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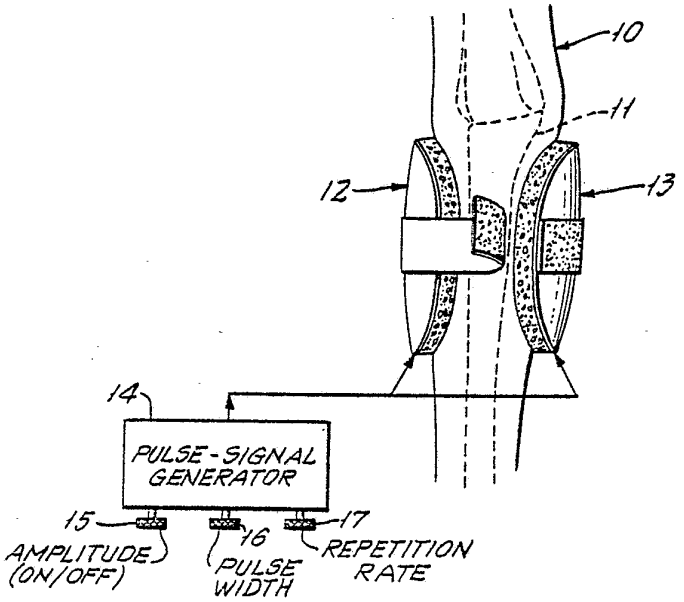
(54) Title: MODIFICATION OF THE GROWTH, REPAIR AND MAINTENANCE BEHAVIOR OF LIVING TISSUES AND CELLS BY A SPECIFIC AND SELECTIVE CHANGE IN ELECTRICAL ENVIRONMENT



(57) Abstract

A pulse signal generator (14) for generating a single pulse to be applied to a pair of coils (12, 13) to induce a current in bone (11) for the promotion of osteosynthesis in the healing of non-union bone fractures. The generated pulse consisting of two portions the first of which is greater in amplitude and lesser in duration than the second to be applied to the patient at a frequency of 6-30Hz. The application of the pulses in the indicated manner acting to enhance mineralization (mineral and collagen) in bone, without deleterious effects on the mytotic index, while also avoiding proteoglycan suppression in cartilage.

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MODIFICATION OF THE GROWTH, REPAIR AND MAINTENANCE BEHAVIOR OF LIVING TISSUES AND CELLS BY A SPECIFIC AND SELECTIVE CHANGE IN ELECTRICAL ENVIRONMENT

Background of the Invention

This invention relates to the treatment of living tissues and/or cells by altering their interaction with charged species in their environment.

Ryaby, et al., Patent Nos. 4,105,017, 4,266,532 and 4,266,533 describe means for effecting surgically non-invasive direct inductive coupling to an afflicted body region, whereby one or more induced electric voltage pulses and concomitant current signals conform to a relatively specific pattern and have been found to develop therapeutically beneficial treatment of the afflicted region, as for example in the enhancement of repair of bone fractures, non-unions, and the like. In general, the involved treatment head or heads have comprised one or more large coils, which have served well for the treatment of large-member bones, as in leg regions.

In bone-treatment cases, substantially the entire experience record has involved pulsed magnetic fields conforming generally to a specific pulse shape, single-pulse rate or pulse-burst pattern, and other parameters which have been within the confines of approval by the Federal Drug Administration. The treatments which have been applied to

post-fracture non-unions now number more than twenty thousand and provide a basis for stating that repair of such non-unions has been successful, solely through physician-supervised use of FDA-approved pulse signals in equipment of said Ryaby, et al. patents, in substantially seventy-five percent of the cases treated; the treatments which have been applied to congenital pseudarthroses are approaching 200, with a success rate of about 55 percent. Successful, in these contexts, is to be understood to mean that the afflicted bones which were previously unable to respond to surgery, grafting, and natural body-healing processes have been induced to become weight-bearing and fully usable, solely by reason of the biological processes and/or environment induced by the non-invasively applied magnetic fields.

Remarkable as one may view this success record, the fact remains that by far the greatest number of treated cases are post-fracture non-unions and that about twenty-five percent of the post-fracture non-union cases have failed to respond successfully to the indicated treatment.

I have addressed myself to a better understanding of body-cell response to pulsed magnetic fields, through extensive and careful research, to the end that this remarkable experience record can be improved.

Brief Statement of the Invention

It is an object of the invention to provide an improved method and means for surgically non-invasively treating

living tissues and/or cells through direct inductive coupling.

More specifically, it is an object to achieve the above object as an aid to bone growth.

Another specific object is to meet the above object with parameters more critically defined than heretofore, and capable of achieving a successful treatment of post-fracture bone non-unions which have failed to respond to previously recommended treatment.

A general object is to achieve the foregoing objects, requiring only minor modification of existing equipment and technique.

The invention achieves the foregoing objects by specifying more critically defined pulsed magnetic-field parameters which differ from currently operative FDA-approved parameters for post-fracture non-union use of Ryaby, et al. equipment of the character indicated. The involved parameters pertain inter alia to pulse shape, repetition rate and amplitude, and are based on my research (using biological specimens) into the separate pulsed-magnetic-field responses (1) of collagen and DNA in bone, as well as calcium uptake and content in bone, and (2) of collagen and DNA in cartilage, as well as the GAG content (glycosaminoglycan) in cartilage. The more critically defined parameters of the invention have thus far been initially applied to "hopeless" cases, namely, to those within the 25 percent of post-fracture non-union cases which did not respond successfully to the FDA-approved parameters and, therefore,

face surgery for an attempted bone-graft or amputation. To date, the success rate within this group of "hopeless" cases has been about 75 percent.

