

# *i-Health®systems*

*A scientific evaluation*

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by:

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***Introduction.***

The i-Health®system contains 3 modules,

- the elektro-dermal-screening module, (Bio-impedance or skin-resistance measurement),
- the thermography module,
- the low level light therapy and
- the pulsating electromagnetic field (PEMF) therapy module.

In this documentation the most important biophysical and physical-chemical as well as biochemical and anatomical principles of the involved modules and functions are condensed.

# *Itronic EDA module.*

A scientific evaluation of electro dermal screening

An overview of the principles of electro-dermal screening at specific skin zones and the validity of these measurements for preventive screening and for monitoring the effects of treatments, as derived from scientific publications are described.

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## ***The System for electro dermal screening***

### ***Intended use:***

System for

- preventive screening;
- detection of pathologies;
- monitoring effects of treatments;

### ***History***

The Itronic EDA-module of i-HEALTH is a copy of the Russian electro-dermal screening system that has been developed for the purpose of monitoring the health of cosmonauts during long term space travel. This Russian system has been used since 1984 during the Bhuran and MIR-space programs. Sagrjadski et al ( 1996) have published a number of studies about the results, that have been endorsed by the Russian Academy of sciences. Similar systems have been developed since for which accessible clinical studies have been carried out (Lurie, 2007; Zimlichman, 2007).

### ***Anatomical, neurological an biophysical Principles***

i-HEALTH Itronic EDA methodology is based on known neurophysiologic principles and research into the reflexological pathways between the body's internal organs and the skin. It is based on the following components:

- The skin and all nervous tissue develop during embryonic growth from the identical metaphase plate, the ectoderm.
- Correspondence among the innervations of visceral structures, organs and their representative skin zones (dermatomes, Heads zones, referred pain zones, metameric overlapping zones, Chinese reflexological zones, zones of autonomic innervations, classical connective tissue zones and muscle meridians). See fig.2.
- Physiology of the standard nervous system pathways, including the visceral-visceral, visceral-somatic, somatic-visceral, somatic-somatic and visceral-cutaneous reflexes.
- Pathophysiology of damage to internal organs and corresponding reflex reaction of the nervous system.
- Changes in the electrical potential and impedance of the cells/issues/organs of human body correspond to various disorders of internal organs.

Changes occur to the inter/extra cellular balances of ions, fluids, metabolic substance, neuropeptides and inflammatory mediators due to physiological and pathophysiological processes within the object (cells/tissues/internal organs). These imbalances provoke changes of electrical impedance in the object and transfer the electrical impulses with abnormal potential to the dorsal horn of the spinal cord and the metameres. The differences in impedance and potential from an internal organ may be registered in several representative dermal-visceral zones (DVZs) both inside and outside the same metamere.

A strict intercommunication between impedance values at certain skin zones, i.e. the Headsche Zones and normal/abnormal conditions of corresponding internal organs has been determined ( Lurie, 2007). Each internal organ has corresponding zones on the trunk and on the limbs. Lurie and Zimlichman (2007) examined DVZs both on the trunk and on the limbs and established that the information from the limb-zones is an average value of the impedance of all zones of a specific dermal-visceral interconnection.

*Interpretation and graphical representation based on norm-values and TCM conventions.*

The norm-values and algorithms that resulted from the Russian studies were made available to i-HEALTH as well as the collection of raw data. These values have been applied in the software, together with the conventions of traditional chinese medicine (TCM) and acupuncture for the representation of meridians and the related functions and organs ( Schnorrenberger, Hempe, 2001, Taschenbuch der Akupunktur). Secondly the technical specifications with respect to measurement pulse, choice of material, sampling and mechanical pressure of the sensor at the skin, have been used as well. These specifications have been chosen because of the minimal impact on the structure and bio-chemistry of the skin, i.e. acupuncture-points ( Sagrjadski et al, 1996. several publications. Treugut, 1999).

In two independent studies the measurements have been validated. (Sponring, 2003; Bosma, 2006). Sponring showed that in a population of healthy athletes the eda-measurements are more reactive and accurate than lactate-values.

The study by Bosma, based on a major animal trial with measurements of several hundred cows, published in the peer-reviewed journal *Livestock Science* 99, 2006 showed that veterinary health parameters, such as Days in milk, estimated recovery of energy balance after calving, body condition score, natural logarithm of somatic cell count, number of ingestions, costs of veterinary, mortality rate, immunological parameters were closely and inversely related to skin resistance values.

**Table Impedance ( $m\Omega$ ) at 6 acupuncture points of lactating 5 dairy cattle in herds with good (n=69) health status or with poor health (n=100); (n for BL 49: 51 and 86, resp.)**

<b>Health status</b>	<b>BL15L</b>	<b>BL15R</b>	<b>BL49L</b>	<b>BL49R</b>	<b>BL52L</b>	<b>BL52R</b>
<b>Good</b>	4.0 0.25	$\pm 3.2$ 0.16	$\pm 3.9$ 0.29	$\pm 3.5$ 0.19	$\pm 3.6$ 0.26	$\pm 3.1$ 0.20
<b>Poor</b>	5.0 0.26	$\pm 4.2$ 0.22	$\pm 5.1$ 0.38	$\pm 4.6$ 0.33	$\pm 4.4$ 0.30	$\pm 4.3$ 0.22

From the literature norm-values are known that indicate the presence or absence of stress or for depletion of energy. These normative values have been the subject of two research projects ( Sponring, 2003, and Bosma, 2006).

Secondly, a parameter-free test has been developed for the characterization of the type of distribution of the measurement-values. The type of distribution is indicative for the nature of the vegetative regulation of the organism ( Klimek, W, 2004; Popp, et.al, 2004): normal adaptation ( elastic, within a certain bandwidth), no adaptation ( blocked), or chaotic ( Gauss) adaptation.

Norm values:

As norm values and thresholds for hyper, normal energy levels and hypo-energetic levels indicating vegetative stress or depletion, we used the following values, cF Sagrjadski i et al (1996):

*Normative range = 1.000 – 2.000 KOhm; with children (depending on age) 400 – 800 KOhm.*

***below 500 KOhm***

***excessive hyper energy:*** possibly caused by moisture at the skin. Therefore the oints of measurement need to be dried with a tissue after which the measurement can be repeated. When the result is the same, the energy excess is true and signifies a blocked energy regulation for example due to excessive stress, overtraining, pain, or a foci, acidification or inflammation. A possible remedy may be to give Calcium-Magnesium tablets, breathing exercise or relaxation, may be even anti-biotics or zappin

***600 – 501***

***Strong hyper energy:*** See above but less strong. It may include a stagnation at the organ-level. dies bedeutet ***eine Verkrampfung*** und eine ***Stauung in diesem Organ***. De-acidification is necessary.

***700 – 601***

***Intermediate hyper energy:*** See above. This also indicates a cramped situation with stagnation at the organ-level.

***800 – 1000***

***Hyper energy:*** Same remedies. Relaxation, breathing exercise, glass of water.

***1001 – 2000***

*Normal Energy level.*

**2001 – 3000**

**Lesser hypo energy level:** This result shows up very often. It has many causes, from a shortage of sleep and to little exercise, running high on processing food to the beginning of energy depletion due to lack of vitamins or a developing chronic situation.

**3001 – 4000**

**Slight hypo energy:** At this level the output, stamina and muscle capacity are diminished, probably due to long lasting stress, too much exercise and too little recovery. Check the persons life-style.

**4001 – 5000**

**Intermediate hypo energetic I:** signifies a reduction of the energy-output and regulative capacity, also at the organ-level of the affected meridians. Recovery is necessary, for example through healthier eating habits, suppletion of vitamins and minerals. Repeat the measurement after a week.

**5001 – 7000**

**Intermediate hypo energetic II:** This indicates a reduction of the functions of the organ(s).

**7001 – 10000**

**Severe hypo energy:** This signifies a reduced activity at the organ-level. Check life-style, stress, foci (teeth !), chronic infection, need for detox, exposure to toxins, exposure to electro-magnetism while being susceptible.

**über 10000**

**Energy depletion:** suspicion for organic failure and also the above.

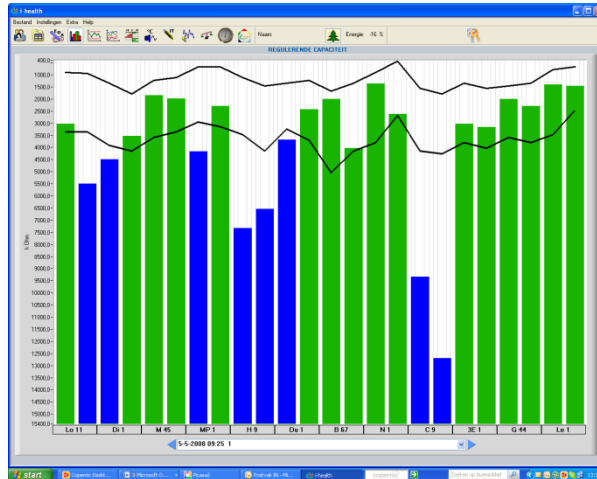
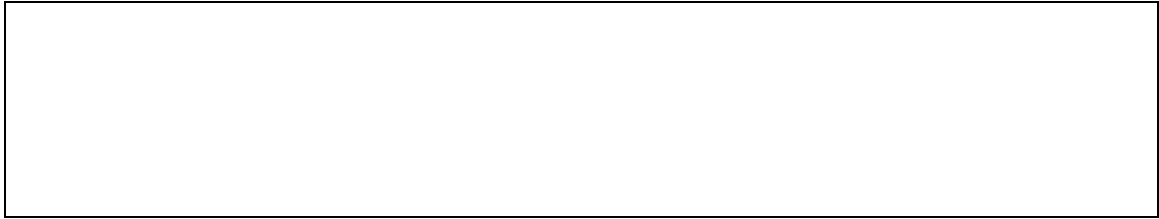


Fig.1. Graphical representation of skin resistance values as compared to norms: Hypo energetic points in blue. Normal energy in green.

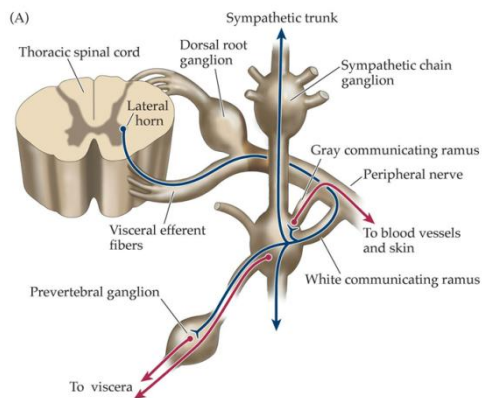
Anatomical aspects of the points of measurement .

