Integration of Silver Iontophoresis Principles in a Device for Bacterial and Viral Infection Treatments, Wound-Healing, Tissue Repair and Regeneration

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The Medical Need

- Germane issues
- “Infections”, mostly internal, are often untreatable
- Wounds more chronic

- Reasons
- Ineffectiveness of agents and/or methods
- Exacerbated by superbugs
- Agent delivery problems
- Overall ecology of local microenvironments
- Viruses little known

Emerging Concepts of “Infection”

Single pathological microbe	-->>	Microenvironment ecology
All microbes “bad”: Presence/Absence	-->>	Symbiotic need for "good" microbes: Trillions of microbes in complex ecologies
Removal / Killing	-->>	Promoting apoptosis & cellular/tissue normalization
Simplified gross area and organ concepts	-->>	Infinitely complex and dynamic cascading multi-category interacting events

Concepts of Treatment

Iontophoretic ion propulsion	**-->>**	Multiple electromagnetic (and) signaling effects: • Direct internal EF/EMF effects via Ag+s • External EF/EMF effects

Diffusion and circulatory transport
• Delivery to (deep) lesions problematic:
  • circulatory problems
  • Barriers
  • abnormal scar tissue
  • organ coverings
	-->>	Direct transport/delivery to targeted area(s):
		• changes affected microenvironments
		• no dependence or interference with GI tract
		• painless, sterile, non-invasive
		• minimum-effective-dose control

Single speciality care	**-->>**	Multi-specialty care

Superbugs

- Bacterial species and strains that have mutated and evolve resistance to antibiotics over decades
- Due to shotgun utilization of antibiotics
- Sped up by close housing of food animals and patients in hospitals for more infections and then more antibiotics
- (Ineffective) antibiotics may be working as placebos
- Antibiotics as growth promoting agents in animals
- Microbial distribution in microenvironments is dynamic with complex ecological relations: New adaptive organisms with 'good' and 'bad' characteristics
- Very limited indication that microbes can adapt to silver over many decades

Internal Abnormalities

- Infections of organs
  - Lung
  - Liver
  - Kidneys
  - Heart
  - Intestines
  - Nerves
  - Muscles
  - Brain
  - Ear
  - Reproductive
  - Etc
- Abscesses
  - Abdominal cavity
  - Brain
  - Lung
  - Liver
  - Subcutaneous
  - Oral
  - Etc.
- Bones
- Sepsis

Stages of Healing

- Inflammatory (acute)
  - red
  - hot
  - swollen
  - painful
- Proliferative
  - scar tissue
  - differentiating cells/tissue
  - normalized cells/tissue
- Maturation/Remodeling
  - clastic processes
  - blastic processes

Wound Care

- Describe wound location, size and other characteristics (electrode placement)
- Identify wound etiology (non SIS things, e.g. systemic nutrition, detoxification)
  - Maximize toxin removal and nutrient provision (follow with BDORT but ancillary part of comprehensive program)
- Assay wound environment characteristics (BDORT; lab micro-assays)
  - Identify colonized pathological microbes (to plan details of dynamic individualized approach)
  - Determine antibiotic sensitivity (BDORT testing; lab culturing)
- Maintain optimal environment for wound healing locally (SIS Ag+ & EF/EMF affects)
- Monitor and dynamically modify treatment program (as above)

Iontophoresis: Targetable Delivery System

Ion (Gk) = “(to) go” i.*e. moving object*

Phoresis (Gk) = “transport, carry”

Silver Iontophoresis = electromotive transport of silver ions (Ag+s) into a living body

Ag+ effects - #1

- **Broad spectrum, stand-alone microbial agent, including antibiotic resistant (MRSA, VRE, etc), gram-negative/positive bacteria**
- **Interruption of bacterial/viral membrane/capsid processes**[1,2]
  - Increases membrane permeability
  - Increases reactive oxygen species (ROS)
  - Interacts with:
    - Fe homeostasis
    - Transcription processes
    - Respiratory processes
- **Enhances standard antibiotic activity**
- **Virus inhibiting effects, including adenovirus, HIV-1, herpes family, influenza virus, Hep B, etc**

