, finally effectively reaching that level at time t3. A predetermined period passes before the pulse repetition rate control unit 34 generates an appropriate timing signal to trigger the control unit 36 to generate a signal to turn gate 32 on again to continue the cycle just explained.

The control units may typically be monostable multivibrators, e.g., to generate appropriate timing signals and which may be variable to control pulse duration and repetition rate within desired limits. Further, the use of a variable dc supply 30 permits variation of the amplitude of the pulse signal as desired.

When pulse train operation (Mode 2) is employed, additional timing circuitry similar to units 34 and 36 in Fig. 4 are employed to provide the burst segment width and the burst segment repetition rate. Referring to Fig. 5, control units 35 and 37 control gate 33 to produce a signal applied to coil(s) 22 of the waveform type as shown in Fig. 5b. The circuit is otherwise the same as in Fig. 4, except that diode clamping unit 38 is omitted to permit the large negative pulse portions as shown in Fig. 5b. The control units 35 and 37 determine the number of pulses in a burst and the time between successive bursts.

It has been found that the signal across the treatment coil 22, and hence the induced signal within the tissue under treatment, should satisfy certain criteria. These criteria will be specified with respect to the signal *as induced in the tissue and/or cells under treatment.* Such induced signal may be monitored, if desired, by use of an auxiliary monitoring pickup coil (not shown) which is positioned at a distance from the treatment coil 22 corresponding to the distance of the tissue under treatment from that coil, as will be explained in more detail below. In any event, it has been found that the following criteria should be satisfied for effective treatment of living tissues and cells, in particular, hard tissue such as bone.

In the following presentation the signals shown in Figs. 5a and 5b constitute the pulses of electrical potential and concomitant current generated by the coil and impressed upon the tissues and/or cells. These pulses have one polarity upon "energization" of the coil (termed herein the "positive" pulse portion and shown as the positive going portion of the waveform on Figs. 5a and 5b). These pulses have an opposite polarity upon "de-energization" of the coil) termed herein the "negative" pulse portion and shown as the negative going portion of the waveforms of Figs. 5a and 5b). The terms "positive" and "negative" are intended to be relative only and are used herein only for the purpose of indicating that pulse portions of opposite polarity, with respect to a reference potential level are involved.

It has been determined that the "positive" pulse portions should bear a predetermined relationship to the "negative" pulse portions in order to modify beneficially and with uniform results the behavior of living tissues and cells. This predetermined relationship has been achieved by the utilization of two different signal modes, as well as combinations thereof.

In Mode 1 (see Fig. 5a), the asymmetrical waveform induced in tissue or cells by the alternate energization and de-energization of an electromagnetic coil is repeated at a frequency such that the overall duty cycle is no less than about 2%. This frequency, in mode 1, has typically been about 10-100 Hz with duty cycles of 20-30%. The basic relationship for mode 1 of the respective frequency amplitude content of the "positive" and "negative" pulse portions is as follows: pulse signal should be of a particular shape, namely, each "positive" pulse portion should be composed of at least three segments, e.g., the segments 39, 40 and 41 in Fig. 5a. As noted above, it has been found that a substantially rectangular shaped "positive" pulse signal portion is particularly useful in the treatment of tissue and cells. However, it is possible that other pulse configurations (other than a simple two-segment spike) may be useful. The peak amplitude of the final segment of each "positive" pulse portion, e.g., the potential v2 in Fig. 5a should be no less than about 25% of the peak amplitude of the first segment 39 of the "positive" pulse portion, e.g., the potential v1 in Fig. 5a.

The peak "negative" portion amplitude is denoted by v3 in Fig. 5a. This peak amplitude should be no more than about 1/3 the peak amplitude v1 of the "positive" pulse portion. The time duration of each "positive" pulse portion (the period that elapses between times t1 and t2 in Fig. 5a) should be no longer than about 1/9 and preferably no longer than about 1/12 the time duration of the following "negative" pulse portion (the time elapsing between times t2 and t3 in Fig. 5a). Because the treatment system utilizes an electromagnetic coil, the energy of each "positive" pulse portion is equal to the energy of each "negative" pulse portion, i.e., the area in Fig. 5a embraced by the "positive" pulse portions is equal to the area embraced by the "negative" pulse portions. By satisfying the criteria just mentioned, the energy of each "negative" pulse portion is dissipated over a relatively long period of time, and the average amplitude of that negative pulse portion is limited. It has been found that such average negative amplitude should be no greater than about 1/6 the average amplitude of the "positive" pulse portion.