The 24 points of measurement have been chosen because they are the most easy to localize, being located next to the nail bed of the toes and the fingers. This reduces the number of mistakes considerably.

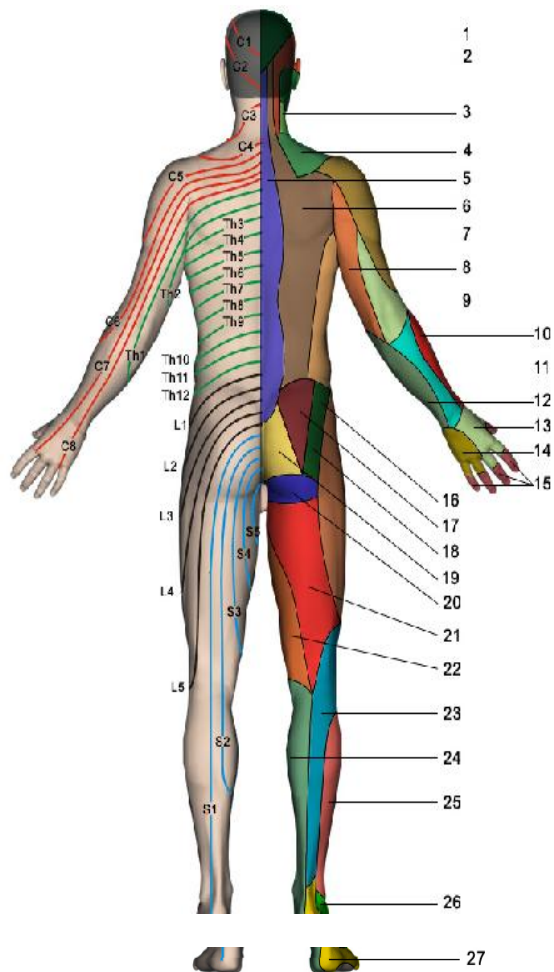
Lu 11:	<i>Nervi digitales palmares proprii des Nervus medianus</i>
Di 1:	<i>Nervi digitales palmares proprii des Nervus medianus</i>
M 45:	<i>Nervus cutaneus dorsalis medialis pedis</i>
MP 1:	<i>Nervus cutaneus dorsalis medialis pedis</i>
H 9:	<i>Nervus digitalis palmaris proprius des Nervus ulnaris</i>
Dü 1:	<i>Nervus digitalis palmaris proprius des Nervus ulnaris</i>

B 67:	<i>Nervus cutaneus doralis lateralis pedis</i>
N 1:	<i>Nervus plantaris medialis</i>
KS 9:	<i>Nervus digitalis palmaris proprius des Nervus medianus</i>
3E 1:	<i>Nervus digitalis palmaris proprius des Nervus ulnaris</i>
G 44:	<i>Nervus cutaneus dorsalis intermedius pedis</i>
Le 1:	<i>Nervus fibularis profundus</i>

These points of measurement are not only connected with the vegetative nervous system but they are also defined as belonging to different dermatomes or Heads zones and thus each point is linked, through the spine, to different organs and different parts of the vegetative nervous system as can be learned from every standard anatomy textbook.



*Fig.2. Anatomy of sectional dermal-visceral innervation.*



1. Greater occipital nerve
2. Lesser occipital nerve
3. Great auricular nerve
4. Supraclavicular nerves
5. Medial cutaneous branches of dorsal nerves
6. Lateral cutaneous branches of dorsal nerves
7. Upper side skin nerve of a shoulder(arm)
8. Medial cutaneous nerve of a shoulder(arm)
9. Back skin nerve of a shoulder(arm)
10. Superior lateral cutaneous nerve of the shoulder
11. Posterior cutaneous nerve of the forearm

**Fig.3. Sectional and skin innervation (dorsal view)**

Since these points of measurement at dermal visceral zones are also beginning or end-points of the meridians, the graphs can be interpreted according to the conventions of traditional chinese medicine (TCM). Begin-points are (Large intestine 1, Spleen Pancreas 1, Small intestine 1, Kidney 1, triple heater 1, Liver 1) or end-points ( Lung 11, St45, H9, B67, P9, Gb 44) of meridians. See for example Schnorrenberger, 1985; Acupunctureatlas, Seirin; Hempe, 2004: Taschenbuch der Akupunktur. EDT-Verlag).

Choice of appropriate technical characteristics.

i-HEALTH decided to apply the technical specifications as used for the device by Sagrjadski since

- the technical specifications with respect to the lowest amperage and the lowest specific pressure at the point of measurement
- the best reproducibility and accuracy, as compared to other systems (Treugut, 1994), is the greatest.
- The measurements with devices that use fixed probes can be manipulated and need much training before reliable measurements can be carried out (Larsen on Ryodoraku, Yamamoto, Voll).

Sagrjadski et al(1996) discusses the extensive research and development project in which 22.500 persons were involved to validate the method by comparison of the eda-data with the results of a conventional integral diagnosis. Depending upon the nature of the condition the eda-screening is 75 to 95% accurate. Zimlichman et.al.(2005) reports about similar accuracy with different conditions.

Determining factors for the reliability and reproducibility of the measurements, according to Sagrjadski, that may irreversibly influence the facies, the connective tissue and the nerves are the measurement current and the mechanical pressure at the point of measurement. It is important:

- to exert a constant pressure at the point of measurement during the sampling.
- An amperage of not more than 4  $\mu$ A. (The itronic eda pulse is 1  $\mu$ A).
- A limited duration of the pulse, i.e. of 200 ms.

These values have been taken as design-criteria for the development of the i-HEALTH itronic EDA device. When higher amperage is used or a higher pressure, the point of measurement will be irreversibly influenced and consecutive measurements become meaningless.

Several studies have shown that with devices that are in conformity with the criteria of Sagrjadskii et al 1996, measurement series are derived that vary only slightly (Treugut,1999, Colbert 2004, Zimlichman, 2007).

Measurements that have been carried out with the Itronic EDA using standard, known resistances, vary less than 1% over the range of measurement 100 – 18000 K $\Omega$ . These outcomes cannot be influenced by the operator. These measurements are part of the standard testing procedure for each device.

Colbert et al (2004) found that the reproducibility increases when the measurements are carried out at exactly the same spot. This can be realized by using a felt-pen for marking the points of measurement. Treugut et al.(1999) came to similar conclusions.

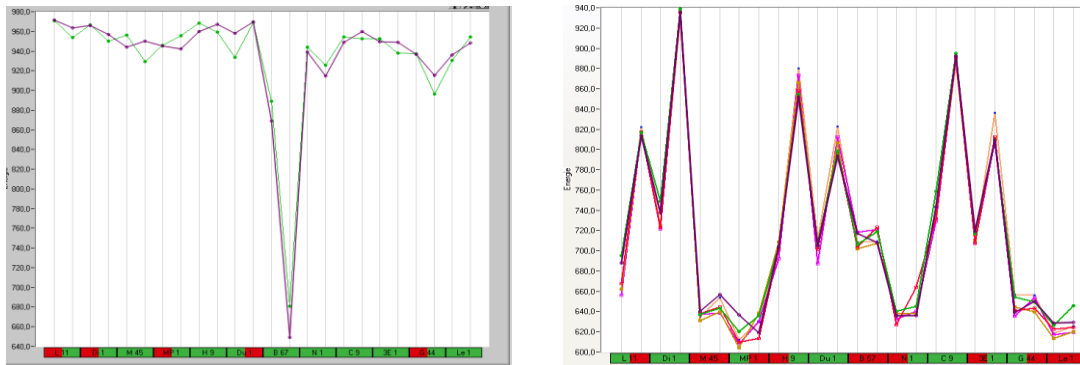


Fig.1. examples of consecutive, reproducible measurements. Left 2 identical measurements, right 5x.

### Clinical results of EDA screenings.

Sagrjanski (1996) reported the following results on the coincidence of EDA-assessment and conventional diagnostic outcomes:

#### Reliability of the energy diagnosis and assessment

Pathological conditions	# of patients	reliability of the diagnosis and prognosis of the therapeutical efficiency
healthy sportsmen with varying degrees of exhaustion	9270	0,95
<b>Neurology:</b>		
Lumbosacral radiculitis	900	0,90
Arachnoiditis	1500	0,92
Syndromes caused by Exposure to chemical toxins	3100	0,90
<b>Cardiology:</b>		
Stenocardy, Myocard.infarct, Hypertony, Combination of syndromes	3820	0,96
<b>Pathology of the lungs:</b>		
Bronchial asthma	670	0,90
Pneumosklerosis	380	0,90
<b>Pregnancy related pathology:</b>		
Toxicosis during first 4 months	380	0,94
Toxicosis during 5- 9 months	220	0,92
<b>Surgical pathology:</b>		
Inflammation of the gallbladder With stones, and without stones, Pancreatitis, Peritonitis with exudate Appendicitis	890	0,94
<b>General pathology:</b>		
Ulcerous growth of the Intestines, cirrhotic-liver Diabetes	980	0,98

Traumatological pathology:		
Crash-syndrom		
Frost		
Traumatic amputation	69	0.98
(Patients that could not be followed until the end of the studies 718)		
Total # of patients included in the Studies		
	22.297	

*Newer clinical research, with a similar skin-resistance screening device, shows even clearer results ( Lurie,2007):*

	Field	Country	Total No of patients in study	Group	No. of cases	Sens.%	Spec. %	FN	FP	ppv	npv	Accur	Kappa
1	Gastro-intestinal	Israel	109	Peptic ulcer	20	80%		20%		Aver.	Aver.		overall 0.8
				IBS	30	90%		10%					
				Colon cancer;	29	69%		31%		96%	82%		
				Control	30		90		10%				
2	Internal department	Israel	146	Cardiology	102	85%	52%	15%	48%			69%	0.39
				Respiratory	36	81%	83%	19%	17%			82%	0.57
				Digestive	37	81%	45%	19%	55%			63%	0.18
				Genitourinary	35	72%	70%	28%	30%			71%	0.35
				Endocrine	49	51%	81%	49%	19%			66%	0.34
3	Hepatology	Israel	258	HCV + HBV + NAFDL	113	85%		15%		95%	82%	90%	
				Control	85		94%		6%				
				HCV biopsy	60	78%							
4	Gerontology	Russia	239	Cardiology	49	78%		22%					
				Respiratory	41	75%		25%					
				Digestive	112	90%		10%					
				Urology	35	86%		14%					
				Gynecology	40	74%		26%					
				Immune	70	87%		13%					
				Spine	109	89%		11%					
5	Colon diseases	Israel	68	Colon disease	28	61%		39%		93%	77%	78%	
				Control	40		90%		10%				