Detailed Description

The invention will be described in detail in conjunction with the accompanying drawings, in which:

Fig. 1 is a simplified diagram to show components of apparatus for use of the invention in a bone-treatment situation; and

Figs. 2 to 10 are graphical representations of various research-data summaries used in selecting a preferred operation of the apparatus of Fig. 1.

Referring initially to Fig. 1, the invention is illustratively shown in application to a portion of a human leg 10 wherein an assumed affliction is a defective bone, such as a fractured tibia 11 or fibula, which must be classified as a non-union case, through demonstrated failure to knit via normal body processes, with or without bone-grafting. It will be understood that the cast or brace, needed to restrain relative motion of damaged bone parts during the healing process, has been omitted from the drawing.

The apparatus to provide a pulsed magnetic-field environment for modification or repair of the afflicted bone may be as generally described in one or more of said Ryaby, et al. patents. More specifically, a pair of like multi-turn electric-coil units 12-13 is removably strapped to leg 10; each of the coils may suitably be a bundle of about 56 turns

of B & S gauge-28 coated copper wire, initially wound to a diameter of 18 to 25 cm before deformation into generally oval shape, and then encased (as shown) in magnetically transparent material such as formed plastic sheet. The connection and positioning of coils 12-13 are such that the coil axes of magnetic-flux development are in alignment through the afflicted region when the coils are excited in flux-aiding relation. As discussed in the second and third of said Ryaby, et al. patents, the size and spacing of coils are such that, when excited in flux-aiding relation, they establish a substantially uniform distribution of flux development in the included geometric volume defined by and between the coils. A pulse-signal generator 14 is shown thus-connected to coils 12-13, with provision for adjustment, at 15 for on/off control and for output-signal pulse amplitude, at 16 for pulse width, and at 17 for repetition rate. Except for certain operational parameters to be discussed below, there should be no need to further describe the apparatus, in view of the disclosures of said Ryaby, et al. patents, but it should be understood that the present showing of adjustment knobs 15-16-17 is purely a schematic indication of variables which are to be set within defined limits; accordingly, these knobs are not intended to suggest that the orthopedic physician or his patient are to be necessarily given the liberty of making adjustments other than for on/off.

Based on my research to date, and upon clinical results

to be discussed, it is my belief that a significant window of improved biological response to pulsed-magnetic fields exists if the following conditions are met:

(a) the output of generator 14 is a repetitive succession of single pulses, wherein

(b) the pulse-repetition rate is in the range of 6 to 30 Hz, and is preferably substantially 15 Hz;

(c) each pulse comprises first and second portions of opposite polarity, wherein one of the pulse portions is of greater amplitude and lesser duration, while the other pulse portion is of lesser amplitude and greater duration;

(d) the pulse portion of greater amplitude has a duration in the range of 50 to 500 microseconds, and preferably substantially 200 microseconds;

(e) the voltage amplitude of said first polarity portion is such as to induce a peak voltage of 10^{-4} to 10^{-2} volts per centimeter in living cells and/or tissues within the pulsed-magnetic field*; and

(f) the pulse is so quasi-rectangular that the rise time of its leading edge is in the order of one microsecond, and its fall time is up to an order of magnitude greater than the rise time.*

To appreciate the foregoing conditions, it must be recalled that the above-noted success factor of substantially 75 percent with post-fracture non-unions is attributable to

* As observed via the in-air probe-coil technique described in said Ryaby, et al. patents.

following the FDA-approved treatment protocol, using apparatus of the Ryaby, et al. patents. According to such protocol, the pulse output of the signal generator to excite coils 12-13 delivers 5-millisecond bursts of pulses, wherein the greater-amplitude portion is of 20 to 25-microsecond duration, and the lesser-amplitude portion is of 200 to 250-microsecond duration, and wherein the interval between bursts is such that the bursts repeat at 15 per second.

The problem is of course, what to do about the 25 percent of non-unions for which the FDA-approved protocol has not been adequate. Rightly or wrongly, I have reasoned that induced cell and/or tissue response to the indicated FDA-approved (pulse-burst) signals may for certain persons and/or other animal systems become blocked, paralyzed, numbed or otherwise frustrated by the presence of such frequent individual pulse stimulation as to effectively foreclose an environment within which chrondrogenesis and osteogenesis can proceed. For example, the approximately twenty individual pulses in each burst of the FDA-approved signals proceed with a dominant characteristic of approximately 4 kHz; and if one assumes that cell-recovery between individual pulses is a factor to be reckoned with, then very little time is afforded for cell recovery between pulses of a burst. Therefore, it is cardinal to the present invention that such rates of stimulation are to be avoided, and that reliance be placed on single pulses, at a repetition rate which allows more assured cell recovery between pulses.

My experiments which led to the above-stated single-pulse criteria, as distinguished from the FDA-approved pulse-burst pattern, were performed in a well-controlled environment, using living bone rudiments of embryonic chickens, 14 days old, and incubated in a chemically defined medium (i.e., no biological additive) for eight days, thus bringing all specimens to the same growth period; whereupon, the specimens were frozen in liquid nitrogen, to stop all biological processes, before final analysis.

More specifically, to select specimens for each experiment, 70 embryos (14 days old) were the source, for 140 tibias dissected therefrom. From that group, selection was made for a length consistency of about 11 mm, thus providing about 120 rudiments for allocation to the various groups of a given experiment. And each rudiment provided one length of bone, i.e., a shaft for the bone-related portion of the experiment, as well as two terminal cartilages, at the proximal and distal ends of the rudiment, for the cartilage-related portion of the experiment.