These relationships also ensure that the "positive" and "negative" pulse portions have

the proper frequency-amplitude characteristics within themselves and to each other such that a beneficial modification of the behavior of tissues and cells is accomplished.

Besides the relationships just mentioned, it has been found that the average magnitude of the "positive" pulse portion peak potential should be within the range of about 0.0001 to 0.01 volt per centimeter of tissue or cells, corresponding to between about 0.1 and 10 microampere per square centimeter of treated tissue and/or cells (based upon typical cell and tissue resistivities). It has been found that higher or lower pulse potentials will not result in a beneficial effect. It has also been found that the duration of each "positive" pulse portion (the time elapsed between times t1 and t2 in Fig. 5a) should be at least about 200 microseconds. If the time duration of each "positive" pulse portion is less than about 200 microseconds, the tissues and cells are not stimulated sufficiently to modify the repair or other processes. From a practical standpoint, the "positive" pulse portion duration should not be greater than about 1 millisecond. It has also been found that the repetition rate of the pulses should be within the range of about 65 to 75 Hz for bone and other hard tissues. Pulse treatments within this range have been found to be particularly effective with reproducible results for tissues and cells of this type. In general, however, pulse repetition rate should be between about 10 and 100 Hz for good results in tissue and cells.

For the treatment of bone disorders, and particularly for the treatment of pseudarthrosis, it has been found that for mode 1 an optimum induced "positive" pulse signal portion having an average peak amplitude of between about 1 and 3 millivolts per centimeter of treated tissue (1 to 3 microamperes per square centimeter of treated tissue and/or cells) with the duration of each "positive" pulse portion being at least, and preferably about, 300 microseconds and the average amplitude of each said second pulse-signal portion is between 0.16 and 0.5 millivolts per centimeter (0.16 and 0.5 microamperes per square centimeter) of treated tissue and/or cells, with the duration of each of the "negative" pulse portions being at least 3000 and preferably about 3300 microseconds, and a pulse repetition rate of about 72 Hz represents a presently preferred and optimum induced pulse treatment as long as the pulse shape requirements noted above are met. Total treatment times may vary. It is presently believed that pulse signal treatments for periods each lasting for at least about 15 minutes, with one or more periods of treatment during a prescribed number of days may be effective in stimulating tissue and cell behavior. A preferred treatment regime using mode 1 has been found to be a minimum of 8 hrs/day for a period for four months in difficult cases and two weeks in less difficult cases.

In Mode 2 treatment (Fig. 5b), the asymmetrical waveform induced in tissue or cells by the alternate energization and de-energization of an electromagnetic coil is applied in a pulse train modality, which contains bursts (pulse groups) of asymmetrical waveforms. Each burst of asymmetrical pulses has a duration such that the duty cycle of the burst portion is no less than about 1%. The burst frequency has typically been about from 5-50 Hz.

The basic relationships for Mode 2 of the respective frequency-amplitude content of the "positive" and "negative" pulses within the burst section of the pulse train are as follows: each "positive" pulse portion should be composed of at least three segments, e.g., the segements 39', 40' and 41' in Fig. 5b. For this mode, it has also been found that a substantially rectangular shaped "positive" pulse signal portion is particularly useful in the treatment of tissues and cells. However, it is possible that other pulse configurations other than a simple two segment spike may be useful. The peak amplitude of the final segment of each "positive" pulse portion, e.g., the potential v2 in Fig. 5b should be no less than 10% and preferably no less than about 25% of the peak amplitude of the first segment 39' of the "positive" pulse portion, e.g., the potential v1 in Fig. 5b.