	Field	Country	Total No of patients in study	Group	No. of cases	Sens.%	Spec. %	FN	FP	ppv	npv	Accur	Kappa
6	Immunology	Italy	108	Immune disease	38	81%		19%				87%	0.65
				Allergies	40								
				Control	30	92%	8%						
7	Oncology	Israel	97	Breast disease;	44	79%	91%	21%	9%			85%	overall 0.67
				Lung disease;	23	76%	95%	24%	5%			86%	
				Prostate disease	30	93%	90%	7%	10%			92%	
8	Cardiology	Israel	123	IHD	123	86%		14%		94%			
9	Occupational medicine	Holland	373	Urology;	42	83%	93%	17%	7%	60%	98%	88%	
				Gynecology	134	87%	80%	13%	20%	82%	86%	84%	
				Digestive	116	89%	86%	11%	14%	74%	94%	88%	
				Cardiology	104	84%	87%	16%	13%	71%	93%	86%	
				Respiratory	47	81%	96%	19%	4%	75%	97%	89%	
				Endocrine	27	82%	95%	18%	5%	58%	99%	89%	
				Immune	41	71%	98%	29%	2%	83%	96%	85%	
				Bilious	37	89%	95%	11%	5%	66%	99%	92%	
				Spine	156	81%	90%	19%	10%	85%	87%	86%	
10	Gynecology	Israel	150	Functional	59		77%		23%	85%	78%	82%	
				Organic	91	86%		14%					
Total:			10	studies									
			1671	patients									
			2332	cases									

Therefore it can be concluded that these measurements are suited for screening for a variety of pathological conditions and that their efficacy and accuracy is generally very good.

Changes in the resistance of dermal-visceral zones of the immuno-respiratory system and the large-intestine, coinciding with acupuncture points within these zones, showed a correlation coefficient of 87% between the measured values and the X-ray pictures. This correlation was not present between the X-ray pictures and randomly chosen points in the dermo-visceral zone of the large intestine organ. Interestingly, no false negative results were found. False positive results were derived with a patient that had an inconsistent shadow at the X-ray, but no evidence of a tumor according to the tomogramme or CT-scan ( Sullivan et.al in print).

Szopinski (2004) has shown that the pathology of an organ is linked to elevated resistances of the corresponding DVZ, Zones of Head and acupuncture-points.

EDA-measurements are considered to be a reliable, non-invasive, risk free bio-electronic method with a high degree of specificity and sensitivity concerning screening for pathology. The values that are mentioned by Szopinski match those of Sagrjanski (1996), Lurie(2007) and Zimlichman (2005).

Krop ( 1997) established that with 41 polysymptomatic allergy-patients 96% of the allergens (housemite, histadine) could be discerned from non-allergens ( saline, water) on the basis of skin-resistance measurements .

Becker (1976 en 1979) found clear correlations between physiological functions and electro-physiological measurements of meridians, dermatomes and acupuncture-points.

Initiated by i-Health two studies have been done, by resp. the Department of Animal Sciences, LU-Wageningen and the University of Innsbruck, Faculty for Sportsphysiology.

Sponring, 2003, concluded that the results of the EDA-tests correlated closely with stress-tests of athletes, more closely than the usual lactate-tests.

Bosma et al, (2006) established that the measurements of skin resistances by cows correlated very closely with the condition and health-parameters. The EDA-measurements were carried out at points that are, according to Kothbauer (1999, Veterinary Acupuncture. Basic principles and their Clinical Applications with Ear Acupuncture on cattle and some references to the Horse. ETH-Zuerich. Zwiemuehlen Verlag) related with the immune system. These eda- measurements were compared with parameters for milk-quality ( somatic Milk-cell count), with the Body Condition Score, and the IA rate ( number of inseminations per gestation). Very high correlation-coefficients were found.

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## *i-HEALTH® Systems*

ITRONIC contact thermography module: a scientific evaluation of the literature and own data.

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### Introduction.

Contact thermography is commonly used for diagnostic imaging, especially as an alternative for mammography. Because of the structure of our nervous system, it is

also suited to mark those moments where the nervous system received input that changes its reflexes ( fig.1) and homeostatic management.

## Summary

During the eighties and following the development and advent of precision temperature measuring instruments known as contact thermometers, contact thermography has evolved as significant and reliable diagnostic method (Rost, 1982). The scientific published evidence has shown that thermography is a very instructive method of showing the interaction between direct changes in heat radiation of the surface of the skin and its relation to reflex processes (Stuttgen, 1982).

Thermography is a simple, non-invasive, highly accurate, inexpensive form of monitoring.

## Review of literature

Contact-Thermography is a rather commonly used method for:

- Establishing zones with vaso-constriction;
- Diagnosis of arterial conditions in the legs;
- Finding inflammations;
- Screening for breast-cancer;
- Evaluation of the effects of treatments;
- The measurement of temporal changes of the micro-circulation.
- (Makarov IV, 2002, Winsor,1985).

Thermoregulation is the control of body temperature. The liver produces a lot of heat, which is transported around the body by blood. Normal body temperature in humans is 37<sup>0</sup> C. Stability and circadian variation in core body temperature are homeostatic responses that have been well documented for many decades (Holtzclaw,2001). Research in thermal physiology has illuminated several of the deficits present in the understanding of temperature regulation, and while discoveries are still evolving, existing information provides valuable clues about physiological responses to heat loss or over-heating that could improve clinical assessment and intervention. Compared to the organism as a whole, the hypothalamus has an incredibly high function per size ratio. Encompassed within it's designated 1 cubic cm of area is the homeostatic regulatory systems for the entire organism. The hypothalamus, connected via nerve fibers to the cerebral cortex, thalamus, and other parts of the

brain stem, receives input from these locations allowing it to regulate many visceral activities as it serves as a link between the nervous and endocrine system, the circulatory system and the skin ( Holmes, 1993).

Among the many functions of the hypothalamus are regulation of heart rate, blood pressure, body temperature, water and electrolyte balance, body weight, hunger, reproduction, and circadian rhythms. Many of these mechanisms, such as temperature regulation, can be traced to specific anatomical locations.

The physiology of thermodiagnosis is intimately associated with the brain, the parasympathetic and sympathetic nervous systems ( fig 1.). Moreover, the skin circulation and its heat output are largely influenced by processes within the body. The physiology and anatomy of the vascular supply to the skin produces a certain temperature and regulation pattern that may be within certain limits that are considered normal. Yet human beings show strong deviations from this ideal pattern.

During the eighties and following the development and advent of precision temperature measuring instruments known as contact thermometers, contact thermography has evolved as significant and reliable diagnostic method (Rost, 1982). The scientific published evidence has shown that thermography is a very instructive method of showing the interaction between direct changes in heat radiation of the surface of the skin and its relation to reflex processes (Stuttgen, 1982).

*The i-HEALTH thermography module is being used for measuring the influence of EM-signals, as these influence reflex-processes, on direct changes in the heat-output. It is also possible to evaluate the effects of treatments and the measurement of temporal changes of the micro-circulation. Especially with the monitoring of the treatment of diabetic ulcers and Claudicatio much experience has been gained.*

Changes in the output of energy are the result of:

- Vasodilatation;
- Changes in the energy-consumption due to an increase of activity, infections, stress, relaxation, exhaustion, intoxication, external stimulation, a.o.;
- Autonomous regulation, meaning sympatico- of parasympaticotone regulation of the microcirculation.

Comparable thermo-regulatory changes may be induced, for example for plethysmographic measurements or to diagnose the degree of atherosclerosis and to mark changes in time. (Winsor, 1985: the non-invasive laboratory; Fushimi, H et al, 1998,Peripheral vascular reactions to smoking ).

