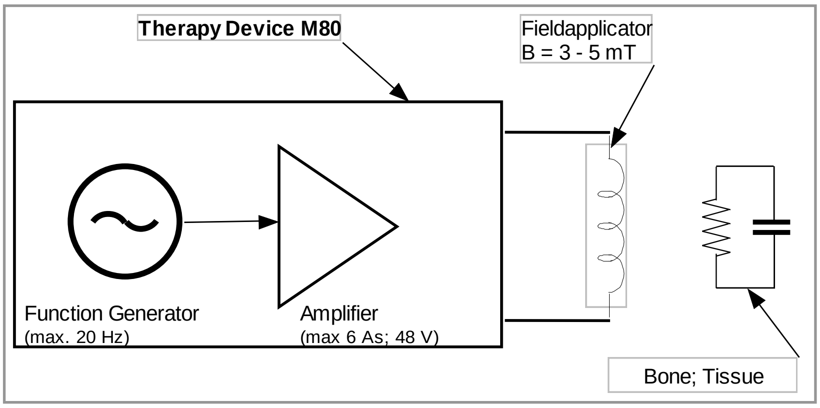
Scientific Background Information

Executive summary

- *In vitro* studies show the accelerated proliferation and enhanced differentiation of fibroblasts and ostepoblasts to postmitotic function cells. The production of cell specific proteins (i. g. Collagen) is significantly increased (up to 10 fold).
- *In vitro* studies show a up regulation in gene expression of growth factors like TGF-β and FGF-2
- *In vitro* studies show that the electromagnetic fields of the Magnetodyn® -System stimulate the osteogenic and chondrogenic differentiation of mesenchymal stem cells.
- *In vitro* studies show that the growth of planktonically cultured bacteria (*Staph. aureus*) is reduced under the influence of electromagnetic fields according to the non-invasive and invasive Magnetodyn® -System. The effectiveness of clinically used antibiotics is increased in combination with the electromagnetic fields.
- The physical parameters of the Magnetodyn® -System are within the most effective range (sinusoidal;15 to 30 Hz) in respect to the osteogenic potential of osteoblasts.
- The frequencies of the Magnetodyn® -System are in the range of zyclotron resonance frequencies of Ca.
- A differentiation dependent modulation of the Calcium oscillation is observed after application of the Magnetodyn® specific fields
- No significant adverse events have been reported within the course of the Magnetodyn® market surveillance and in the MAUDE database.

Technique

From the technical point of view, the device consists of a functional power generator with a downstream amplifier and a current-carrying coil (primary inductor) sheathed with plastic. The magnetic field generated in the coil is proportional to the current flowing through the coil and the number of turns on the coil. The dimensions and the geometry of the field applicators are adapted to the indication and the area to be treated.



Treatment Parameters

The magnetic field is characterized by a pure sinusoidal wave form with very low harmonics, a magnetic flux density of 3 – 5 mT and a frequency of 2 – 20 Hz.

Treatment duration is typically 2 x 45 min/day, overall treatment time is depependant on indication but normaly between 2 and 4 months.

Theoretical Fundamentals

The selection of the treatment parameters is based on physiological parameters:

The frequency and the temporal course of the pulse wave, the respiration, the muscle contractions and the piezoelectric potential of the bone and the connective tissue when strained and relaxed (10 - 30 Hz) as well as the membrane potential of blastic cells (50 - 100 mV). The electric deformation potentials of the supportive and connective tissue run bipolarly and sinusoidally when strained and relaxed continuously. By means of the Fourier transform, all types of oscillation that are not sine-shaped may be described as a superposition of partial sinusoidal oscillations of different frequencies and phases.