The peak "negative" amplitude is denoted by v3 in Fig. 5b. This "negative" peak amplitude should be no more than about 40 times the "positive" peak amplitude (in this case v1). This requirement may be met by utilizing "negative" pulse portions having several different waveshape forms, e.g., substantially rectangular, trapezoidal with exponential decay, bell shaped, or single spike with exponential decay as in representative waveforms a, b, c and d in Fig. 6.

The duration of each "positive" pulse portion (the time elapses between times t1 and t2 in Fig. 5b) should be at least about 4 times the duration of the following "negative" pulse portion (the time that elapses between times t2 and t3 in Fig. 5b). As noted above, since the treatment system utilizes an electromagnetic coil, the energy of each "positive" pulse portion is equal to the energy of each "negative" pulse portion, i.e., the area in Fig. 5b embraced by the "positive" pulse portions is equal to the area embraced by the "negative" pulse portions.

The pulse repetition rate of the pulses within the burst segment of the Mode 2 pulse train (the time elapsing between times t1 and t4) can be between about 2000 Hz and 10,000 Hz.

The width of the burst segment of the pulse train (the time elapsed between t1 and t5)

should be at least about 1% of the time elapsed between t1 and t6, and preferably no more than 1/2 of the time duration between successive bursts.

By satisfying the criteria just mentioned, these relationships also ensure that the "positive" and "negative" pulse portions have the proper frequency-amplitude characteristics within themselves and to each other such that a beneficial modification of the behavior of tissues and cells is accomplished.

Besides the relationships just mentioned, it has also been found that the average magnitude of the "positive" peak potential should be within the range of about 0.00001 to 0.01 volts per centimeter of tissues and/or cells (between about 0.01 and 10 microamperes per square centimeter of treated tissues and/or cells).

It has been found that higher or lower pulse potentials will not result in a beneficial effect on tissues and/or cells. It has also been found that the duration of each "positive" pulse portion in the burst segment of the pulse train (i.e., the time elapsed between t1 and t2 in Fig. 5b) should be at least about 100 microseconds. It has also been found that the repetition rate of the burst segment should be within the range of about 5-15 Hz and preferably at least 10 Hz for bone and other hard tissues.

Each negative pulse portion within the burst segment of the pulse train should be of a duration at least 10 microseconds and no greater than about 50 microseconds and of an average amplitude no greater than about 50 mv/cm of treated tissue and/or cells (about 50 microamperes per square centimeter of treated tissue and/or cells).

For the treatment of bone disorders and particularly, for the treatment of pseudarthroses and non-unions, it has been found that an optimum induced "positive" pulse signal portion having a peak amplitude of between about 1 and 3 millivolts/centimeter of treated tissue (i.e., 1 to 3 microamperes per square centimeter of treated tissue and/or cells), with the duration of each "positive" pulse portion being at least, and preferably about, 200 microseconds and the duration of each of the "negative" pulse portions being less than 40 and preferably about 30 microseconds and a time elapsed between times t3 and t4 of Fig. 5b of 10 microseconds, and a pulse repetition rate of about 4000 Hz, and a burst segment width of about 5 milliseconds and a burst repetition rate of about 10 Hz represents a presently preferred and optimum induced pulse treatment in bone for Mode 2, as long as the pulse requirements noted above are met. The combined duration of a "positive" and a "negative" pulse portion should be no more than 300 microseconds.

It is also believed that a single asymmetrical pulse as described in the burst segment of Mode 2 can be employed at a repetition rate similar to that used in Mode 1 for beneficial modification of tissue growth and repair.

Treatment of living tissues and cells by the above methods herein, in particular for hard tissue such as bone, has demonstrated an increased repair response and generally uniform results have been attained throughout all patient and animal treatments. Particularly beneficial results have been obtained in the cases of treatment of pseudarthrosis in which a bone union has been achieved following previous unsuccessful attempts by other treatment methods and in which amputation has been discussed as a possible alternative to regain function.