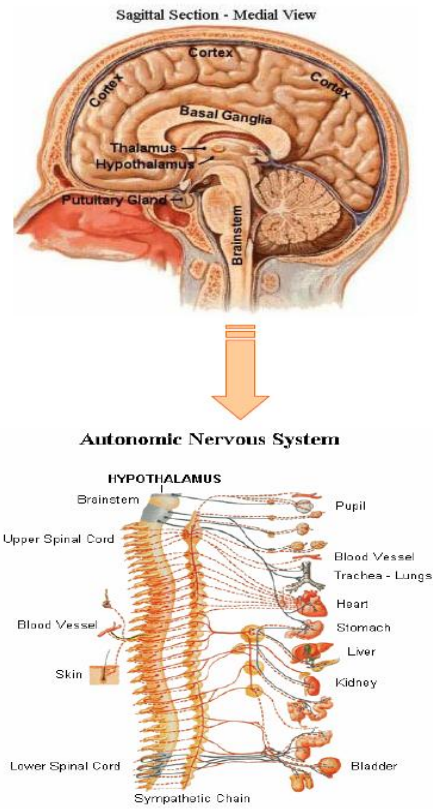


Figure 1 – Brain and autonomic nervous system

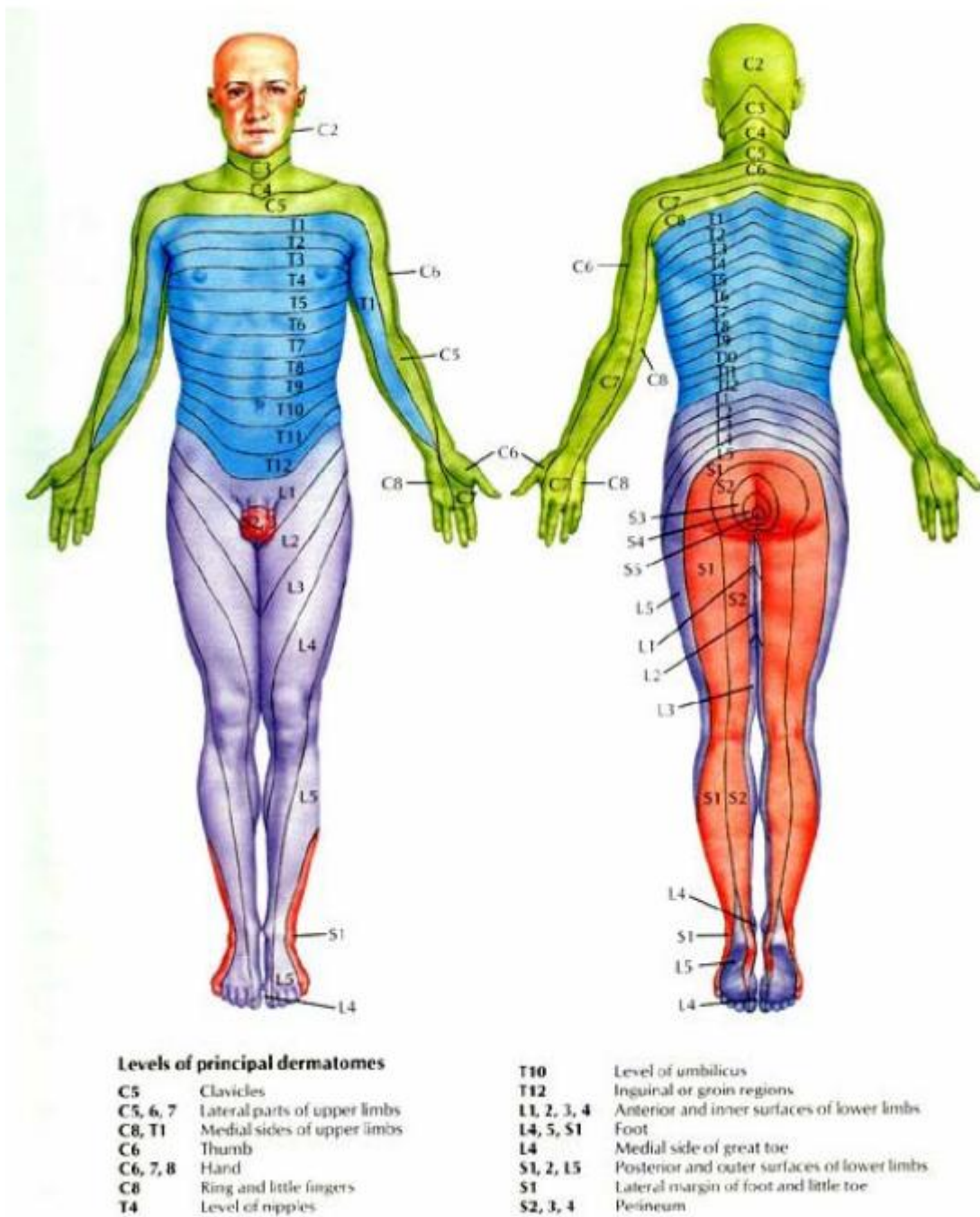


Fig.2. The segmental innervation of the skin-dermatomes.

**The i-HEALTH system uses contact thermography for:**

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- Selecting moments of increased vasodilatation that occur during a sweep of different pulsating magnetic fields. Those signals can be selected that effectuate the strongest vasodilatation.

By means of electro-magnetic (EM) frequency-sweeps, those frequencies can be selected that generate the strongest effect on the output of energy, vasodilatation or the balance between sympathetic/ parasympathic regulation.

Figure 4 shows the increase of skin-contact temperature that occurs as a reaction to one of the signals during an EM- frequency sweep. This frequency can be applied successfully to stimulate the micro-circulation and to stimulate the parasympathic nervous-system. At 966 Hz the temperature change was the most marked. Clear reactions such as in this case occur in a percentage of approx. 3 %, but usually the thermographic changes are less outspoken, shorter lived and more subtle.

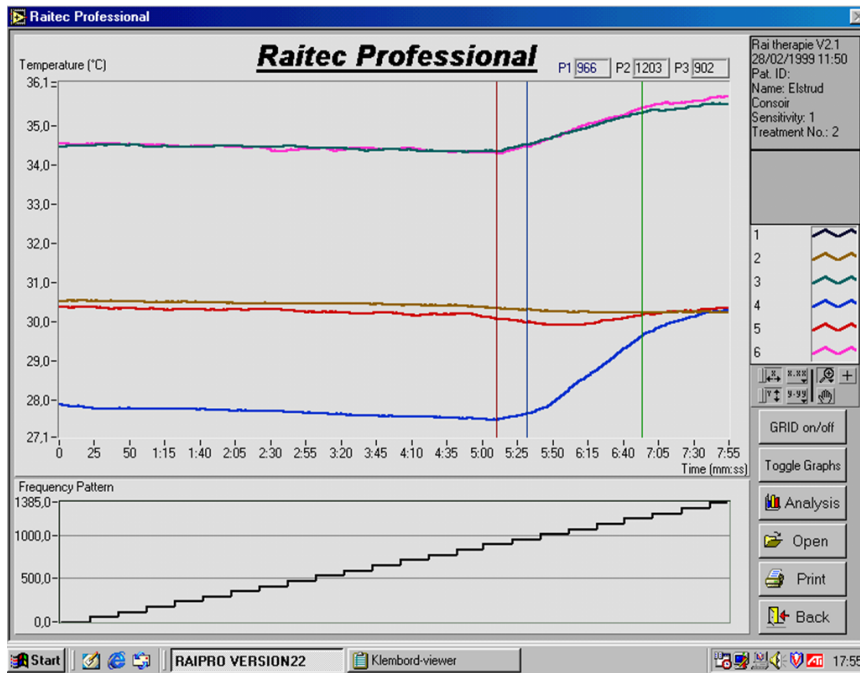


Fig 3.: example of routine thermographic scan. Increase of the skin temperature of 2°C within 90 s. during an EM-frequency sweep. Practice as well as research have shown that the EM-signal that triggers such a reaction is a very effective signal to stimulate vasodilatation and thereby increase the micro-circulation.

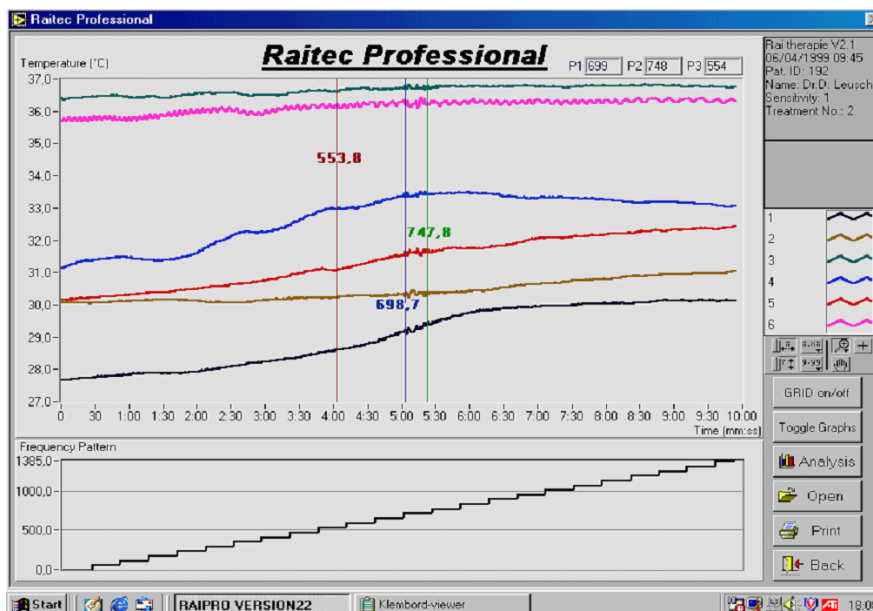
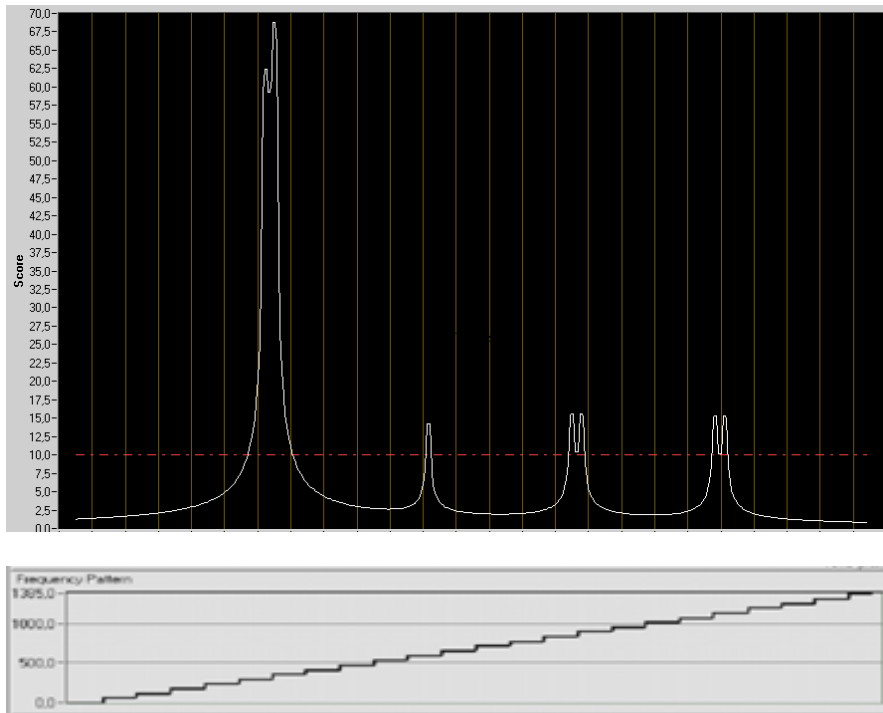


Fig. 4 Example of routine thermographic scan. showing the more common, short lived reaction during a sweep of different EM-frequencies. Treatment with the frequency where this reaction occurred effectively stimulates the micro-circulation and vasodilatation.



*Fig.5. Automated evaluation, where moments of regulatory changes induced by input to the nervous system are pin-pointed.*

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# *i-HEALTH® Systems*

*ITRONIC Therapy module. A scientific evaluation of therapeutic effects of low level light therapy (photomedicine)*

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## Introduction

As taken from the literature **light therapy** or **phototherapy** consists of exposure to daylight or to specific wavelengths of light using lasers, LEDs, fluorescent lamps, dichroic lamps or very bright, full-spectrum light, for a prescribed amount of time and, in some cases, at a specific time of day. It has proven effective in treating Acne vulgaris, seasonal affective disorder, and is part of the standard treatment regimen for delayed sleep phase syndrome. It has recently been shown effective in non-seasonal depression. Proponents claim demonstrable benefits for skin conditions such as psoriasis.

The i-Health therapy module applies led-light of low intensity and variable coloration (RGB-balance). The light may be used at skin zones, such as dermatome, around fractures, at bruises, rashes, etc. but also at acupuncture-points. This paper summarizes the scientific literature on the principles and therapeutic results.

## Conclusion on biophysical pathways:

Literature in the fields of biophysics, cell biology, medicine leads to some specific conclusions ( Oschman, 2001):

- Living cells, tissues and entire organisms emit light in the spectral range from infrared to visible to ultraviolet.
- Some of these light emissions consist of coherent biophotons; some are not coherent.
- Coherent biophotons are produced by cooperative molecular vibrations taking place in highly ordered arrays found in DNA, the cytoskeleton, cell membranes and extracellular connective tissues, including bone.
- Quantum physics predicts that the behaviour of highly coherent molecular domains can be described as Bose-Einstein condensates. This is a state of matter that has been well characterized for inorganic systems such as liquid helium and lasers.