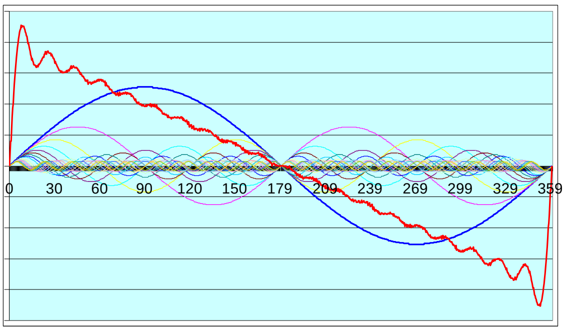


Fig. 1 Fourier syntheses of a saw-tooth signal, generated by superposition of sinusoidal waves of different frequencies, intensities and phases:

$$x_S(t) = \sin(\omega_0 t) + \tfrac{1}{2}\sin(2\omega_0 t) + \tfrac{1}{3}\sin(3\omega_0 t) + \ldots$$

Research published in the USA supports the selection of this frequency range. **Otter et al. (1998)** provide a survey of experimental works on the efficiency of static (d.c.) and alternating (a.c.) electromagnetic fields used in the sector of bone healing. In particular, he considered the trials performed by **Rubin et al. (1993),** dealing with the spectral energy distribution of pulsed electromagnetic fields. They examined the spectral distribution of the electric fields induced into the bones and the surrounding tissue within various therapeutic systems making use of pulsed electromagnetic fields (PEMF). It turned out that the low frequency sinusoidal proportion of these electromagnetic fields prevent the bone loss and induce the osteogenesis. Sinusoidal fields within the range of 15 - 20 Hz proved to be most efficient. This provides an explanation for the superior results of the Magnetodyn® -System compared to PEMF devices with burst signals. They conclude that the frequencies and field intensities most effective in the exogenous stimulation of bone formation are similar to those produced by normal functional activity.

Mode of Action

‘Actual research shows that the underlying mechanism is fundamental. The low frequency magnetic field affects direct the inner membrane system amongst others with Ca^{2+} ions. Ca^{2+} ions are essential regulatory components of all organisms. Being a second messenger Ca^{2+} is involved in regulations at all stages of cellular growth and development, including proliferation, differentiation, assembling and disassembling of cytoskeleton elements.

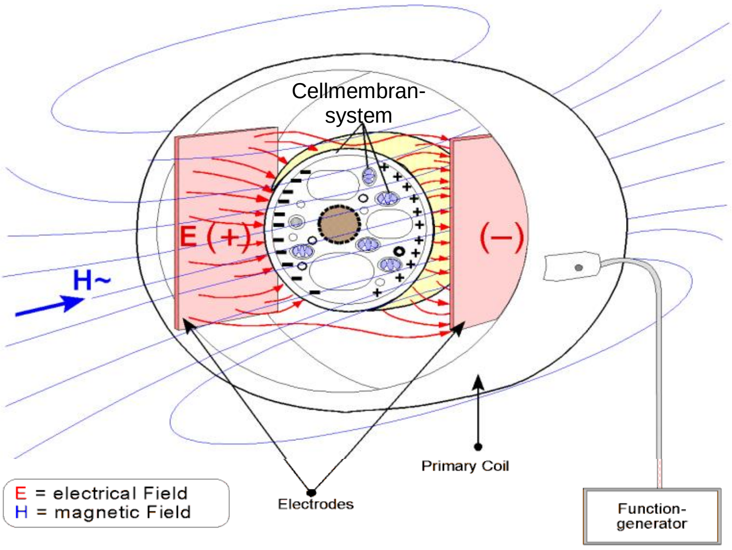


Fig. 2 The plasma membrane is influenced by the electrical field **(E)** The plasma membrane and the inner membrane system are affected by the alternating magnetic field **(H)**. It initiates the signal transduction and -amplifying (e.g. Ca^{++}-Oscillation, cAMP, NO) and accelerates the cell-differentiation

In can be shown that in the presence of the magnetic field of the earth there are resonance effects with Ca ions when low frequency fields between 15 and 30 Hz are applied. Furthermore the calcium oscillation, that is the change of the cytosolic calcium, is affected by the magnetic fields (**Löschinger, Thumm, Hammerle et al. (1999)**).