In practice, it is believed desirable to utilize as large a coil "window" as possible and to position the coil such that an adequate flux density is impressed upon the tissue and/or cells being treated. As is known, a time varying magnetic field induces a time varying voltage field orthogonal to it. That is, the geometry of the magnetic field lines determines the geometry of the induced voltage field. Because a relatively uniform induced voltage field is desired, the geometry of the magnetic field lines should be as uniform as possible, which may be achieved by rendering the size of the coil relatively large with respect to the area under treatment. At this time, it is not believed that there need be a particular orientation between the magnetic field lines and the tissue and/or cells being treated.

It is believed that the uniformity of the induced voltage field possible through electromagnetic treatment is responsible in many respects for the good treatment results which have been obtained, in distinction to the non-uniform fields which may be probably do result with other types of treatments, for example, utilizing electrostatic fields or by the creation of a potential gradient through the use of electrodes implanted within or on tissues or cells. In particular, an induced voltage field is present in a vacuum as well as in a conducting medium or an insulator. The field characteristics will in general be the same (within one percent) in these three cases, except in the case for which an induced current flow is sufficiently great to create a black electromotive force to distort the magnetic field lines. This condition occurs when the conducting medium has a high conductivity, e.g. a metal, and is large enough to intercept a substantial number of magnetic field lines. Living systems, i.e. tissue and/or cells, are much less of a conductor than a typical metal (generally by at least 10^5, i.e. five orders of magnitude). Because of these considerations, the geometry of the magnetic field present in tissue and/or cells is undisturbed and remains

unchanged as the tissue and/or cell growth process continues. Thus, with non-invasive electromagnetic treatment, it is believed that the potential gradient that is produced within the tissue and/or cells is constant regardless of the stage of condition of the treatment.

Such uniformity of induced potential is virtually impossible to be achieved through the use of implanted electrodes or by electrostatic coupling or by a transformer coupled to electrodes, or by implanted coils coupled to electrodes. Since these latter types of treatments are dependent upon conductivity, which will vary within tissue and/or cells, the induced potential gradient will not be constant as the condition of the tissue and/or cells changes. Additionally, at any particular time within tissue and/or cells, individual localities of the material being treated will have different conductivity characteristics, which will result in differing potential gradients throughout the material treated.

For these reasons it is believed that a surgically non-invasive electromagnetic treatment of tissue and/or cells is greatly preferably to electrical treatment by other means.

Regarding typical coil parameters, it is believed that for typical bone breaks, coil windows of about 2.0" × 2.75" (for an adult) and 2" × 1.5" (for a child) are suitable. The wire employed in the coils may be B&S gauge 12 copper wire that is varnish coated to insulate the turns one from another. Coils of about 60 turns for an adult and 70 turns for a child seem to be suitable. For treatments in the oral cavity, coil sizes would be correspondingly smaller.

It is believed that the inductance of the treatment coil should be between about 1-5000 microhenries, and preferably between about 1000 and 3000 microhenries, with sufficiently low resistance (e.g. 10^{-3} to 10^{-1} ohms) and a high input coil driving signal between about 2 and 30 volts to induce the appropriate pulse potential in the tissue and/or cells treated. The lesser the inductance of the treatment coil, the steeper the slope of the curve 40 as shown in Figures 5 and 5a; the greater the inductance the flatter or more rectangular is the "positive" pulse that is produced.

The monitoring of the induced potential may be by actual electrodes making contact with the tissue and/or cells being treated or by use of a pickup coil positioned adjacent to the treatment coil 22 at a distance corresponding to the distance of the material under treatment from the coil. A typical pickup coil that has been employed is circular, about one-half centimeter in diameter, with about 67 or 68 turns of wire. The potential developed by the coil is divided by the length of the wire (in centimeters) to provide an induced voltage per centimeter number that is closely related to the volts per centimeter induced in the tissue and/or cells under treatment.