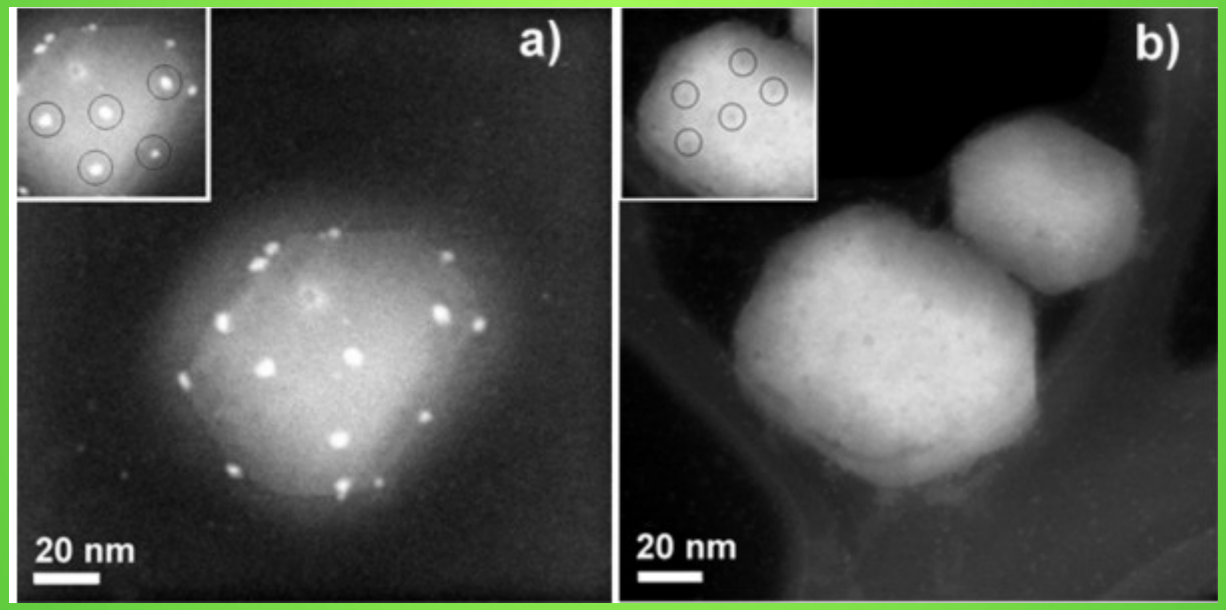
1. Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. Silver Enhances Antibiotic Activity Against Gram-negative Bacteria. Science translational medicine 2013;5(190):190ra81.

2. Elechiguerra JL, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, Yacaman MJ. Interaction of silver nanoparticles with HIV-1. J Nanobiotechnology. 2005 Jun 29;3:6.

Ag+ effects - #2

Example of silver particles binding with a virus capsule:

Ag+s attach to protein-specific sites of virus[2]



Matching protein-related spatial arrangements on surface of HIV-1 virus

2. Elechiguerra JL, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, Yacaman MJ. Interaction of silver nanoparticles with HIV-1. J Nanobiotechnology. 2005 Jun 29;3:6.