For each experiment, there were at least 10 rudiments in each group, all specimen in each group being grown at the same time, at carefully controlled uniform temperature, 38.2°C $\pm$ 0.5°; the different groups were exposed to different variations of pulsed magnetic-field conditions, and in every case, some of each group would be withheld from magnetic-field exposure, for control purposes. Throughout the experiments, conditions (a), (c), (e) and (f) above were

held without variation, the peak voltage of the first polarity portion being such as to induce in the shafts a peak voltage, equivalent to 14.5 millivolts in the probe* within the pulsed-magnetic field; the second polarity portion was -2.8 millivolts. The individual variables, reduced to one variable for each experiment, were pulse length (380, 200, 100, 50 microseconds, respectively) for the larger-amplitude first-pulse portion, fractional proportions of exposure time vs. non-exposure (e.g., 9 hours on, 3 hours off; 6 hours on, 6 hours off; 3 hours on, 9 hours off, etc.) repetition rate of the single pulses (6, 15, 30, and 72 Hz**, respectively), and magnetic field orientation (aligned, vs. transverse, vs. random orientation) with respect to shaft axes.

The different measured quantities, at conclusion of the eight days of each experiment, will appear from discussion of the various graphs of Figs. 2 to 10, segregated according to observations for collagen-content, DNA-content, and calcium-uptake, respectively.

Collagen Content -- Hydroxyproline was taken as the indicator of collagen content, there having been like last-day hydroxyproline analyses of all involved groups of

* Probe-measured in air, as above noted.

**72 Hz and 380 microseconds were selected because they have been the standardized rate and pulse duration for all prior treatments of congenital pseudarthroses; 6 Hz and 15 Hz approximate sub-multiples of 72 Hz, and 30 Hz is harmonically related to both 6 Hz and 15 Hz, as well as being below the 35-Hz lower limit of single-pulse protocol under FDA approval.

specimens, at conclusion of the consistent 8-day duration of all experiments. The bar chart of Fig. 2 displays measurements for hydroxyproline (micrograms per rudiment, μg/R), for each of the different single-pulse durations, plotted against the control, showing collagen-content improvement of 10 to 30 percent (over control), with the maximum of 30 percent for the case of 100 microsecond duration of each pulse. Limits of a central vertical line at the top of each bar designate standard deviation for the depicted mean.

The bar chart of Fig. 3 displays another dimension of collagen-content improvement through measurements for the hydroxyproline, for different pulse-repetition rates of 6, 15, 30 and 72 Hz, with additional comparative display of measurements for the 9 hours-on/3 hours-off condition, and for the 6 hours-on/6 hours-off condition. Clearly, from these measurements, collagen content is most promoted for the 15-Hz condition, and it is enhanced for the 9 hours-on/3 hours-off condition.

DNA Content -- ^{3}H-thymidine uptake was taken as the indicator for measuring mytotic index (cell multiplication), being administered alike to further groups of specimens, prior to conclusion of the eight-day experiment. The bar charts of Fig. 5a respectively show these measurements for the different pulse widths, vs. control and in conjunction with DNA content (Fig. 4b), for the case of single pulses at 15 Hz, and for 9/3 on/off hours dosage. Clearly, mytotic

index has not been suppressed, as compared with control, nor have the cells been thrown into logarithmic growth, for any of the pulse widths.

Fig. 5 is analogous to Fig. 3, to show measurements of ^{3}H-thymidine uptake for the different repetition rates, and for the different fractional proportions of pulsed magnetic-field exposure. The results of Fig. 5 show no material change from control up to 30 Hz, but there is a deleterious result at higher frequency, e.g., 72 Hz.

Bound-Calcium Uptake -- ^{45}Ca was taken as an indicator of mineralization, in still further groups of specimens within a given experiment, the exposure being for the 24 hours preceding end of the 8-day experiment. In the bar chart of Fig. 6, the measurement at end of day 8 shows calcium uptake (bound) to be at least double the level of control specimens, with a maximum of three times, for the 200-microsecond pulse width, pulses being repeated at 15 Hz and on a 9 hours-on/3 hours-off fractional proportion.

Fig. 7 is analogous to Figs. 3 and 5, to show the ^{45}Ca uptake measurements, with schematic indication that the ^{45}Ca exposure ran for the last day. A phantom profile, drawn through peaks of the various bars, strongly suggests a peaking of the calcium uptake for pulse-repetition rates in the range 10 to 30 Hz, with maximum at or near 15 Hz.

In Fig. 8, calcium content is reported, as measured at end of day 7, compared to day zero and to the end of day 8, for the respective pulse-repetition rates of 15 and 72 Hz,

and for the respective fractional proportions of 6/6 and 9/3 hours on/off. Clearly, the mineralization (absolute calcium content) associated with osteogenesis is enhanced over control for the 15-Hz repetition of single pulses, and any enhancement is open to question at 72-Hz pulse repetition.

In Fig. 9, ^{45}Ca uptake is displayed to illustrate observations of differences as a function of shaft orientation, for the 15-Hz rate and for the 6/6 hours on/off situations. Clearly, orientation of the applied field parallel to the longitudinal axis of the shaft produces a materially enhanced effect, almost double the uptake of the transverse-field situation and more than three times that of normal growth in the control.