A typical treatment utilizing a coil having a "window" 2" × 2.75" and 60 turns of number 17 gauge wire, including a diode at the coil such as the diode 27 in Figure 1, produced the following induced voltages in a pickup coil, for the pulse times (in microseconds) as follows (voltages and times are with reference to the waveform of Figure 5*a* and the voltage values may be translated into millivolts per centimeter of tissue, by dividing by a factor of substantially ten):

Induced Voltage	*v1*	*v2*	*v3*	*t1-t2*	*t2-t3*
Maximum (at face of treatment coil)	22	17	3.7	300	4200
5/8" from face of treatment coil	15	11.5	2.5	300	4200
1 1/2" from face of treatment coil	6.0	4.2	1.0	300	4200

The use of pulsing electromagnetic fields to control bone formation in a variety of conditions, now, is on a sound experimental and clinical basis. Thus far, the developments have had application in treating successfully congenital and acquired pseudarthorosis and fresh fractures in humans, increasing the rate of fracture and reactive periostitis repair in animals, and reducing bone loss in disuse osteoporosis of long bones. Success with the method hinges on the discovery of pulse patterns with specific time-frequency-amplitude relationships as outlined above.

EXAMPLES

In order to demonstrate efficacy, the utilization of direct inductive coupling of electromagnetically induced pulsing voltages and concomitant current via modes 1 and 2 and combinations thereof for hard tissue growth and repair was initially applied in cases of congenital and acquired pseudarthrosis. In a group of patients, only individuals who had been treated previously by one or more unsuccessful surgical attempts (grafting, internal fixation) were accepted. For most of these patients, amputation had been recommended by

at least one qualified orthopedist. Throughout this study the necessity for pulse specificity was illustrated again and again. For example, when lack of ossification was the primary problem (usually the case for congenital pseudarthroses) mode 1 treatment was utilized with final functional bony union occurring *only* when the parameters of the pulse corresponded to those given above. On the other hand, when lack of bony matrix was the primary problem, mode 2 treatment was employed in order to achieve the production of collagen which is the primary supporting protein in bone structure. Since protein production and ossification are two completely different steps in bone formation, the highly selective nature of each of the signals utilized in modes 1 and 2 could be synergistically combined when neither matrix production nor ossification were present in a given patient's treatment history. Thus, a combination of modes 1 and 2 was utilized with benefit in this type of situation. One or more mode 1 pulses may be employed in sequential interlace with one or more mode 2 pulse bursts.

In the case of congenital pseudarthroses the typical patient is between one and ten years of age. The afflicted part is normally the distal tibia of one extremity. The patients were presented with an average of three prior unsuccessful surgical procedures and had the condition for an average of 5 years, and all were candidatas for amputation.

The treatment of such a patient was normally carried out using mode 1 treatment regime since the primary problem was due to a lack of ossification in the affected ares.

The patient is prescribed the appropriate equipment by the attending orthopedic surgeon and carries out his treatment on an out-patient basic. Treatment time is typically 12 to 16 hours a day for about an average of 4 months.

Some 20 of this type of disorder have been treated to date with successful ossification achieved in approximately 90% of the treated individuals.

For acquired pseudarthrosis, either traumatic or operative, patients are mostly adults and had an average number of three failed operations and an average of 2.5 years from onset of non-union. Amputation had been discussed for seventy percent of these individuals. Since in some cases the primary problem was lack of bony matrix typically visible radiographically as gaps in the bone of more than 2 mm in the fracture site, such a patient was treated commencing with mode 2 modality. When it was thought that sufficient non-ossified bony matrix was present mode 1 modality was employed to gain rapid immobilization of the fracture site.

Because of the particular pathology of several patients in this group, a combination of modes 1 and 2 was employed with this treatment being specifically mode 2 followed by mode 1. As in the case of congenital pseudarthrosis, the proper equipment was prescribed by the attending orthopedic surgeon and treatment was performed on an out-patient basis. Treatment time is typically 10-14 hours/day for periods ranging from 3 to 9 months. Instead of one mode following the other they may be applied simultaneously.

Some 30 of this type of disorder have been treated to date with successful bony union observed in 75% of the treated individuals.

These clinical results clearly demonstrate that once the particular pathology of a bone disorder is diagnosed it can be selectively beneficially treated by the application of properly encoded changes in electrical environment.