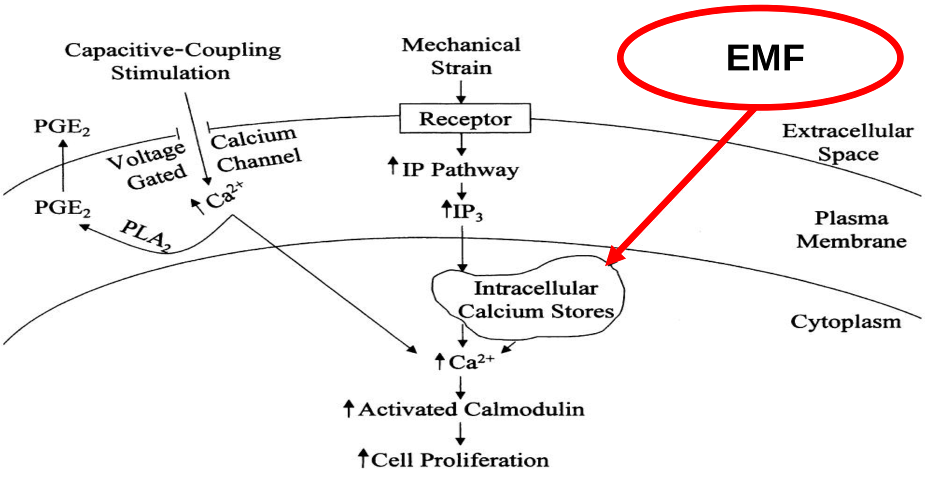


Fig. 3 Signal transduction pathway accordin to Aaron (2004)

According to **Aaron et al. (2004)** different magnetic fields influence the regulation of the intracellular calcium through trans-membrane coupling and stimulate the synthesis of growth factors like TGF-β.

Summary of experimental investigations on the Magnetodyn®-System relevant to the indications

In vitro Studies

We successfully completed to projects on the efficacy and mechanisms on action, funded by the Bavarian Research Foundation (BFS), in cooperation with the Technical University München, Prof. Dr. Dr. A. Stemberger, and the Ludwigs-Maximilians-University, Munich, Prof. Dr. med. Dipl.-Ing. V. Jansson and PD Dr. med. Susanne Mayer.

The following results were obtained:

- The influence of electromagnetic fields in combination with specific growth factors like Fibroblast Growth Factor (FGF 2) and Transforming Growth Factor β3 (TGF- β3) on the chondrogenic and osteogenic differentiation of human mesenchymal stem cells (hMSC) was investigated within the supported project „Electromagnetic stem cell differentiation“ **Mayer-Wagner et al. (2011); Mayer and Stephan (2010)**. The results show that by an electromagnetic stimulation with specific parameters (5 mT, 15 Hz, sinusoidal signal) the chondrogenic potential of chondrocytes and hMSC is increased. The osteogenic differentiation of hMSCs could also be improved. An improved production of cell specific proteins is essential for the application of regenerative therapies on degenerative diseases and healing disorders of the bone. The results regarding the differentiation of fibroblasts and osteoblasts, published by **Löschinger, Thumm, Hämmerle et al. (1999); Rodemann et al. (1989); Thumm, Löschinger, Glock et al. (1999); Thumm, Löschinger, Hämmerle et al. (1999)**, were confirmed in preliminary studies. Further studies will be performed.

- The influence of low frequency electric and magnetic fields on the growth of clinical relevant bacteria has been investigated under the framework of the project "Infect-treatment with electromagnetic fields". The investigation has been carried out with *Staphylococcus aureus,* unquestionably the most frequently occurring pathogen in bone infections.

  Clinical observations have shown that in infected pseudarthrosis the Magnetodyn® Therapy improves bone healing and decreases bone infections. Cohort studies show a higher healing rate compared to the standard therapy without electromagnetic stimulation [**Ascherl et al. (1985); Konrad (1996); Lechner et al. (1981); Lechner et al. (1979); Schmit–Neuerburg (2001); Stephan and Kraus (2008)**]. These studies have been discussed in detail in the Clinical Report 2002.