Ag+ effects - #3-1

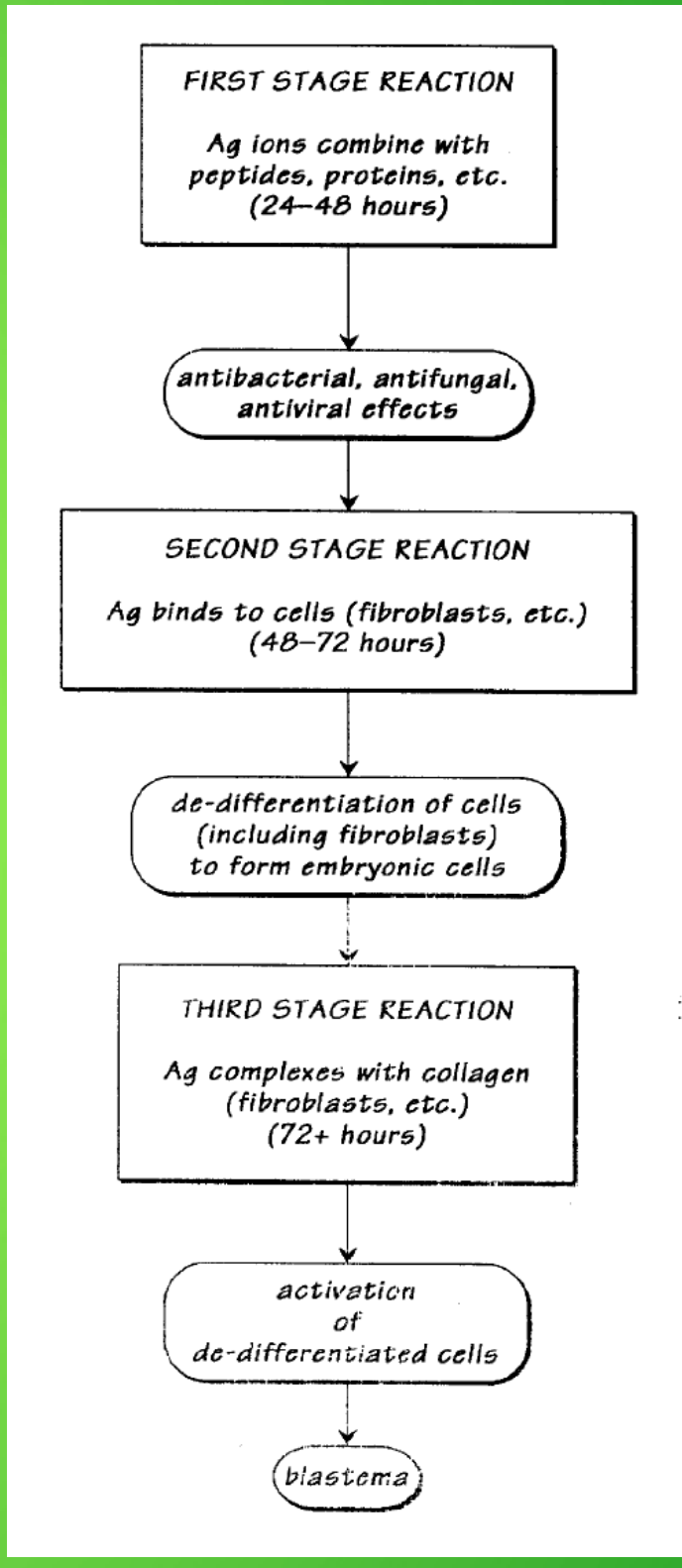
Becker's Ag+ microenvironment signalling tissue regeneration 'trick'

- Iontopheretic system for stimulation of tissue healing and regeneration US Patent 5814094 A
- Harrington DB, Becker RO. Electrical stimulation of RNA and protein synthesis in the frog erythrocyte. Exp Cell Res. 1973 Jan;76(1):95-8.

Ag+ effects - #3-2

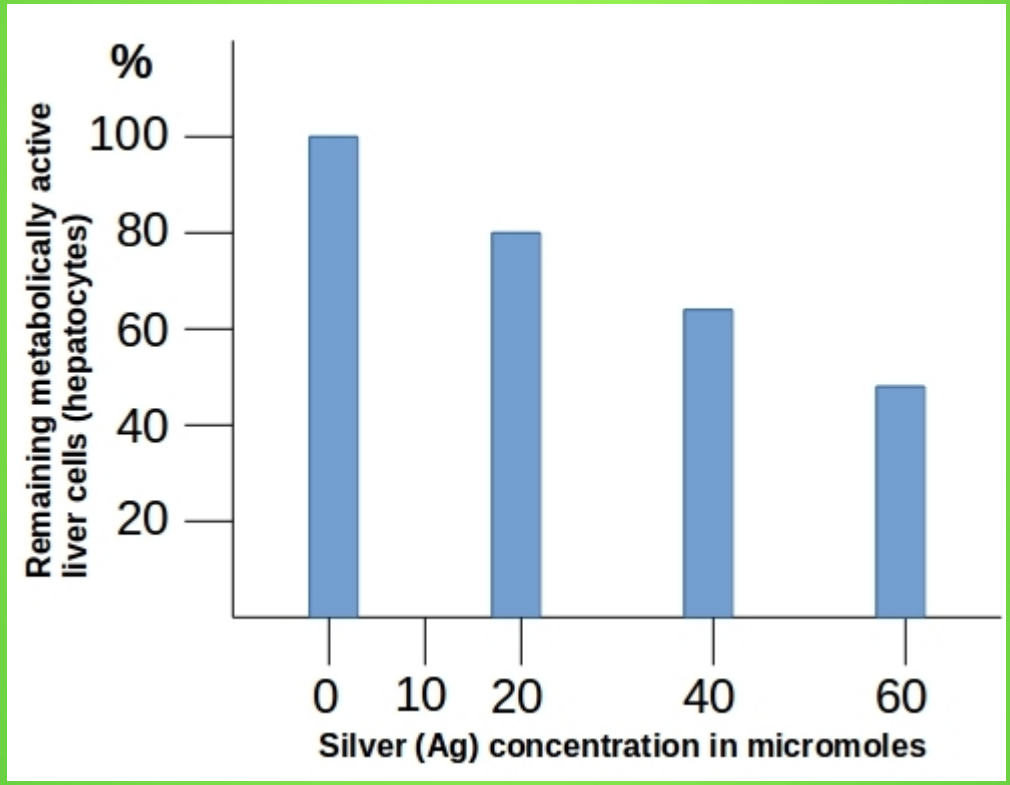
Microenvironment signaling for multi-type tissue healing and regeneration