Similar findings have been obtained from a study of bilateral fermoral and radial osteotomies in 160 rats. These animals were divided into two major groups; field exposed and control for an interval of 14 days after operation. Following sacrifice, the extent of fracture repair was judged on the basis of X-ray and histologic evaluation, coupled with non-destructive mechanical testing. These animal models were employed to evaluate the effectiveness of treatment modalities of Modes 1 and 2 and combinations thereof. Generally, when the osteotomy gap was less than 0.1 mm, a Mode 1 signal was effective since very little bony matrix was required for solidification. On the other hand, for wider osteotomies, substantially increased matrix production was observed over control animals when Mode 2 was employed in the latter case to obtain a stiffer repair site for an equivalent treatment time.

This was further evaluated by the response of these bones to mechanical testing. This was performed by subjecting the bone of the rats following sacrifice to cantilever loading at various deformations in accordance with the testing procedures described in "Acceleration of Fracture Repair By Electromagnetic Fields. A surgically Non-invasive Method" by C.A.L. Bassett, R. J. Pawluk and A. A. Pilla published on pp. 242-262 of the *Annals of the New York Academy of Sciences* referenced above. The specimens were deformed in the antero-posterior, lateral-medial, postero-anterior, medial-lateral and again the antero-posterior positions.

The average response of a femur to this test at a deformation of 0.05 inch is shown in Table I as follows:

Table I

Mechanical Load Values in Electrical Stimulation of Artificial Osteotomies in Adult Female Rat Femur

Stimulation	*Load at 0.05 in. Deformation*
Control (untreated)	42 gms. ± 5.2 gms.
Mode 1 Signal Figure 5a	580 gms. ± 65 gms.

In addition to radiographic and mechanical evidence of the effectiveness of the signal employed, histologic evidence further attests to this effectiveness.

Hemotoxylin and eosin stained longitudinal specimens show a much higher degree of maturation for the Mode 1 signal than in the control case.

For wider osteotomy gaps, treatment times of fourteen days showed that the active animals had a significantly larger callus than controls. Histologic evidence shows that the increase is at least 150% over controls.

Limited tooth extraction studies have been performed and show that pulses of the Mode 1 type may have a highly beneficial effect on the rate of healing and on bone loss in the oral cavity. The latter effect in the oral cavity is particularly important for the maintenance of mandibular and maxillar crestal bone height, a very important factor for implant fixation.

These observations all point to the fact that electromagnetic fields with highly specific pulse characteristics can be non-invasively inductively coupled to biological systems to control cell behaviour. In the initial application of these principles, effects on bone cells have been investigated. Other biological process, however, may eventually be proven to be controlled by similar techniques, e.g. malignancy, neuro-repair, inflammatory processes and immune response, among others.

In summary, it is believed that a unique electromagnetic and surgically non-invasive treatment technique has been discovered. Induced pulse characteristics appear to be highly significant, especially those relating to the time-frequency-amplitude relationships of the entire pulse or pulse sequence. It is believed that selection of particular time-frequency-amplitude relationships may be the key to successful treatments of varying cellular behaviour in a variety of tissues.

It will be appreciated that the methods and apparatus described above are susceptible of modification. For example, while Figures 1 and 2 illustrate a treatment unit which may be strapped to the leg, treatment units incorporated in casts, e.g. may be employed. Further, treatment may be carried out by use of one or more coils of varying shapes positioned adjacent to tissue and/or cells to be treated. In fact, some treatments of humans have involved coils positioned upon opposite sides of a bone break and operated in flux-aiding polarity and phase. Coils with metal cores may also be used. In the case of treatment within the oral cavity, it is believed that double coils are advantageous, positioned, for example, on opposite sides of a tooth socket to stimulate repair of that socket.

Throughout the specification for Mode 1, a preferred pulse repetition rate of between about 65 and 75 hertz has been specified for bone and other hard tissue. The exact limits of the pulse repetition rate are not known for all types of tissues and cells. It is believed that preferred operating ranges will vary depending on the tissue and cell type. Positive results have been obtained. for example. in soft tissue treatment at 20 hertz.

Thus, the following claims should be taken to define the invention.