- These coherent domains have key roles in the absorption, storage and mobilization of energy within the organism.
- Biological coherence also explains the extreme sensitivity of living systems to tiny signals in the environment.
- Cells are responsive to very low levels of light, particularly if the light is pulsed on and off.
- Even a single photon can produce a cascade of effects on a population of cells or tissues.
- Cells respond to light in predictable ways
  - by dividing,
  - by migrating,
  - by altering their metabolism

One important role of light is in activating cell division, a process that is essential in wound healing as it provides in replacement of damaged cells, and carry out repair and replacement. Optimal results appear when light therapy takes place when the light is of low intensity that it does not heat tissues, short duration and pulsed on and off. The i-HEALTH i-light possesses all three characteristics.

#### Conclusions on light therapy

#### Wavelength sensitivities of different photobiological responses:

260 nm: DNA absorption (max and in vitro damage of DNA)

280 nm: Protein absorption max ( mainly due to tryptophan and tyrosine)

290 nm: Sun burn

320 – 400 nm: long wavelength ultraviolet, also known as UV-A. Vitamin D production

405 -420 nm: activates porphyrine

419 nm± Absorption maximum for the blue cones in the human retina.

450 nm: phototropism in land plants

470 nm: Bioluminescence in most marine organisms

496 nm: Absorption maximum for the rods in the human retina

505 nm Human vision at low light levels extends from about 400 nm to 600 nm

531 nm absorption max. for the green cones in the human retina

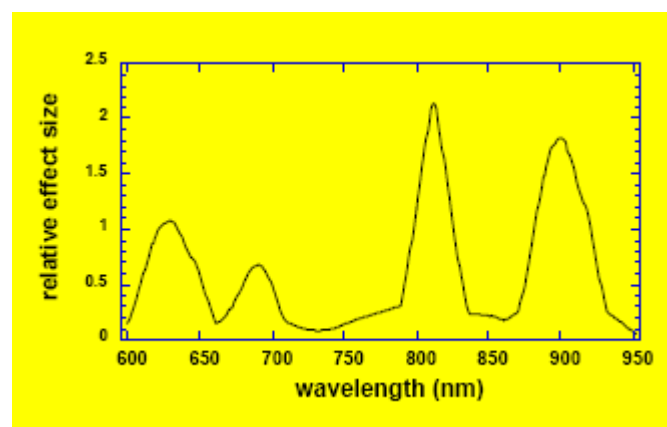
555 nm Human vision at high light levels extends from about 450 nm to above 700 nm

568 nm: absorption max. for the red cones in the human retina.

668 nm: Formation of Pfr form of phytochrome

730 nm: Formation of Pr form of phytochrome

760 nm: water vapor absorption band



*Fig.1. Action spectra for low level light therapy. Peaks coincide with the spectra of red, green, blue diodes. Derived from multiple literature references. See also Karu et.al, 2005:Exact action spectra for cellular responses relevant to phototherapy.*

Colours and their specific fields of application as has evolved in practice (Ghadiali, 1927.

Babbitt, 1942):

Violet is the highest colour in the visible spectrum. This colour is known as one of the "cool" colours. It has a very calming effect on us and is, therefore, very helpful for those people experiencing sleep difficulties or stress. However, it can be contra-indicated for those suffering from depressive disorders.

Indigo: problems treated with indigo: tension headache, migraine, visual defects, short-sightedness, long-sightedness, glaucoma, cataracts, catarrh, sinus problems, some ear problems.

Blue: Thyroid problems - over active/ under-active; Anorexia nervosa this is a multi-chakra problem, but has a strong connection to the throat chakra; asthma; bronchitis; hearing problems; tinnitus - may also be connected to problems with the brow

chakra; problems of the upper digestive tract; mouth ulcers, sore throats, tonsillitis. Neonatal jaundice, injured tissue. Eating disorders, depression.

Green: heart diseases, diseases of the Immune system, for example, Aids and ME (myalgia encephalomyelitis, sometimes referred to as chronic fatigue syndrome or post viral syndrome); other problems related to the immune system and allergies, cancer of the breast.

Yellow: diabetes, pancreatitis, liver disease, peptic ulcer, Coeliac's disease, gall stones

Orange: pre-menstrual syndrome, problems with menstrual flow, uterine fibroids, ovarian cysts, irritable bowel syndrome, endometriosis, testicular disease, prostatic disease.

Red: constipation, diarrhea, piles, colitis, Crohn's disease, cold fingers and toes, frequency of urination, hypertension (high blood pressure), kidney stones, impotence, problems with hips, legs and feet.

White: seasonal affective disorder. Cancer.

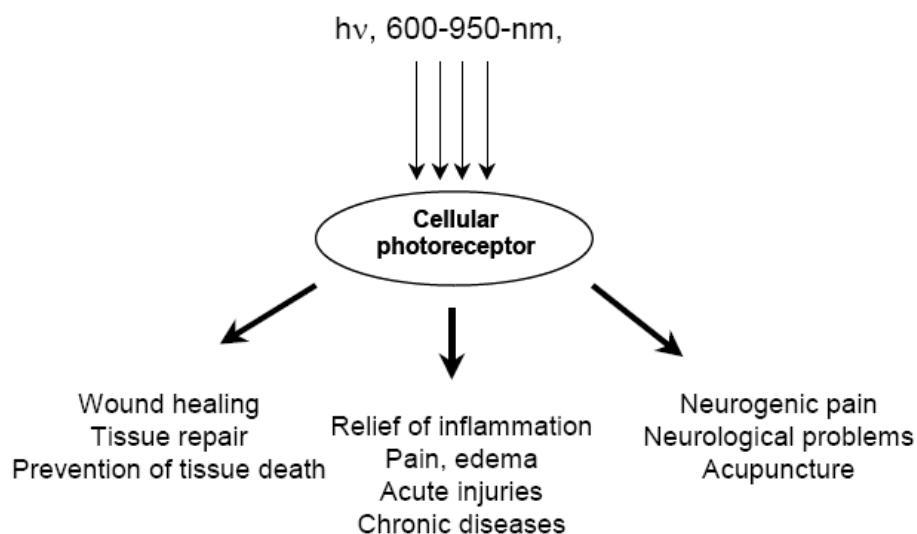


Figure 1. Schematic representation of the main areas of application of LLLT

## *Therapeutic effects as reported in the literature*

### *Skin related*

#### Acne vulgaris

##### Blue/red light treatment

Sunlight was long known to improve acne, and this was thought to be due to antibacterial and other effects of the ultraviolet spectrum; which cannot be used as a treatment due to long-term skin damage. However, artificial UV didn't work as well as sunlight.

It was found that some of the visible violet light, present in sunlight, in the range 405-420 nm activates a porphyrin (Coproporphyrin III) in *Propionibacterium acnes* which damages and ultimately kills the bacteria by releasing singlet oxygen. A total of 320 J/cm<sup>2</sup> of light within this range renders the bacteria non viable<sup>[1]</sup>. This part of the spectrum is just outside the ultraviolet and produces little if any tanning or sunburn.

Application of the light for 3 consecutive days has been shown to reduce the bacteria in the pores by 99.9%. Since there are few porphyrins naturally found in the skin, the treatment is believed safe except in patients with porphyria;<sup>[2]</sup> although eye protection is necessary due to light sensitive chemicals in the retina. The light is usually created by fluorescent lamps, bright LEDs or dichroic filament bulbs.

Treatment is often accompanied with application of red light which has been shown to activate ATP in human skin cells (essentially a photobiomodulation effect), and seems to improve response rates.

Overall improvements of on average 76% for 80% of patients occurs over 3 months; most studies show that it performs better than benzoyl peroxide and the treatment is far better tolerated. However, approximately 10% of users see no improvement.<sup>[1]</sup>

Home use light boxes usually work well, are effective for people with long-term acne, are likely to be cheaper than dermatologist office light treatments, and can be repeated over several years for negligible cost, as opposed to once weekly or fortnightly. The light at a dermatologist clinic is likely to be much of a higher intensity, however, possibly negating the disadvantage of infrequent use. As of 2007 even though most light boxes are considered expensive, the cost is on a par with the total cost of benzoyl peroxide, moisturiser and facial washes over the total life of the light box.<sup>[citation needed]</sup>

### Photodynamic therapy

Application in a dermatologist's office is usually much more costly, and not necessarily any more effective, but the visible blue light is sometimes used with off-label use of aminolevulinic acid; this causes the bacteria to generate more than normal quantities of porphyrins which greatly improves response. Whilst temporary redness and edema is experienced, this can give over a year of clearance with just a few applications.

There is some skepticism and lack of data over some of the treatments of acne vulgaris through visible light, mainly for the newer and relatively experimental photodynamic treatments. For more information.<sup>[3]</sup>

### Psoriasis and eczema

A feature of psoriasis is localised inflammation mediated by the immune system. UV radiation is known to suppress the immune system and reduce inflammatory responses. Light therapy for skin conditions like psoriasis or eczema use UVA (315-400nm waveband) or UVB (280-315nm waveband) light waves. UVA, combined with a drug taken orally, is known as PUVA treatment. Narrow Band UVB is the 310nm wave length and is given as a light therapy treatment rather than full spectrum UVB.

### Tanning

Tanning is caused by the effects of two different types of ultraviolet radiation: UVA and UVB. UV exposure in doses used in tanning parlors may be associated with carcinogenesis.

### Wound healing and neuropathy

Monochromatic infrared light emitted at a wavelength of 890 nm has been shown effective, through limited clinical studies, to help restore sensation and reduce pain in patients with neuropathy and to improve circulation of non-healing ulcers, thus increasing their healing rate. It is thought that the infrared light helps to release nitric oxide into the bloodstream, which aids in increasing local circulation and improving blood flow. People with diabetes have poor circulation due to their naturally low levels of nitric oxide and sedentary habits.

## Mood and sleep related

### Seasonal affective disorder

While full sunlight is preferred for seasonal affective disorder, there are a number of products (such as light boxes) using very intense artificial illumination that are effective for seasonal affective disorder. These lamps, at a prescribed distance, provide 10,000 lux directed angularly at the user's eyes, without harmful ultraviolet radiation.