GAG Content -- In the bar graph of Fig. 10, glycosaminoglycan was taken as an indicator of protoeoglycan and, thus, of cartilage presence, wherein the day-0 level is indicated for each of the bars, representing control and pulse repetition at various rates. Clearly, cartilage is able to grow best without any exposure to pulsed magnetic fields, but the lower the pulse rate, the less inhibiting the effect on cartilage, being virtually without effect at 15-Hz.

Having considered implications of the graphs of Figs. 2 to 10, I concluded that a superior effect is involved in the pulse-rate area of 6 to 30 Hz and in particular at substantially 15 Hz. This 15-Hz rate, with the other signal data given above, then became the protocol for treatment of a number of non-unions in human beings. More specifically, for

sixteen patients whose prior treatment with the FDA-approved protocol had been unsuccessful, twelve (or 75 percent) experienced success with the 15-Hz single-pulse protocol which I prescribed, the prescription being for a pulse width of 380 microseconds; further subjected to this protocol were three new non-union cases (i.e., not previously treated by pulsed magnetic fields), and all of these cases were successful. In a separate group of patients, the 15-Hz protocol called for 200 microsecond pulses; four of the patients were previous failures (FDA-approved protocol), but three of the four responded successfully to my protocol, and one failed. There are others still on treatment, but the results are not yet reportable, for their prescription periods of treatment.

It should be noted that the average power requirements to produce the single-pulse 15-Hz magnetic fields of the invention are so substantially reduced from those of the pulse-burst technique previously used for repair of non-unions, that there is no longer need to rely on an external source of power, in that rechargeable self-contained light-weight battery operation is feasible for all single three to nine-hour dosages that may be involved.

The availability of such light-weight battery operation has enabled successful application of my single-pulse 15-Hz signals to quite different pathological situations, notably in relief of tendonitis of the arm/shoulder joint, sometimes known as "frozen shoulder". The treatments have involved a

single generally oval coil, initially wound to 14 -cm diameter, i.e., large enough to take the projection of the shoulder through the window of the coil, with excitation for at least four hours per day. The patients who were exposed to the treatments had all failed to respond to conventional therapy (i.e., cortisone, ultrasound, physiotherapy, aspirin, exercise, etc.), but in two to four weeks of pulsed magnetic-field treatment, response was successful in more than 90 percent of the cases. In addition, clinical trials to date indicate further successes for the pulsed-magnetic therapy in other tendon and joint-related lesions.

WHAT IS CLAIMED IS:

1. In the surgically non-invasive therapeutic treatment of living cells and/or tissues by subjecting the cells and/or tissues to a time-varying magnetic field wherein the time-variation is a single-pulse signal having first and second portions of opposite polarity in which one of the portions is of greater amplitude and lesser duration while the other of said portions is of lesser amplitude and greater duration, the method of improving mineralization in bone without deleterious effect on mytotic index while also avoiding proteoglycan suppression in cartilage, which method comprises repeating said pulses at a rate in the range of 6 to 30 Hz.

2. The method of claim 1, in which the repetition rate is substantially 15 Hz.

3. The method of claim 1 or claim 2, in which the pulse portion of greater amplitude has a duration in the range of 50 to 500 microseconds.

4. The method of claim 1 or claim 2, in which the pulse portion of greater amplitude has a duration in the range of 100 to 300 microseconds.

5. The method of claim 1 or claim 2, in which the pulse portion of greater amplitude has a duration in the range of 300 to 500 microseconds.

6. The method of claim 1 or claim 2, in which the pulse portion of greater amplitude has a duration of substantially 200 microseconds.

7. The method of claim 1 or claim 2, in which the pulse portion of greater amplitude has a duration of substantially 380 microseconds.

8. The method of any one of the preceding claims, in which the continued repetitive application of said pulses is a period in the order of at least one hour, with a dwell in the order of at least one hour to define an interval between successive periods.

9. The method of any one of claims 1 to 7, in which the continued repetitive application of said pulses is a period in the order of substantially six hours, with a dwell in the order of substantially six hours to define an interval between successive periods.

10. The method of any one of claims 1 to 7, in which the continued repetitive application of said pulses is a period in the order of substantially nine hours, with a dwell in the

order of substantially three hours to define an interval between successive periods.

11. In the surgically non-invasive therapeutic treatment of cells and/or tissues within a local region of a living body by locally subjecting said region to a time-varying magnetic field wherein the time-variation is a single-pulse signal having first and second portions of opposite polarity in which one of the portions is of greater amplitude and lesser duration while the other of said portions is of lesser amplitude and greater duration, the method of improving mineralization in bone without deleterious effect on mytotic index while also avoiding proteoglycan suppression in cartilage, all within said region, which comprises repeating said pulses at a rate in the range of 6 to 30 Hz.

12. The method of claim 11, wherein the cells and/or tissues to be treated in said region have a predominant orientation, and wherein said magnetic field is oriented for substantial alignment with said predominant orientation.

13. The method of any one of the preceding claims, in which said first polarity is of amplitude to induce a peak voltage of 10^{-4} to 10^{-2} volts per centimeter in cells and/or tissues within said field.

14. In apparatus for electromagnetically treating living

tissue and/or cells, comprising coil means adapted to be placed in therapeutically beneficial proximity to a body region containing the tissue and/or cells to be treated, and pulse-generator means connected to said coils for exciting the same with a repetitive single-pulse signal output wherein each pulse has first and second portions of opposite polarity and one of the portions is of greater amplitude and lesser duration while the other of said portions is of lesser amplitude and greater duration, the improvement which is characterized by a repetition rate in the range of 6 to 30 Hz.

15. The apparatus of claim 14, in which said characterized repetition rate is substantially 15 Hz.

16. The apparatus of either of claims 14 and 15, in which the time duration of said one pulse portion is in the range of 50 to 500 microseconds.