WHAT WE CLAIM IS:

1. Apparatus for treating living tissues and/or cells. by electromagnetically inducing voltage and current pulses within said tissue and/or cells. said apparatus comprising coil means adapted to be positioned in proximity to the tissue and/or cells to be treated. and pulse-generator means connected to said coil means and adapted to excite the same to create when in use within said tissue and/or cells therapeutic pulses of electrical energy that satisfy the following criteria:

(a) each pulse is composed of a first pulse-signal portion of a first polarity and greater magnitude and lesser time duration, followed by a second pulse-signal portion of opposite polarity and lesser magnitude and greater time duration;

(b) the peak magnitude of said second pulse-signal portions is no greater than one third the peak magnitude of said first pulse-signal portions; and

(c) the time duration of each of said first pulse-signal portions is no greater than one ninth the time duration of an adjacent one of said second pulse-signal portions;

(d) each of said first pulse-signal portions has an average amplitude of between about

Table I

Mechanical Load Values in Electrical Stimulation of Artificial Osteotomies in Adult Female Rat Femur

Stimulation	*Load at 0.05 in. Deformation*
Control (untreated)	42 gms. ± 5.2 gms.
Mode 1 Signal Figure 5a	580 gms. ± 65 gms.

In addition to radiographic and mechanical evidence of the effectiveness of the signal employed, histologic evidence further attests to this effectiveness.

Hemotoxylin and eosin stained longitudinal specimens show a much higher degree of maturation for the Mode 1 signal than in the control case.

For wider osteotomy gaps, treatment times of fourteen days showed that the active animals had a significantly larger callus than controls. Histologic evidence shows that the increase is at least 150% over controls.

Limited tooth extraction studies have been performed and show that pulses of the Mode 1 type may have a highly beneficial effect on the rate of healing and on bone loss in the oral cavity. The latter effect in the oral cavity is particularly important for the maintenance of mandibular and maxillar crestal bone height, a very important factor for implant fixation.

These observations all point to the fact that electromagnetic fields with highly specific pulse characteristics can be non-invasively inductively coupled to biological systems to control cell behaviour. In the initial application of these principles, effects on bone cells have been investigated. Other biological process, however, may eventually be proven to be controlled by similar techniques, e.g. malignancy, neuro-repair, inflammatory processes and immune response, among others.

In summary, it is believed that a unique electromagnetic and surgically non-invasive treatment technique has been discovered. Induced pulse characteristics appear to be highly significant, especially those relating to the time-frequency-amplitude relationships of the entire pulse or pulse sequence. It is believed that selection of particular time-frequency-amplitude relationships may be the key to successful treatments of varying cellular behaviour in a variety of tissues.

It will be appreciated that the methods and apparatus described above are susceptible of modification. For example, while Figures 1 and 2 illustrate a treatment unit which may be strapped to the leg, treatment units incorporated in casts, e.g. may be employed. Further, treatment may be carried out by use of one or more coils of varying shapes positioned adjacent to tissue and/or cells to be treated. In fact, some treatments of humans have involved coils positioned upon opposite sides of a bone break and operated in flux-aiding polarity and phase. Coils with metal cores may also be used. In the case of treatment within the oral cavity, it is believed that double coils are advantageous, positioned, for example, on opposite sides of a tooth socket to stimulate repair of that socket.

Throughout the specification for Mode 1, a preferred pulse repetition rate of between about 65 and 75 hertz has been specified for bone and other hard tissue. The exact limits of the pulse repetition rate are not known for all types of tissues and cells. It is believed that preferred operating ranges will vary depending on the tissue and cell type. Positive results have been obtained, for example, in soft tissue treatment at 20 hertz.

Thus, the following claims should be taken to define the invention.

WHAT WE CLAIM IS:

1. Apparatus for treating living tissues and/or cells, by electromagnetically inducing voltage and current pulses within said tissue and/or cells, said apparatus comprising coil means adapted to be positioned in proximity to the tissue and/or cells to be treated, and pulse-generator means connected to said coil means and adapted to excite the same to create when in use within said tissue and/or cells therapeutic pulses of electrical energy that satisfy the following criteria:

(a) each pulse is composed of a first pulse-signal portion of a first polarity and greater magnitude and lesser time duration, followed by a second pulse-signal portion of opposite polarity and lesser magnitude and greater time duration;

(b) the peak magnitude of said second pulse-signal portions is no greater than one third the peak magnitude of said first pulse-signal portions; and

(c) the time duration of each of said first pulse-signal portions is no greater than one ninth the time duration of an adjacent one of said second pulse-signal portions;

(d) each of said first pulse-signal portions has an average amplitude of between about

0.0001 and 0.01 volts per centimeter of treated tissue and/or cells corresponding to between about 0.1 and 10 microamperes per square centimeter of treated tissue and/or cells.