Newer research indicates that using a lower intensity of certain wavelengths of light, i.e., the "blue" wavelengths, may be at least as efficacious as using 10,000 lux,<sup>[4]</sup> at least until one approaches old age, when blue light is no longer more effective than red or green. The most effective wavelengths of blue light are given as ranging between 460 nm and 485 nm by most sources, with some sources specifying peak photopigment sensitivity at 479 nm (in mice).<sup>[5]</sup>

### Non-seasonal depression

Only recently have clinical studies been conducted which specifically excluded all patients with any degree of seasonality.<sup>[6]</sup> Before these studies, there was suspicion that any depressed patients who benefited from light treatment were really only having the SAD component of their depression treated. However, light therapy is now an established treatment for depression, regardless of seasonality.<sup>[7][8]</sup> One advantage it may have compared with drugs is that results may appear more quickly; antidepressant drugs typically take several weeks to reach full effectiveness.

### Delayed sleep phase syndrome

In the treatment of delayed sleep phase syndrome (DSPS), the timing of light exposure is critical. The light must be provided as soon after spontaneous awakening as possible to achieve the desired effect, as shown by the phase response curve for light in humans. Some users have reported success with lights that turn on shortly before awakening (dawn simulation).

## Neonatal jaundice

[For more details on this topic, see Neonatal jaundice.](#)

Light energy creates isomerization of the bilirubin and consequently transformation into compounds that the newborn can excrete via urine and stools.

## Jet lag

Light therapy is considered a viable treatment for jet lag<sup>[9]</sup>. Exposure to bright light during the appropriate time periods before, during and after air travel can reduce the symptoms of jet lag and accelerate the recalibration of the body clock. NASA has used timed doses of bright light to prepare astronauts for late night launches since 1991.<sup>[10]</sup>

## Heliotherapy

Within the tanning and spa industry the term "heliotherapy" has become popular to describe medical therapy by exposure to light, usually in the UVA/UVB range. This could include direct sunlight but more often refers to the use of tanning beds, lamps and booths which make use of both ultraviolet and infrared. The treatment of psoriasis, eczema, vitamin D deficiency and seasonal affective disorder are included. As with any exposure to UV, there are some risks associated, but these are usually outweighed by the benefits provided by the treatments. Often, UV treatments are given at a doctor's office, but it is becoming more common for a doctor to prescribe regular visits in a tanning bed for persons who have moderate problems, as this is lower in UV than medical devices, and is more convenient and less expensive for the patient. In very rare and extreme cases, the purchase of home tanning beds is prescribed by doctors and covered by insurance.

There is also evidence that exposure to some frequencies of light (UV in particular) causes the body to release small amounts of endorphins,<sup>[11]</sup> which would explain the benefit for some disorders such as SAD, as endorphins are often called "the body's own morphine", as well as the concerns for potential tanning addiction, not to be confused with what is commonly called anorexia, a psychological syndrome wherein patients see themselves as pale, even if they have a substantial tan.

## Disadvantages

### Safety of phototherapy

Ultraviolet light causes progressive damage to human skin. This is mediated by genetic damage, collagen damage, as well as destruction of vitamin A and vitamin C in the skin and free radical generation.

Visible blue light has been suggested to cause DNA breaks, but carcinogenesis has not been demonstrated, and enzymes within the cells are believed to repair the breaks reasonably well.<sup>[citation needed]</sup> However, cancer has been induced in cells with deliberately damaged repair mechanisms. Also, researchers have questioned

whether limiting blue light exposure could reduce the risk of age-related macular degeneration (ARMD).<sup>[12]</sup>

Modern phototherapy lamps used in the treatment of seasonal affective disorder and delayed sleep-phase syndrome do not emit ultraviolet light and are considered safe and effective for the intended purpose, as long as photosensitizing drugs are not being taken at the same time and in the absence of any existing eye conditions. Light therapy is a mood altering treatment, and just as with drug treatments, there is a possibility of triggering a manic state from a depressive state, causing anxiety, and other side effects. While these side-effects are usually controllable, it is recommended that patients undertake light-therapy under the supervision of an experienced clinician, rather than attempting to self-medicate.<sup>[13]</sup>

### Contraindications

There are few absolute contraindications to light therapy, although there are some circumstances in which caution is required. These include when the patient 1) has a condition that might render his or her eyes more vulnerable to phototoxicity, 2) has a tendency toward mania, 3) has a photosensitive skin condition, or 4) is taking a photosensitizing herb (such as St. John's wort) or medication.<sup>[14]</sup> Patients with porphyria should avoid most forms of light therapy. Patients on certain drugs like methotrxate or chloroquine should use caution with light therapy as there is a chance that these drugs could cause porphyria

### Side effects

Side effects of light therapy for sleep phase disorders include jumpiness or jitteriness, feeling "wired," headache, and nausea. Some nondepressive physical complaints (such as poor vision and skin rash or irritation) may improve with light therapy (M. Terman and Terman 1999).<sup>[15]</sup>

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# *i-HEALTH® Systems*

ITRONIC Therapy module. A scientific evaluation of therapeutic effects of pulsating electro-magnetic fields (PEMF)

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## ***Introduction.***

The Handbook 'Biological Effects of Electromagnetic Fields' ( Pilla, 2006) gives an extensive overview of the therapeutic effects as well as the principles of the physics.

The major chapters from this handbook that are relevant have been added because it gives an extensive overview of principles and effects.

According to 'Biological Effects of Electromagnetic Fields' (2006), Electromagnetic fields of surprisingly low levels can have a profound effect on a large variety of biological systems. Positive effects on the healing process of fresh fractures, osteotomies, spine fusion, chronic and acute wound repair, post traumatic and post operative pain and edema, pressure ulcers, soft tissue injury, growth factor synthesis, increase in cell-proliferation, increase in IGF-II release. Well designed and statistically powered double blind clinical trials have validated these effects.

By means of regulation-thermography those frequencies can be established that achieve the most-efficient coupling between the EM-signal and the receptors in the living tissue.

## ***i-HEALTH PEMF Signals.***

The pemf-signals that the i-health system is using have characteristics, (field strength in 1-4  $\mu$ Tesla, frequency range 80 – 100 kHz, wave-forms: sinusoidal, sawtooth, blockwaves) in conformity with the signals that have proven physiological effects. Sinusoidal waves of 20 to 200 kHz are typically employed to induce 1-100 mV/cm electric fields in the repair site **(1)**. The inductive coupling (PEMF) technique induces a time-varying electric field at the repair-site by applying a time-varying magnetic field via one or two electrical coils. The induced electric field parameters are determined by frequency characteristics of the applied magnetic field and the electrical properties of the tissue target **(2,3,4,5)**(15,30,50,51). Several waveform configurations have been shown to be physiologically effective. Peak time-varying magnetic fields of 0.1 - 20 G ( 1  $\mu$ T = 10 G), inducing 1- 150 mV/cm peak electric fields in a 3 cm diameter target ( the size of the i-HEALTH-beamer), have been used **( 4,6)**.

***In: Handbook of Biological Effects of Electromagnetic Fields, 3rd Edition.  
Barnes F, Greenebaum B, eds, CRC Press, 2006, in press***

There are a considerable number of peer-reviewed publications which show EMF can result in physiologically beneficial *in vivo* and *in vitro* bioeffects. The number of people who have received substantial clinical benefit from exogenous EMF is certainly in the millions worldwide and increasing rapidly as new clinical indications emerge. EMF therapies also present as alternatives to many pharmacologic treatments with virtually no toxicity or side effects. Timevarying electromagnetic fields consisting of rectangular or arbitrary waveforms, referred to as pulsing electromagnetic fields (PEMF), pulse modulated radio frequency waveforms, particularly in the 15–40 MHz range, referred to as pulsed radio frequency fields (PRF) and low frequency sinusoidal waveforms (< 100 Hz) have been shown to enhance healing when used as adjunctive therapy for a variety of musculoskeletal injuries. Indeed, peer-reviewed meta-analyses clearly show both PEMF and PRF modalities, now approved by regulatory bodies worldwide and widely used on patients to enhance bone and wound repair, are clinically effective **(7,8)**. Although still not completely elucidated, the mechanism of action of EMF signals at the molecular and cellular level is now much better understood and strongly suggests ion/ligand binding in a regulatory cascade could be the signal transduction pathway **(9-23)**. Furthermore, *a priori* configuration of physiologically effective waveforms via tuning the electrical properties of the exogenous EMF signal to the endogenous electrical properties of ion binding has recently been reported **(24,25)**.

This chapter provides a brief overview of the basic and clinical evidence that time-varying magnetic fields (EMF) can modulate molecular, cellular and tissue function in a physiologically significant manner. The fundamental questions relating to the biophysical conditions under which EMF signals could modulate cell and tissue function will be discussed in detail.

## **TISSUE REPAIR**

### **1.0 Orthopedic Applications**

Five million bone fractures occur annually in the United States alone. About 5% of these will become delayed or nonunion fractures with associated loss of productivity and independence **(26)**. Several techniques are available to treat recalcitrant fractures such as internal and external fixation, bone grafts or graft substitutes including demineralized bone matrix, platelet extracts and bone matrix protein, and biophysical stimulation, such as mechanical strain applied through external fixators or ultrasound, and electromagnetic fields. The electrical properties of bone tissue have been extensively investigated. Yasuda in Japan hypothesized that endogenous electrical activity observed in bone was the mediator of repair and adaptive remodeling responses to mechanical loading and that an exogenous electrical signal alone could stimulate the response **(27,28)**. A seminal report soon followed on bone piezoelectric properties from the pioneering work of Fukada and Yasuda **(29)**. These authors showed a voltage could be obtained upon deformation of dry bone. Several

groups, notably led by Becker at the State University of New York, Bassett at Columbia University and Brighton at the University of Pennsylvania, soon reported the generation of electrical potentials in wet bone on mechanical deformation **(30-34)**. Similar observations were subsequently made in collagen and cartilaginous tissues **(35-38)**. The important conclusion from these studies was the revelation that bone and other tissue could respond to electrical signals in a physiologically useful manner. This ultimately led to the use of electromagnetic fields to modulate bone repair.