[Becker et al, 1998]



Therapeutic Index

Lethal dose vs therapeutic concentration ratio of Ag+ within FDA approved antibiotics therapeutic index ranges[1]



1. Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. Silver Enhances Antibiotic Activity Against Gram-negative Bacteria. Science translational medicine. 2013;5(190):190ra81.

Iontophoresis

CLINICAL APPLICATION

1. Electro-physiological parameters

Internal infections/lesions: Skin

Electrical resistance (R): Intact skin

Approximate range

DRY SKIN: 10MΩ+

WET SKIN: 10-100kΩ

Wound Stimulation - Summary

1) Silver ions for 'infection' - prevention and treatment

2) Real-time measurement/calculation of wound-generated electric field

- Bioelectrically matching magnitude and polarity voltage drop generation at wound edges:
  - » Real-time scaled supplementation or replacement

3) Becker's tissue regeneration method

- Silver ions for fibroblast de-differentiation and more 'stem-like' cells for repair
- Voltage real-time scaling to wound/electrode size

Operation regardless of 'infection' status

Finding and testing Ag+ microcurrents for microbial/microenvironment effects

- **Clinical presentations**
    - Symptomatic → asymptomatic
- **Laboratory pathology results**
- **Organ/tissue/cellular/microenvironment assays**
    - Bi-Digital O-Ring Test (BDORT) resonance phenomena [Omura Y] antimicrobial effect predictive testing
        - BDORT reference control substance mono- poly-clonal antibody slides
        - Microbe antigen samples

Stimulation Current Comparison

‘Medicine’	**Drug solution iontophoresis**	**Silver-nylon (Ag+) iontophoresis**
Stimulation current range (amperes)	3-5 **milli**ampere (approximate)	0.5-10 **micro**ampere (approximate)