17. The apparatus of either of claims 14 and 15, in which the time duration of said one pulse portion is substantially 200 microseconds.

18. The apparatus of either of claims 14 and 15, in which the time duration of said one pulse portion is substantially 380 microseconds.

FIG. 1.

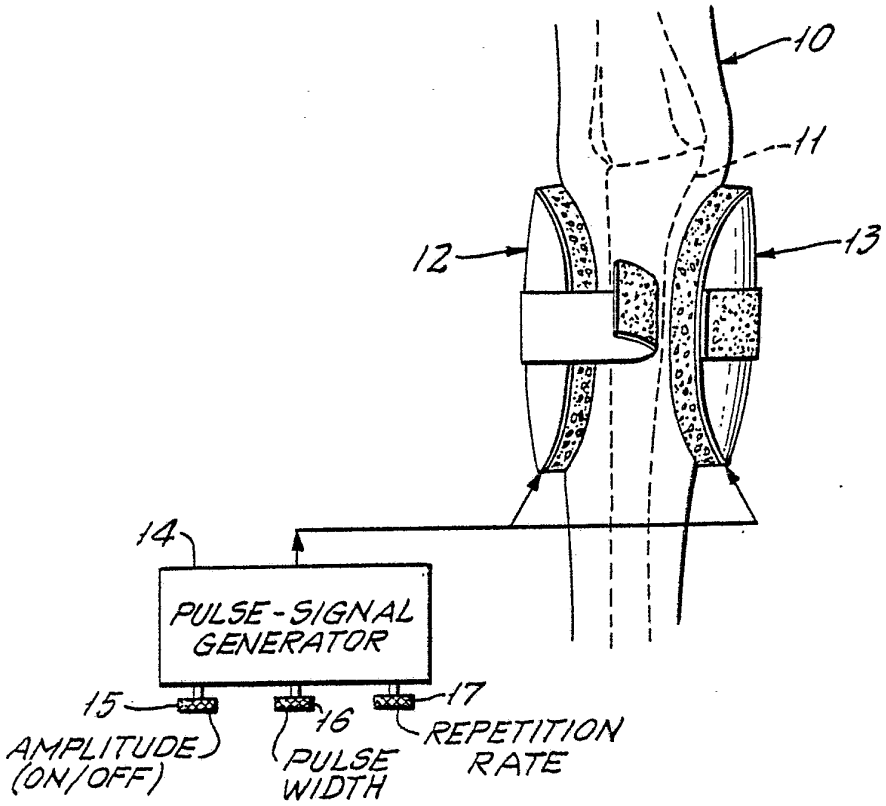


FIG. 2.

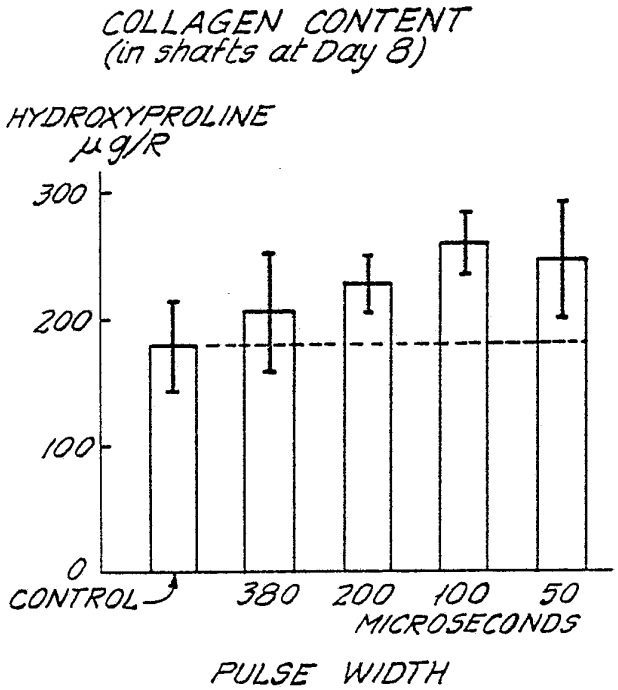


FIG. 3.

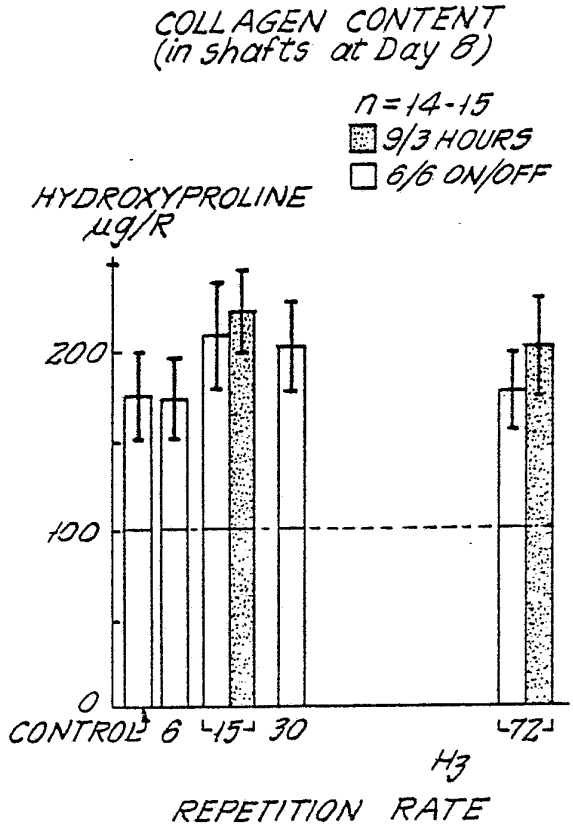


FIG. 4a. MYTOTIC INDEX, SINGLE PULSES, at 15 Hz
(^{3}H THYMIDINE UPTAKE, 24-hour contact)
Shafts, at Day 8