The development of modern EMF therapeutics was stimulated by the clinical problems associated with non-union and delayed union bone fractures. It started with the pioneering work of Yasuda, Fukada, Becker, Brighton, and Bassett, mentioned above, who responded to the fundamental orthopedic question of how bone adaptively and structurally responds to mechanical input by suggesting that an electrical signal may be involved in the transduction of the mechanical signal to cellular activity. This naturally led to the suggestion that superimposing an exogenous EMF upon the endogenous fields accompanying normal cellular activity could help in the treatment of difficult fractures. The first animal studies employed microampere level DC currents delivered via implanted electrodes. Remarkably, this resulted in new bone formation particularly around the cathode **(39)**. As these studies progressed it became clear that the new bone growth resulted from the chemical changes around the electrodes caused by electrolysis **(40)**. However, it has been shown that a mechanical stimulus also plays a role in DC bone stimulation **(41)**. The first therapeutic devices were based on these early animal studies and used implanted and semiinvasive electrodes delivering DC to the fracture site **(42)**. This was followed by the development of clinically preferable externally applied electromagnetic field modalities **(43,4,5,44)**. Subsequent studies concentrated on the direct effects of electromagnetic fields leading to modalities which provided a non-invasive, no-touch means of applying an electrical/mechanical signal to a cell/tissue target. Therapeutic uses of these technologies in orthopaedics have led to clinical applications, approved by regulatory bodies worldwide, for treatment of recalcitrant fractures and spine fusion **(45-51)** and recently for osteoarthritis of the knee **(52-54)**. Additional clinical indications for EMF have been reported in double blind studies for the treatment of avascular necrosis **(55,56)** and tendonitis **(57)**. This spectrum of applications clearly demonstrates the potential of this biophysical modality to enhance musculoskeletal tissue healing.

At present, the clinical modalities in use for bone repair consist of electrodes implanted directly into the repair site or noninvasive capacitive or inductive coupling. Direct current (DC) is applied via one electrode (cathode) placed in the tissue target at the site of bone repair and the anode placed in soft tissue. DC currents of 5-100 DA are sufficient to stimulate osteogenesis **(39)**. The capacitive coupling (CC) technique utilizes external skin electrodes placed on opposite sides of the fracture site **(58)**. This requires openings in the cast or brace to allow skin access. Sinusoidal waves of 20 to 200 kHz are typically employed to induce 1-100 mV/cm electric fields in the repair site **(1)**. The inductive coupling (PEMF) technique induces a time-varying electric field at the repair site by applying a time-varying magnetic field via one or two electrical coils. The induced electric field parameters are determined by frequency characteristics of the applied magnetic field and the electrical properties of the tissue target **(2,3,4,5)**. Several waveform configurations have been shown to be physiologically effective. Peak time-varying magnetic fields of 0.1 - 20 G, inducing 1-150 mV/cm peak electric fields in a 3 cm diameter target, have been used **(4,6)**. The

relationship between inductively coupled waveform characteristics and their ability to produce physiologically significant bioeffects will be considered in detail below. One version of the inductive technique utilizes a specific combination of DC and AC magnetic fields (CMF) that are believed to tune specifically to ion transport processes (12).

## 1.1 Cellular Studies

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Cellular studies have addressed effects of electromagnetic fields on both signal transduction pathways and growth factor synthesis. The important overall result from these studies is that EMF can stimulate the secretion of growth factors (e.g., insulin-like growth factor-II) after a short duration trigger stimulus. The clinical benefit to bone repair is enhanced production of growth factors upregulated as a result of the fracture trauma. The induced electric field thus acts as a triggering mechanism which modulates the normal process of molecular regulation of bone repair mediated by growth factors. Studies underlying this working model have shown effects on calcium ion transport (59), a 28% increase in cell proliferation (60), a fivefold increase in IGF-II release (61), and increased IGF-II receptor expression in osteoblasts (62). Increases of 53% and 93% on IGF-I and II respectively have also been demonstrated in rat fracture callus (63). Stimulation of TGF- $\beta$  mRNA by threefold with PEMF in a bone induction model in the rat has been reported (64). This study also suggests the increase in growth factor production by PEMF may be related to the induction of cartilage differentiation (65). It also suggests the responsive cell population is most likely mesenchymal cells (66), which are recruited early in the duration of PEMF stimulus to enhance cartilage formation. Upregulation of TGF- $\beta$  mRNA by 100%, as well as collagen, and osteocalcin synthesis by PEMF has been reported in the human osteoblast-like cell line MG-63 (67,68). PEMF stimulated a 130% increase in TGF- $\beta$ 1 in bone non-union cells (69). That the upregulation of growth factor production may be a common denominator in the tissue level mechanisms underlying electromagnetic stimulation is supported by studies from the Brighton (70,71), Stevens (72) and Aaron (73) groups. Using specific inhibitors, the Brighton group suggests EMF acts through a calmodulin-dependent pathway (71). This follows reports by the Pilla group (74-80) that specific PEMF and PRF signals, as well as weak static magnetic fields, modulate Ca<sup>2+</sup> binding to CaM by a twofold acceleration in Ca<sup>2+</sup> binding kinetics in a cell-free enzyme preparation. The Stevens group has shown upregulation of mRNA for BMP2 and BMP4 with PEMF in osteoblast cultures. The Aaron group has reported extensively on upregulation of TGF- $\beta$  in bone and cartilage with PEMF. All of these studies have utilized EMF signals identical to those which have demonstrated clinical success. The ion binding target pathway has recently been confirmed in other studies using static magnetic fields (81,82). PEMF has been reported to increase angiogenesis by threefold in an endothelial cell culture (83). A recent study confirms this and suggests PEMF increases in vitro and in vivo angiogenesis through a sevenfold increase in endothelial release of FGF-2 (84).

## 1.2 Animal Studies

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Bassett et al. (85,86) were the first to report a PEMF signal could accelerate bone repair by 150% in a canine tibial osteotomy model. A bilateral cortical hole defect model in the metacarpal bones in horses showed PEMF treated holes produced a statistically significant increase in amount of new bone formation and mineral apposition rate (87,88). A capacitively coupled signal was shown to prevent osteopenia due to both sciatic-denervation and castration in rat osteopenia models (89,90). PEMF inhibited bone loss in an ovariectomized canine model (91). Combined magnetic fields reversed osteopenia in ovariectomized rats (92). An avian ulna disuse model showed a significant increase in bone formation when treated with PEMF (93). The frequency dependence of EMF effects was also studied in this model. The results showed maximal response was observed with a 15 Hz sinusoidal waveform producing 10 DV/cm peak electric field in tissue. Experimental models of bone repair show enhanced cell proliferation, calcification, and increased mechanical strength with DC currents (94,95). Capacitive coupled fields have been reported to improve the mechanical strength of experimental fractures and healing osteotomies (1). Several studies with PEMF showed increased calcification and enhanced mechanical strength in healing bone (96,97). Exposure time studies report a linear effect of daily exposure with a 6-hour stimulation being most effective (6). A series of animal studies reported that DC, CC, and PEMF techniques enhance the formation of bone and improves fusion rates in spinal arthrodeses (98-99). DC currents of 10 DA per cm of cathode length showed the best acceleration of spinal fusion (100). The mechanical strength of late phase osteotomy gap healing in the dog was 35% stronger in PEMF treated limbs (101). PEMF increased bone ingrowth into hydroxyapatite implants in cancellous bone by 50% (102). PEMF produced a 10% increase in the diameter of arteriolar microvessels in rat muscle from which the authors suggested increased local blood flow could play a role in the PEMF acceleration of bone repair (103). The use of in vivo micro-computed tomography showed PEMF reduced bone loss in a non-union fibular model in the rat by threefold (104). In a related study the effect of PEMF waveform configuration was examined. The results showed callus stiffness in a rat fibular osteotomy was increased twofold by a PEMF signal routinely employed for clinical bone repair, whereas a second PEMF waveform with much higher frequency content was ineffective (105).

## 1.3 Clinical Studies

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Electromagnetic stimulation modalities have been used clinically to treat fresh fractures, osteotomies, spine fusions, and delayed and nonunion fractures. The efficacy of EMF stimulation on bone repair has been studied in a formal meta-analysis (106). Twenty randomized control trials were identified. Fifteen trials supported EMF effectiveness and five failed to show effectiveness. Most studies used PEMF. In all cases, the primary outcome measure was bone healing assessed by radiographs and clinical stability test. Results from pooled trials of 765 cases supported the effectiveness of PEMF stimulation of bone repair. However, because of the inability to pool data from all studies, conclusions regarding PEMF efficacy in

bone repair were only suggestive. PEMF significantly accelerated union of femoral and tibial osteotomies in randomized, placebo controlled studies by approximately 50% **(107-109)**.

PEMF, CC and DC have been used to promote healing of spine fusions for the treatment of chronic back pain from worn or damaged intervertebral discs. This is measured by the increase in successful fusions from 50% to approximately 80% using EMF as adjunctive treatment. This application has also been subjected to meta-analysis (13). Five randomized, controlled trials and five nonrandomized case controlled studies showed positive results for the enhancement (by 60%) of spine fusion by electrical and electromagnetic stimulation. There are many studies and reviews which show electrical and electromagnetic stimulation is effective in promoting spinal arthrodesis **(110-115)**.

The effectiveness of EMF in promoting healing of recalcitrant fractures has been reviewed **(116)**. Twenty-eight studies of ununited tibial fractures treated with PMF were compared with 14 studies of similar fractures treated with bone graft with or without internal fixation. The overall success rate for the surgical treatment of 569 ununited tibial fractures was 82%, while that for PMF treatment of 1718 ununited tibial fractures was 81%, suggesting it is significantly more advantageous for the patient to use PEMF rather than submit to invasive surgery for the first bone graft. There are several observational studies suggesting the efficacy of DC, CC, or PEMF techniques in stimulating healing of delayed unions and nonunions **(117-125)**. Interestingly, Bone morphogenetic proteins. Development and clinical efficacy in the treatment of fractures and bone defects. and of huge clinical significance, studies comparing PEMF with bone graft show their equivalence in promoting union of delayed union or nonunion fractures **(116,126-128)**. Finally, there is a promising study on the effects of PEMF on distraction osteogenesis for the correction of bone length discrepancies **(129)**. Thus, several physical modalities have been shown to effectively manage nonunions and delayed unions of bone. Implantable direct current stimulation is effective as an adjunct in achieving spinal fusion. Pulsed electromagnetic fields induce weak non-thermal time-varying currents at the fracture site. Inductively and capacitively coupled electromagnetic fields appear to be as effective as surgery in managing extremity nonunions and lumbar and cervical fusions. Low-intensity ultrasound has also been used to speed normal fracture healing and manage delayed unions.

Although these modalities seem vastly different, there appears to be a common mechanism of action. This will be discussed below. All of the modalities discussed above now constitute the standard armamentarium of orthopaedic clinical practice. Since the success rate for these modalities has been reported equivalent to that for the first bone graft, a huge advantage to the patient ensues because PEMF therapy is non-invasive and is performed on an out-patient basis. PEMF therapy also provides significant reductions in the cost of health care since no operative procedures or hospital stays are involved. This also applies for the increased success rate of spinal fusions with EMF. Thus, the clinical effects of EMF on hard tissue repair are physiologically significant and often constitute the method of choice when standard of care has failed to produce adequate clinical results. It is interesting to note that EMF may be the best modulator of the release of the growth factors specific to each stage of bone repair, certainly more so than the exogenous application of the same growth factors **(130)**.