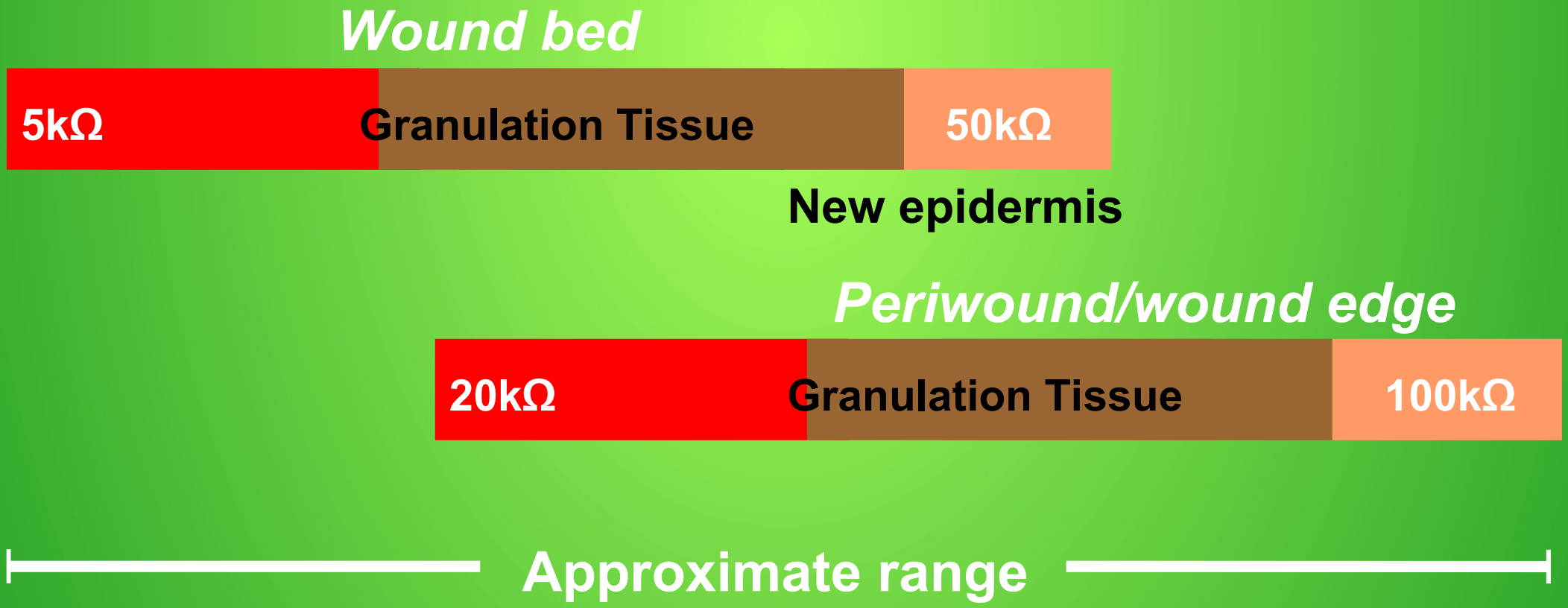
Narrow 'window' of effective Ag+ delivery without applied voltage damaging skin - and so increasing skin electrical resistance.

2. Electro-physiological parameters:

Wounds

Electrical resistance (R): Wound

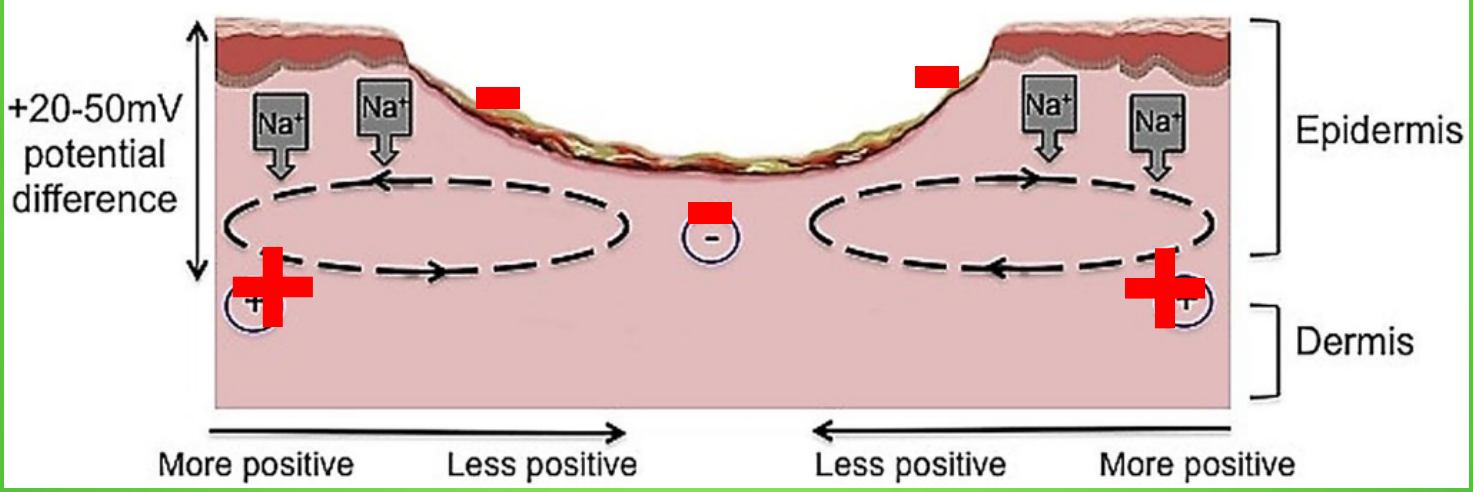
→ 1st - 3rd degree, full thickness



Trans-epidermal-epithelial Potential (TEP)