  The influence on the growth of planktonically grown cultured bacteria of the electric and magnetic fields alone and in combination with Gentamicin has been investigated. The results are shown in **Error! Reference source not found.**. The blue coloured olumns represent the results for the fields with the physical parameters of the Magnetodyn® -System. The results confirm the clinical observations: The growth of bacteria is decreased and the efficacy of the antibiotic Gentamicin is improved [**Matl (2009); Matl et al. (2011); Obermeier (2007); Obermeier et al. (2009)**].

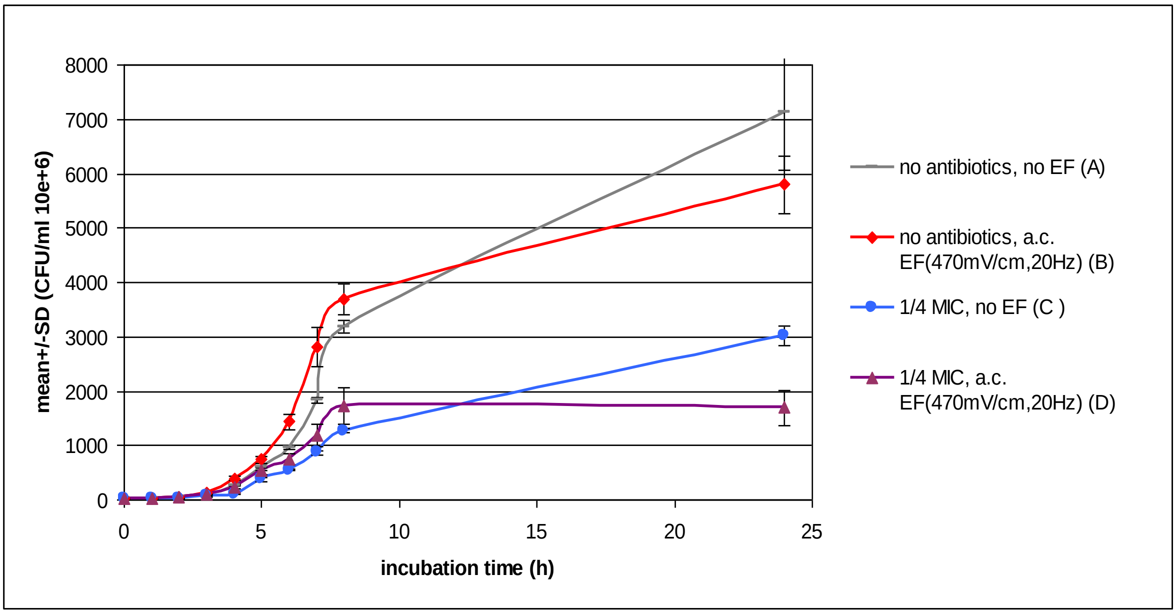


Fig. 4 Bacterial growth over 24 h: (A) Control; (B) Stimulation with a.c. electric field (470 mV/cm, 20 Hz); (C) only Gentamicin; (D) combined application of Gentamicin and electric field. (B) statistically significant compared to control at 24 h; (D) statistically significant compared to control and to Gentamicin alone at 24 **h**

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Rodemann et al. (1989); Rodemann et al. (1992), **Löschinger et al. (1998); Löschinger, Thumm, Hämmerle et al. (1999)** and **Thumm, Löschinger, Glock et al. (1999)** examined the impact of the fields typical of the method on normal fibroblasts from human skin as well as chicken osteoblasts of a homogeneous degree of differentiation. The cell lines used are distinguished by the fact that the differentiation stages of mitotically active precursor cells of postmitotic fibrocytes and osteocytes have been examined and described assiduously by means of morphological and biochemical parameters.