Chronic wounds and their treatment are an enormous burden on the healthcare system, both in terms of their cost (\$5 billion to \$9 billion annually) and the intensity of care required **(131)**. There is even more cost to society from attendant human suffering and reduced productivity. More than 2 million people suffer from pressure ulcers and as many as 600,000 to 2.5 million more have chronic leg and foot wounds **(132)**. Diabetic foot ulcers are the most common chronic wounds in western industrialized countries. Of the millions who have diabetes mellitus, 15 per cent will suffer foot ulceration which often leads to amputation (100,000 per annum in the US alone).

There is an emerging and substantial clinical application of EMF in wound healing. Soft tissue healing has been reported by the use of direct electrode coupled devices delivering waveforms similar to those produced by several TENS devices currently approved by the FDA.

Regulatory and reimbursement issues have prevented more widespread use of PEMF modalities. However, the clear clinical effectiveness of PEMF signals has resulted in significantly increased use **(7)**. In fact, the Center for Medicare Services (CMS) has now determined PEMF produces sufficient clinical outcome to permit, and reimburse for, use in the off-label application of healing chronic wounds, such as pressure sores and diabetic leg and foot ulcers (138). In addition, PRF devices have been cleared by the FDA for the relief of acute and chronic pain and the reduction of edema, all symptoms of wounds from post surgical procedures, musculoskeletal injuries, muscle and joint overuse, as well as chronic wounds.

As for bone repair, application of EMF to soft tissue repair appears to have begun with observations of the electrical events associated with wound repair **(133-137)**. Injury currents which develop in the presence of dermal wounds are postulated to play an important role in the healing process **(138,139)**. These currents are, however, at least two orders of magnitude larger than the endogenous currents from SGP and are DC, or near DC, currents. Cells involved in wound repair are electrically charged and endogenous DC currents may facilitate cellular migration to the wound area **(130,141)**. In a manner similar to that for bone repair, the original working hypothesis was that exogenous EMF signals may enhance the endogenous electrical signals to accelerate wound repair. It has also been suggested that externally applied EMF may interact with the current of injury or trigger a relevant growth factor cascade **(142,143)**. Wound healing can be accelerated 2.5 fold with 200-800 DA direct current **(144)**. Both DC current and PEMF have been reported to reduce edema, increase blood flow, modulate upregulated growth factor receptors, enhance neutrophil and macrophage attraction and epidermal cell migration, and increase fibroblast and granulation tissue proliferation **(141,143)**. Most wound studies involve arterial or venous skin ulcers, diabetic ulcers, pressure ulcers and surgical and burn wounds.

### 2.1 Cellular and Animal Studies

The PEMF signal currently utilized for bone repair (see figure 2, top) accelerates vascularization by several fold using cells from human umbilical vein and bovine aorta **(144)**. Studies on human umbilical vein cells showed that endothelial cell migration to a wounded area is accelerated by about 14% if cell cultures are exposed to an induced electrical field similar to the pulse burst currently used for bone repair (2 mT peak, 25 Hz repetition rate) **(144)**. Chronic stimulation of rat muscles increased blood vessel density by 14-30%, possibly through angiotensin and vascular endothelial growth factor pathways **(145)**. PEMF produced a significant increase in the rate of growth of the vascular tissue in the rabbit ear chamber **(146)** showing a dependence on signal configuration (repetitive pulse burst significantly better than repetitive single pulse). Sinusoidal signals (300 Hz) improved microcirculation and stimulated proliferation and differentiation of fibroblasts **(147)**. Amplitude, frequency and orientation dependence of EMF modulation of fibroblast protein synthesis has been reported **(148)**. Inductively coupled sinusoidal fields (0.06-0.7 mT, 50, 60 and 100 Hz) increased chick embryo fibroblast proliferation up to 64% **(149)**. Human fibroblasts exposed to 20 or 500 mT 50 Hz sinusoidal signals exhibited no effect on fibroblast proliferation **(150)**. Fibroblasts exposed to a PRF signal consisting of a 65 Dsec burst of 27.12 MHz sinusoidal waves repeating at 600/sec (1G peak amplitude) showed enhanced cell proliferation by 130-220% **(151,152)**. Tissue cultures of human foreskin fibroblasts, when exposed to high 2 V/cm induced electric fields at either 1 or 10 Hz, demonstrated a six-fold increase in internal calcium, but excitation at 100 Hz had no significant effect **(153)**. Recent animal studies have reported that PRF signals produced a statistically significant several fold increase in neovascularization in an arterial loop model, suggesting an important clinical application for angiogenesis **(154,155)**. PRF signals, configured a priori assuming a Ca/CaM transduction pathway, accelerated wound repair in a rat cutaneous wound model by approximately 60% as measured by tensile strength **(156)**. However, treatment of identical wounds in the rat with PEMF of the type and intensity used for bone healing (see Figure 2, top) failed to produce significant increases in soft tissue fibroblast counts or improvement in wound closure **(157)**. PEMF increased the degree of endothelial cell tubulization and proliferation (threefold) in vitro **(84)**. In the same study PEMF increased fibroblast growth factor  $\beta$ -2 by fivefold from which the authors conclude that PEMF augments angiogenesis primarily by stimulating endothelial release of FGF-2.

## 2.2 Clinical Studies

Non-thermal PRF signals were originally utilized for the treatment of infections in the preantibiotic era **(158)** and are now widely employed for the reduction of post-traumatic and postoperative pain and edema. Double-blind clinical studies have been reported for chronic wound repair, wherein PRF treated pressure ulcers closed by 84% vs 40% closure in untreated wounds in one study **(159)** and 60% closure vs no closure in the control group in another study **(160)**; acute ankle sprains, wherein edema decrease was sevenfold vs the control group **(161,162)**; and acute whiplash injuries, wherein pain decreased by 50% and range of motion increased by 75% in the treated vs control patients **(163,164)**. PRF signals have been reported to enhance skin microvascular blood flow by about 30% in both healthy **(165)** and diabetic **(166)** individuals. PRF reduced postmastectomy lymphedema by 56% and increased skin blood flow fourfold **(167)**.

PEMF at 600 and 800 Hz, 25 DT mean amplitude, significantly reduced the size of venous ulcers by 63%, and decreased pain by 72%, in a randomized control study (168). A modulated EMF signal at 10 and 100 Hz relieved the main clinical symptoms of diabetic peripheral neuropathy, improved peripheral nerve conduction by about 40% and the reflex excitability of functionally diverse motoneurons in the spinal cord (169).

A meta-analysis was performed on randomized clinical trials using PEMF on soft tissues and joints (7). The results showed both PEMF and PRF were effective in accelerating healing of skin wounds (170-176), soft tissue injury (161-164,177) and hair regrowth (178-180), as well as providing symptomatic relief in patients with osteoarthritis and other joint conditions (53,54). PEMF has been successfully used in the treatment of chronic pain associated with connective tissue (cartilage, tendon, ligaments and bone) injury and joint-associated soft tissue injury (181,182).

As for bone repair, EMF clinical effects on soft tissue repair are substantial and often constitute the method of choice when standard of care has failed to produce adequate clinical results. This is particularly true for chronic wounds which often do not respond to standard of care and can be lifethreatening if not resolved. It is interesting to note that EMF can increase angiogenesis several fold in chronic wounds, significantly more than that achieved to date with growth factors such as VEGF (vascular endothelial growth factor), for which there have been generally disappointing clinical results (184). This may be the primary reason that EMF is so effective with problem wounds wherein increased blood supply is always one of the primary clinical objectives. It is also interesting to note that EMF can provide an alternative to NSAIDs (e.g., ibuprofen, cox2 inhibitors, etc.) and other pharmacological analgesics for the relief of chronic and acute pain.

## THE FUTURE of PEMF

This review has attempted to provide the reader with enough information to show there is an abundance of experimental and clinical data demonstrating that exogenous electromagnetic fields of surprisingly low levels can have a profound effect on a large variety of biological systems. Both Electrical and electromagnetic devices have been demonstrated to positively affect the healing process in fresh fractures, delayed and nonunions, osteotomies, and spine fusion in orthopedics and for chronic and acute wound repair. These clinical results have been validated by well designed and statistically powered double blind clinical trials and have survived meta analyses. The FDA has approved labeling for these biophysical devices, limited at present to these indications. EMF stimulation technologies provide an additional arm to current treatment management strategies for these pathologies. However, the potential clinical applications of EMF therapeutics extend far beyond those considered here and the clinical rewards are certain to be huge. Great strides have been made in the use of PEMF for chronic and acute wound repair. It is often the only effective treatment for chronic wounds and has been chosen as the treatment of choice for post operative pain and edema reduction in plastic and reconstructive surgery. The advent of new more effective signals may even expand applications in bone repair. There is a significant emerging application for the treatment of osteoarthritis (53,185 -187) and rheumatoid arthritis (188).

The state of knowledge in EMF therapeutics has significantly advanced in the past decade. The mechanism of action is much better understood. So much so it is often

possible to configure, a priori, pulsing waveforms for an expected bioeffect. The example is PEMF and PRF signals have been successfully configured for a Ca/CaM ion binding transduction pathway which the biologists have established as a primary regulatory pathway. As we continue to learn to properly match dosimetry to pathology the dreams that many of us had more than 35 years ago may well be realized. Cancer, cardiac muscle regeneration, diabetes, arthritis and neurological disorders are just some of the pathologies which have already been shown to be responsive to EMF therapy.

Successful applications of low-frequency electromagnetic fields have been reported for treatment of bronchial asthma, myocardial infarction and venous and varicose ulcers. There is emerging research on EMF effects on angiogenesis and the manner in which this may increase stem cell survival in the treatment of Alzheimer's and Parkinson's diseases. There are also many studies which point to the possibility of the use of EMF for peripheral nerve regeneration (189-192). There are numerous reports suggesting a role for EMF in the treatment of cancer. In 1979-81 Larry Norton studied the effect of PEMF (using a 50 msec burst version of the PEMF signal in figure 2, top) on transplanted tumors in mice. Initial results suggested PEMF significantly increased survival time and led to preliminary clinical trials (193,194). More recent studies have continued and the basic and animal data are strong and certainly suggest human clinical applications are not far in the future (344-196,197,198, 199). EMF therapy modalities are simple, safe and significantly less costly to the health care system. They offer the ability to treat the underlying pathology rather than simply the symptoms. The time is particularly opportune given the increased incidence of side effects from the use of pharmacological agents. EMF therapeutics will have a profound impact upon health and wellness and their costs worldwide.

Lebring, 02.10.2008

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