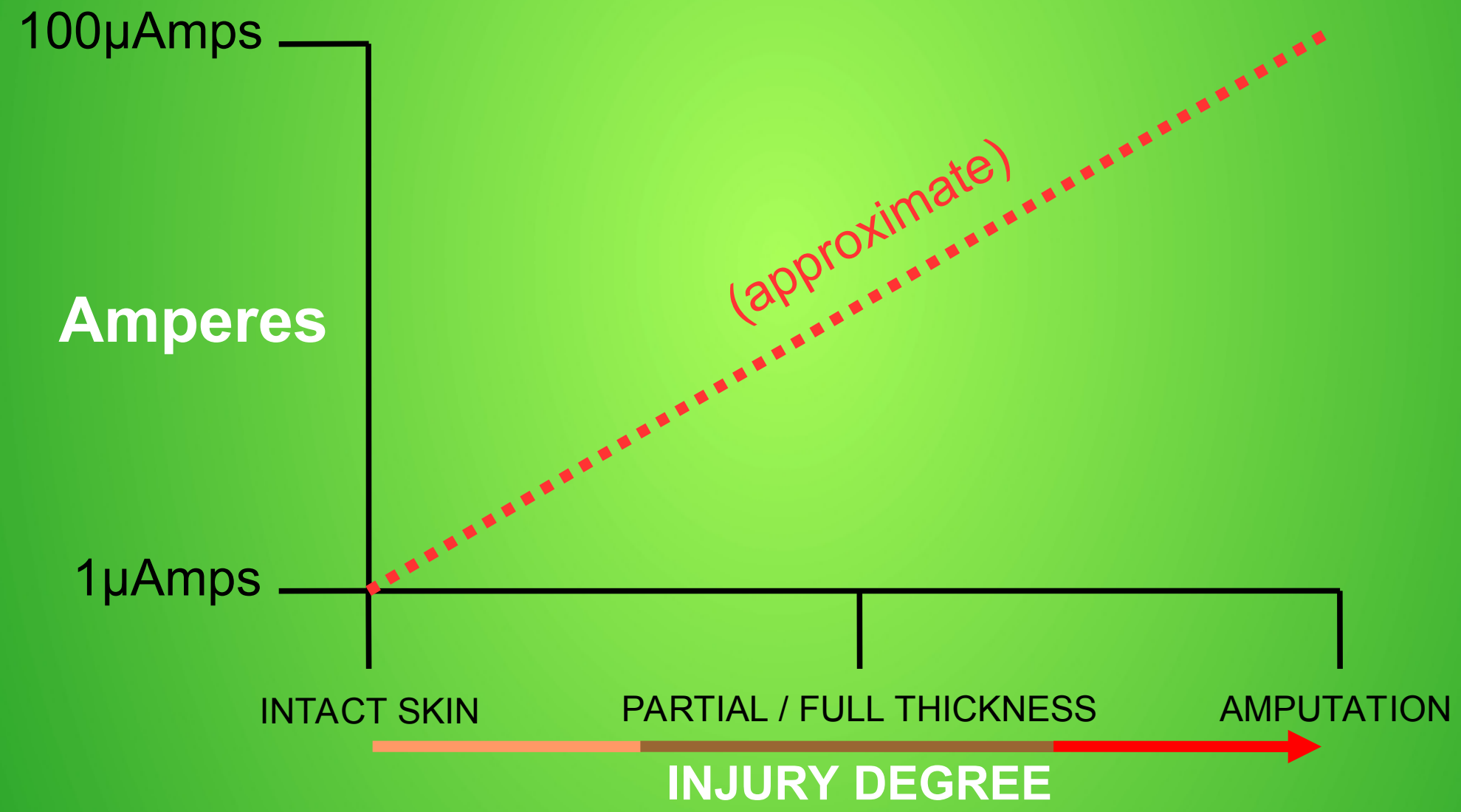
~20-70millivolts

Ohms Law: Current of Injury (COI) = $\frac{\text{TEP (V)}}{\text{R}}$

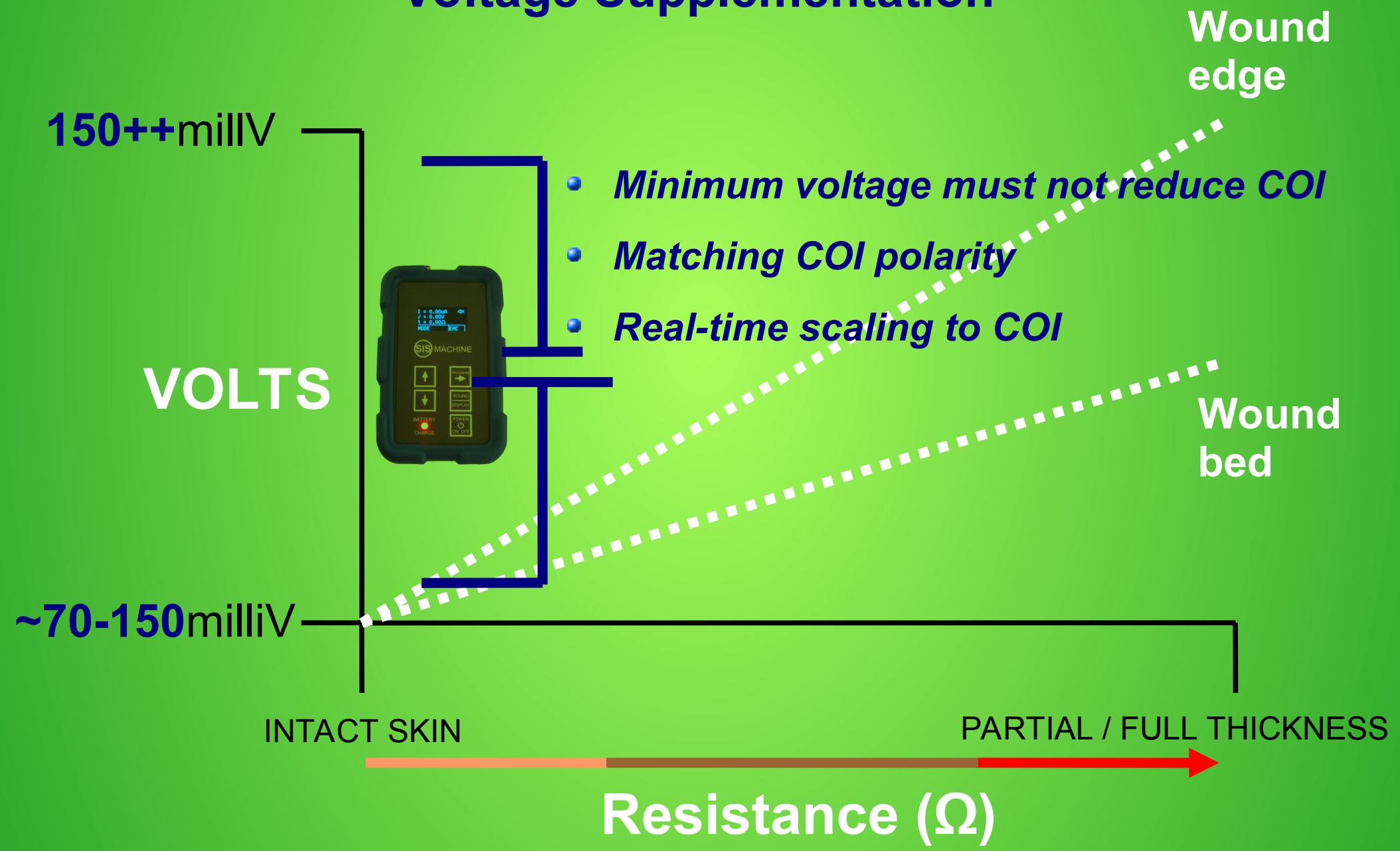


Current of injury image: Ud-Din S, Bayat A. Electrical Stimulation and Cutaneous Wound Healing: A Review of Clinical Evidence. Healthcare 2014, 2(4), 445-467.