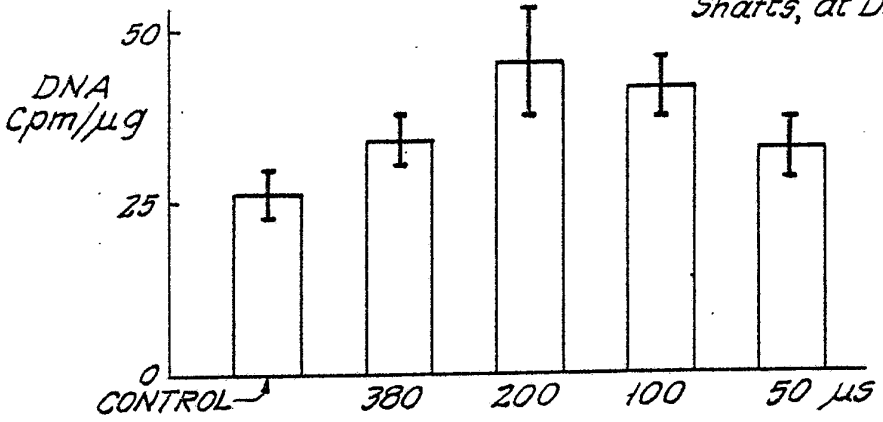


FIG. 4b. DNA CONTENT, SINGLE PULSES, at 15 Hz
Shafts, at Day 8

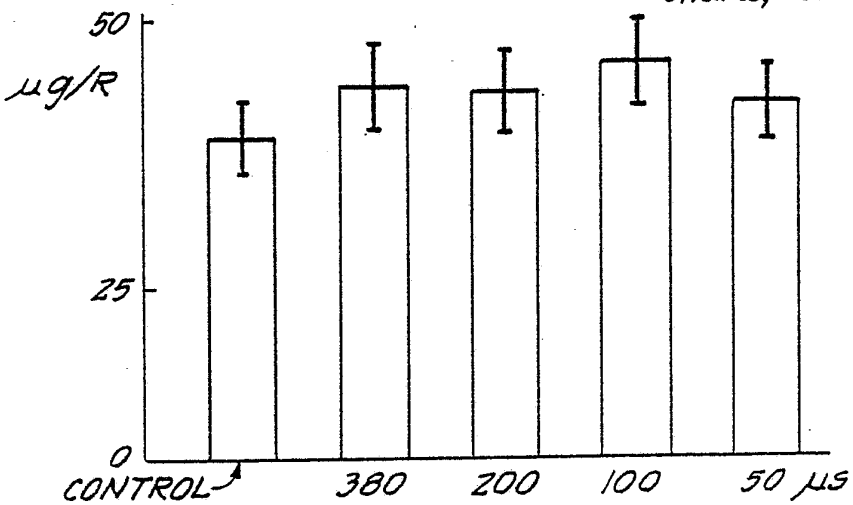


FIG. 5. MYTOTIC INDEX IN SHAFTS
(^{3}H THYMIDINE UPTAKE, 24-hour contact)

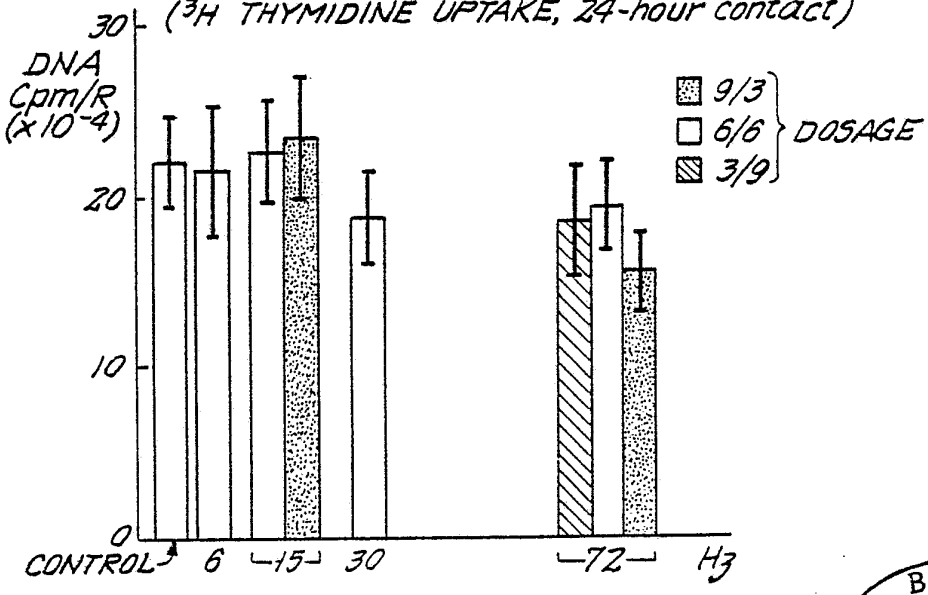


FIG. 6.