As compared to the results of the control, the long-term exposure (6 hrs/day) accelerates the differentiation of the cells into postmitotic fibrocytes and osteocytes. In comparison with the screenings, the fibrocytes, differentiated by means of the electromagnetic field (EMF)

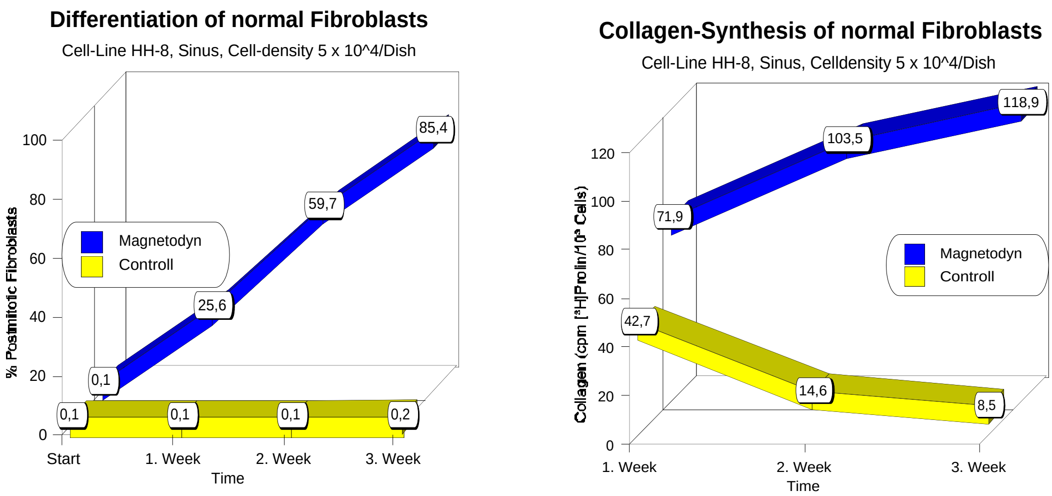

Fig. 5 Differentiation and collagen sythesis of normal human fibroblasts, Rodemann et al. 1989

treatment, produce 10 - 13 times more interstitial collagen than is required for the formation of the bone matrix after 21 days. The results are significant at $p < 0.05$ (Fig. 5).

Examining individual cells for the intracellular calcium activity of dermal fibroblasts through the confocal laser scanning microscope, a differentiation stage-dependent modulation of the Ca^2 oscillation could be observed after 40 minutes of EMF exposure (Fig. **6**). Experiments on mitotic precursor cells revealed that the proportion of cells oscillating at a higher frequency increased by the factors 2 - 4, as opposed to the results of the experiments on postmitotic cells. The relatively unconfined calcium activity was determined as the maximum of the fluorescence per individual cell. As compared to the screening results, it increased by the factor 5. The examined oscillation patterns are in keeping with the hypothetically feasible and experimentally described coupling patterns of electromagnetic fields into biological systems via the Ca^2 regulation pathway.

Examinations of the protein kinasis A-activity (PKA) and rat osteoblasts revealed a statistically significant increase of the PKA by the factor 2 after 60 minutes of EMF exposure. **Heermeier et al. (1998)** examined the effects of the electromagnetic fields characteristic of the method on the collagen expression type I mRNA and the formation of the extracellular matrix, as compared to the growth factors on osteoblastic cells within a three-dimensional cell-culture model. The cells were taken from a trabecular bone of a healthy test person (HO-197) and a patient suffering ossifying myositis (MO-192) and were then cultivated in a three-dimensional collagen sponge. The maximum increase of the type I expression after the EMF treatment was 3.7-fold in HO-197 cells and 5.4-fold in MO-192 cells. A comparable increase could be observed after the treatment with the transforming growth factor-beta (TGF-Beta) and the insulin-like growth factor I (IGF-I). The data suggest that the effects of the EMF on the osteoblastic differentiation may be compared with the effects of the TGF-Beta and IGF-I. Therefore, the authors conclude that the effects of the EMF treatment (in cases of defective bone function or as an orthopaedically adjuvant therapy) are imparted through the increase of the collagen type I mRNA, resulting in an increased extracellular matrix synthesis.