2. Apparatus as claimed in claim 1, wherein said criteria include the following:

(e) the repetition rate of said pulses is between 10 and 100 Hz.

3. Apparatus as claimed in claim 1, in which said criteria further include the following:

(f) each of said first pulse-signal portions is composed of three segments, of which the peak amplitude of the final segment is no less than 25 percent of the peak amplitude of the first segment.

4. Apparatus as claimed in claim 1, in which said criteria further include the following:

(f) each of said second pulse-signal portions has an average amplitude no greater than 1/6 the average amplitude of each of said first pulse-signal portions.

5. Apparatus as claimed in claim 1, in which said criteria further include the following:

(f) each of said second pulse-signal portions has a peak amplitude from which it exponentially decays to about a zero reference level.

6. Apparatus as claimed in claim 1, in which said criteria further include the following :

(f) the product of magnitude and time of said first pulse-signal portion being substantially equal to the product of magnitude and time of said second pulse-signal portion, whereby the average amplitude of said first and second pulse-signal portions is substantially zero.

7. Apparatus as claimed in claim 1, in which said pulses occur at a pulse repetition rate of between 65 and 75 Hz.

8. Apparatus as claimed in claim 1, in which the average amplitude of each said second pulse-signal portion is between 0.16 and 0.5 millivolts per centimeter of treated tissue and/or cells, corresponding to between 0.16 and 0.5 microamperes per square centimeter of treated tissue and/or cells, and in which the average peak amplitude of each said first pulse-signal portion is between 1 and 3 millivolts per centimeter of treated tissue and/or cells, corresponding to between 1 and 3 microamperes per square centimeter of treated tissue and/or cells.

9. Apparatus as claimed in claim 8, in which the duration of each said first pulse-signal portion is at least 300 microseconds, and the duration of each of said second pulse-signal portions is at least 3000 microseconds.

10. Apparatus as claimed in claim 1, in which the duration of each of said first pulse signal portions is no more than 1/12 the duration of an adjacent one of said second pulse-signal portions.

11. Apparatus as claimed in claim 1, wherein said pulse generating means is further adapted to electromagnetically induce an additional set of voltage and concomitant current pulses within said tissue and/or cells, wherein the waveform of said additional set of voltage and concomitant current pulses is a repetitive sequence of discrete pulse bursts, each pulse burst including a series of asymmetrical pulses.

12. Apparatus as claimed in claim 11, in which said first-mentioned voltage and concomitant current pulses and said additional set of pulses are either sequentially or simultaneously applied to said tissue and/or cells.

13. Apparatus as claimed in claim 11, in which said first-mentioned voltage and concomitant current pulses and said additional set of pulses are sequentially applied to said tissue and/or cells, said sequential application comprising one or more pulses of said first voltage and concomitant current pulses in sequential interlace with one or more pulse bursts of said additional set of pulses.

14. Apparatus as claimed in any preceding claim, in which said coil means comprises two electrical treatment coils adapted for placement of said coils on opposite sides of the tissue and/or cell region to be treated, said coils being connected for excitation in flux-aiding polarity and phase.

15. Apparatus as claimed in any preceding claim, wherein the coil means is provided with means adapted to attach it to a human body.

16. Apparatus as claimed in any preceding claim, wherein the coil means is or are metal cored.

17. Apparatus substantially as hereinbefore described with reference to Figures 1 to 4 and 5a of the accompanying drawings.

R.G.C. JENKINS & CO.,
Chartered Patent Agents,
Chancery House,
53-64 Chancery Lane,
LONDON WC2A 1QU.
Agents for the Applicants

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1981.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.