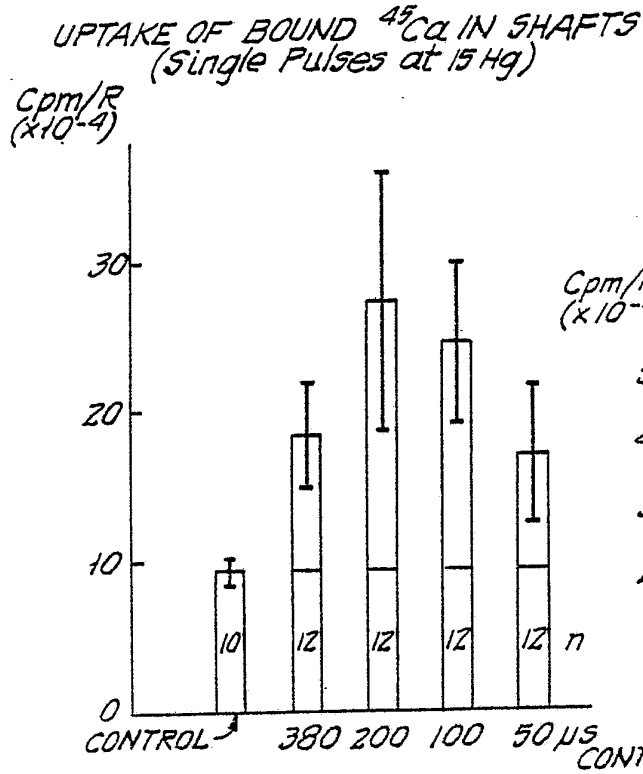


FIG. 7.

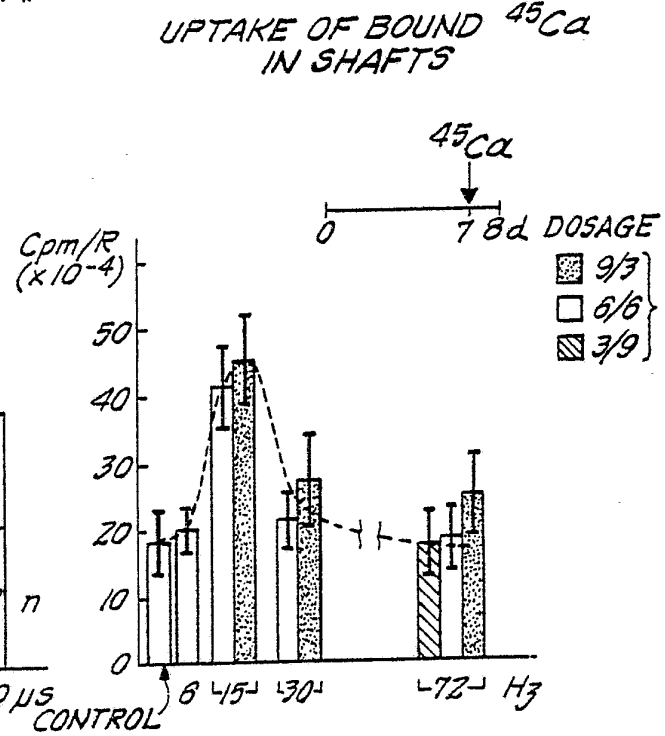


FIG. 8.

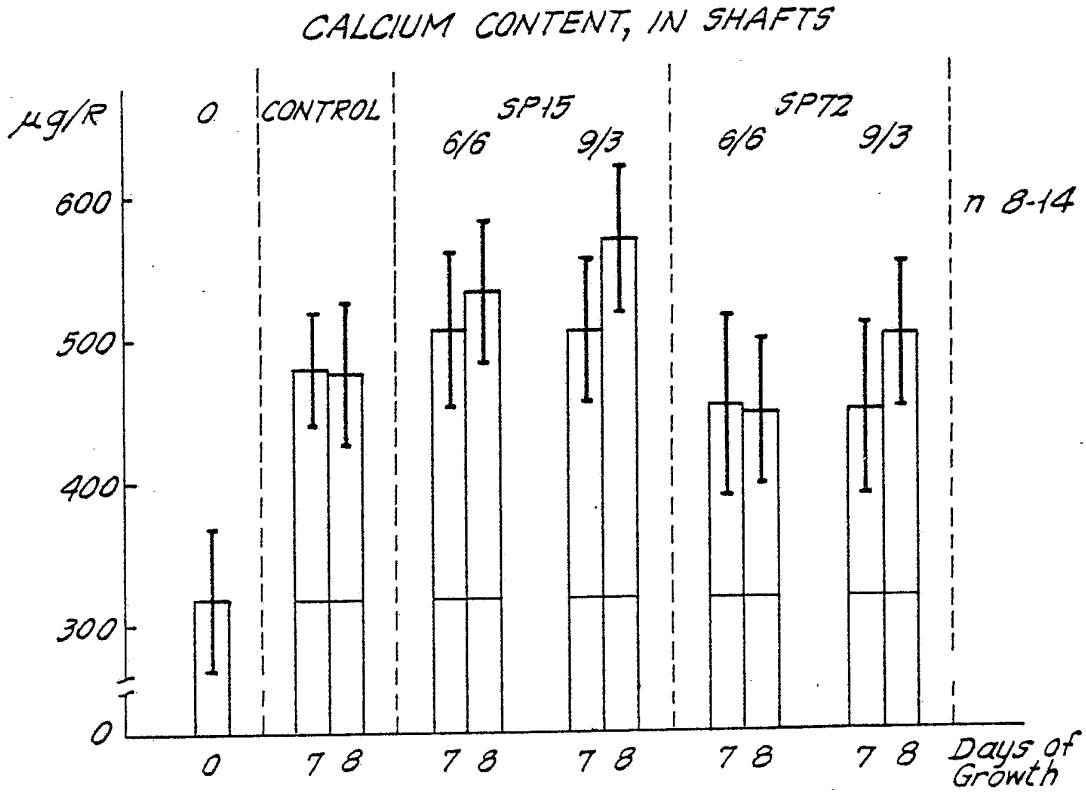


FIG. 9.