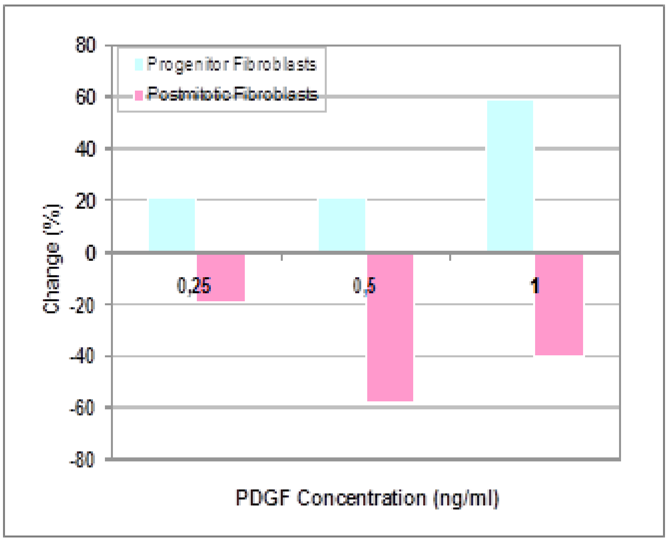

Fig. 6 Differentiation stage dependent response to the EMF stimulation upon the simultaneous administration of sub optimal concentrations of a growth factor. Changes as compared to the control, Löschinger et al. (1999)

Animal Experiments

By means of animal experiments, **Aldinger et al. (1994)** examined the impact of the fields characteristic of the method on the osteogenesis in rats, using the model of the matrix-induced osteogenesis: Osteoinductive matrix preparations were implanted in the front abdominal musculature distant from the skeleton and in turn quantitatively examined for osteogenesis. The animals of each therapy group were exposed to a frequency of 20 Hz sine and a flux density of 6.4 mT under controlled conditions.

In the first experiment, they submitted the test animals to an EMF treatment for 13 days, using denatured bone matrix as osteoinductive implant material (4 implants/animal, each n = 12 for the therapy and control group). After the experiment, they withdrew the implants and histologically examined them for osteogenesis. Then they quantitatively determined the bone tissue regeneration on the basis of both the calcium content (Ca content) and the alkaline phosphatasis activity (AP activity) of the explanted tissue. As compared to the control group, which had been kept under identical conditions, the EMF group displayed an AP activity significantly increased by 25% and a Ca implant activity significantly increased by 15%. After another 13 days of therapy, they used native bone matrix as implant material for the second approach, and they, as compared to the control group, traced a significant 56% increase of the Ca activity of the EMF group, with 6 grafts being implanted per animal and with each group consisting of 12 animals. In the third approach, they used less active and chemically pretreated bone matrix as implant material. After 19 days of treatment, they observed a Ca activity increase by 29 % within the EMF group, as compared to the control group (n = 11) (Fig. 7).

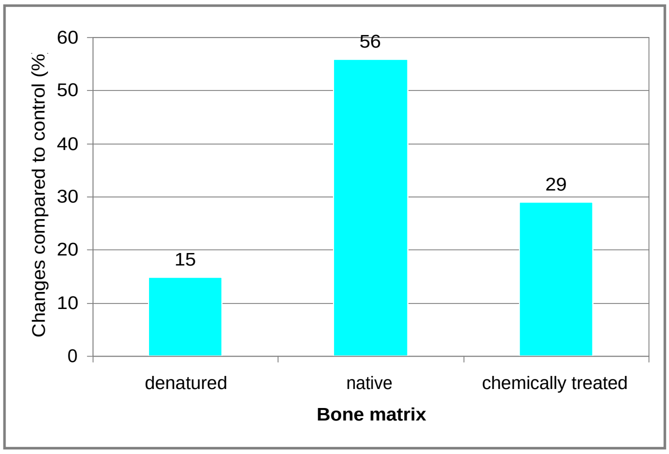

Fig. 7 Increase of calcium activity as compared to the ctnrol. Results are satistically significant at $p < 0.05$, Aldinger et al. 1994

In this model, the EMF treatment results in a reproducible accelerated bone formation the extent of which depends on the type of the osteoinductive implant material used. The authors take the view that, in comparison with a rat, a stronger osteostimulative effect can be expected, as both the osteo-inductive activity of the transplanted human bone tissue and the human metabolic activity index are considerably lower.

Under randomised conditions, **Böhm and Kinner (1996)** examined 30 rats to find out whether the fields characteristic of the method accelerate the take of autoclaved bones. On the basis of autogenic autoclaved diaphysary tibia segments, they observed the take, applying radiologic, microradiographic and histological criteria and measuring the bone mineral content over a period of 4 weeks. After the 2nd and 3rd week, the semiquantitative evaluation of the radiologic progress revealed a significant acceleration of the take processes ($p < 0.01$) in the EMF group and after 4 weeks, a significantly increased remodelling of the autoclaved bone. The radiologic results could be verified microradiographically and histologically. Within 4 weeks, massive callus bridges had formed in the active group. In the control group, they always observed a parting line consisting in the fibrous connective tissue located between the implant and the bone. Only in the active group did they observe first signs of the revascularisation and transformation of the autoclaved bone, apart from the proximal callus, endostal consolidation within the osteotomy line and osteoanagenesis within the dorsal area of the reimplant. The remainder of the examined parameters revealed a promising tendency toward an accelerated take but they were of no significance ($p < 0.1$) due to the marked scattering range.

Within the framework of a trial supported by the former German Ministry of Research and Technology, **Mühlbauer (1982)** examined the impact of low-frequency magnetic fields (Magnetodyn), featuring 22 Hz and 8 mT, on the wound healing process, using a defined model of a necrotising skin wound. Rectangular pieces of 4 cm^2, 12 cm^2 and 20 cm^2 were cut out of the dorsal skin of 30 Wilstar rats with the uncovered subcutis being cauterised by putting hydrochloric acid pads on it. Thereupon, he measured the reduction of the wound area until the wound closed and compared the treated animals with the screenings. He then analysed 20 animals histologically. From the 10th day after the start of treatment on, the difference could be seen clearly and was statistically significant ($p < 0.05$ after 12 days and $p < 0.01$ after 20 days) in all groups. The effect could be noticed most clearly in the largest wounds (20 cm^2). Under the influence of EMF, these wounds closed after 21 - 26 days of treatment while the control animals still featured open wound areas and scab after 50 days ($p < 0.01$). Histologically, he observed an accelerated restoration of the fibrillar system. In addition, the oedemas of the treated animals healed more quickly. These results coincide with the experiences the users made, applying the magnetically induced electroosteotherapy. All of them observed an uneventful and accelerated healing of their wounds as well as a faster decomposition of their postsurgical oedemas (**Schmit–Neuerburg (2001)**)

In a rat wound model there was a statistically significant acceleration of the healing rate for the first 9 days in the PEMF-stimulated group, whereas a qualitative improvement of healing progress was identified by histological examination at all time points, compared to the control group **Athanasiou et al. (2007)**.

In another animal model wounds in the magnet group (0,23 mT, static) healed in an average of 15.3 days, significantly faster than those in either the sham group (20.9 days, $P=0.006$) or control group (20.3 days, $P<0.0001$). There was no statistically significant difference between the sham and control groups ($P = 0.45$) **Henry et al. (2008)**.

In another study, diabetes was induced in male Wistar rats. One month after the induction of diabetes, a full-thickness dermal incision (35 mm length) was made on the right side of the paravertebral region. The wound was exposed to ELF PEMF (20 Hz, 4 ms, 8 mT) for 1 h per day. Wound healing was evaluated by measuring surface area, percentage of healing, duration of healing, and wound tensile strength. Obtained results showed that the duration of wound healing in diabetic rats in comparison with the control group was significantly increased. In contrast, the rate of healing in diabetic rats receiving PEMF was significantly greater than in the diabetic control group. The wound tensile strength also was significantly greater than in the control animals. In addition, the duration of wound healing in the control group receiving PEMF was less than the sham group. Based on the above-mentioned results the authors conclude that this study provides evidence to support the use of ELF PEMFs to accelerate diabetic wound healing [**Goudarzi et al. (2010)**]

Pullar (2009) measured and modelled the endogenous fields in different types of chronic wounds. These findings together with advanced knowledge on how electromagnetic fields alter cell behaviours will further optimise the use of electromagnetic stimulation for healing of chronic wounds.

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