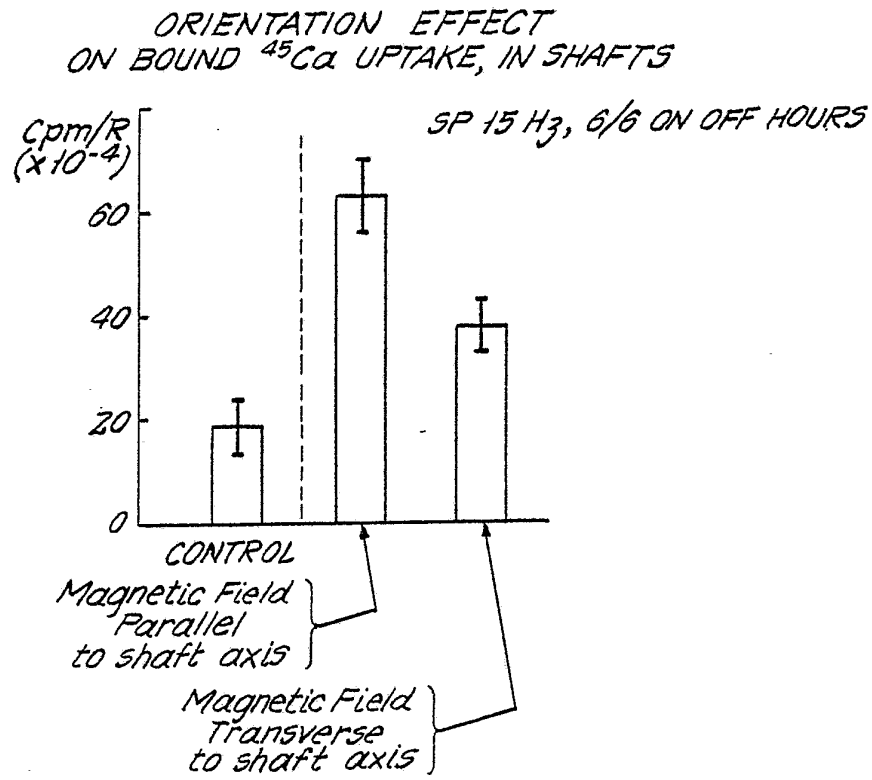
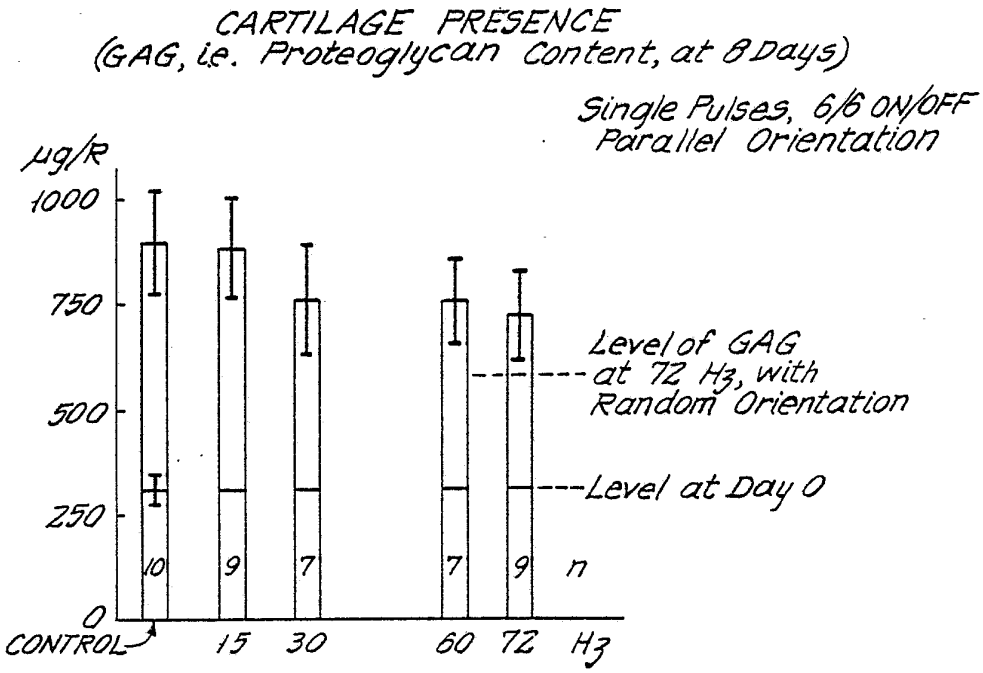


FIG. 10.



INTERNATIONAL SEARCH REPORT

International Application No PCT/US84/01088

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL. 3 A 61N 1/40
U.S. CL. 128/419F

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	128/419F, 421, 422, 82.1

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US,A, 4,266,533 12 May 1981 RYABY et al	1-18
X	US,A, 4,266,532 12 May 1981 RYABY et al	1-18
A	US,A, 3,918,440 11 November 1975 KRAUS	
A	US,A, 3,911,930 14 October 1975 HAGFORS et al	
A	SU,A, 782,815 30 November 1980 LATV EXP CLIN MEDIC	

* Special categories of cited documents: [15]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
10 September 1984	24 SEP 1984
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	MITCHELL J. SHEIN