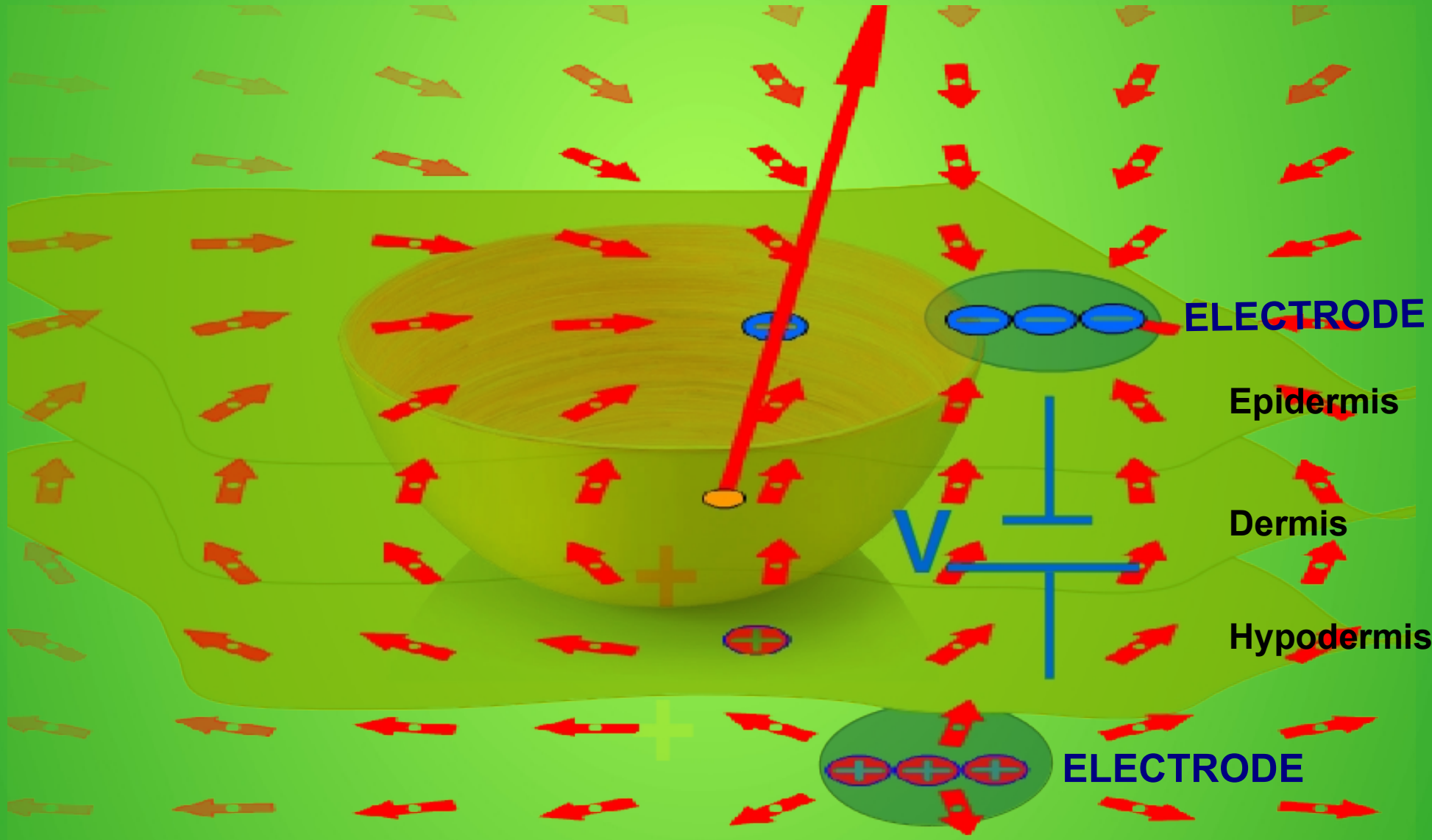
Current of Injury (COI): Amperes



Current of Injury (COI):
Voltage Supplementation



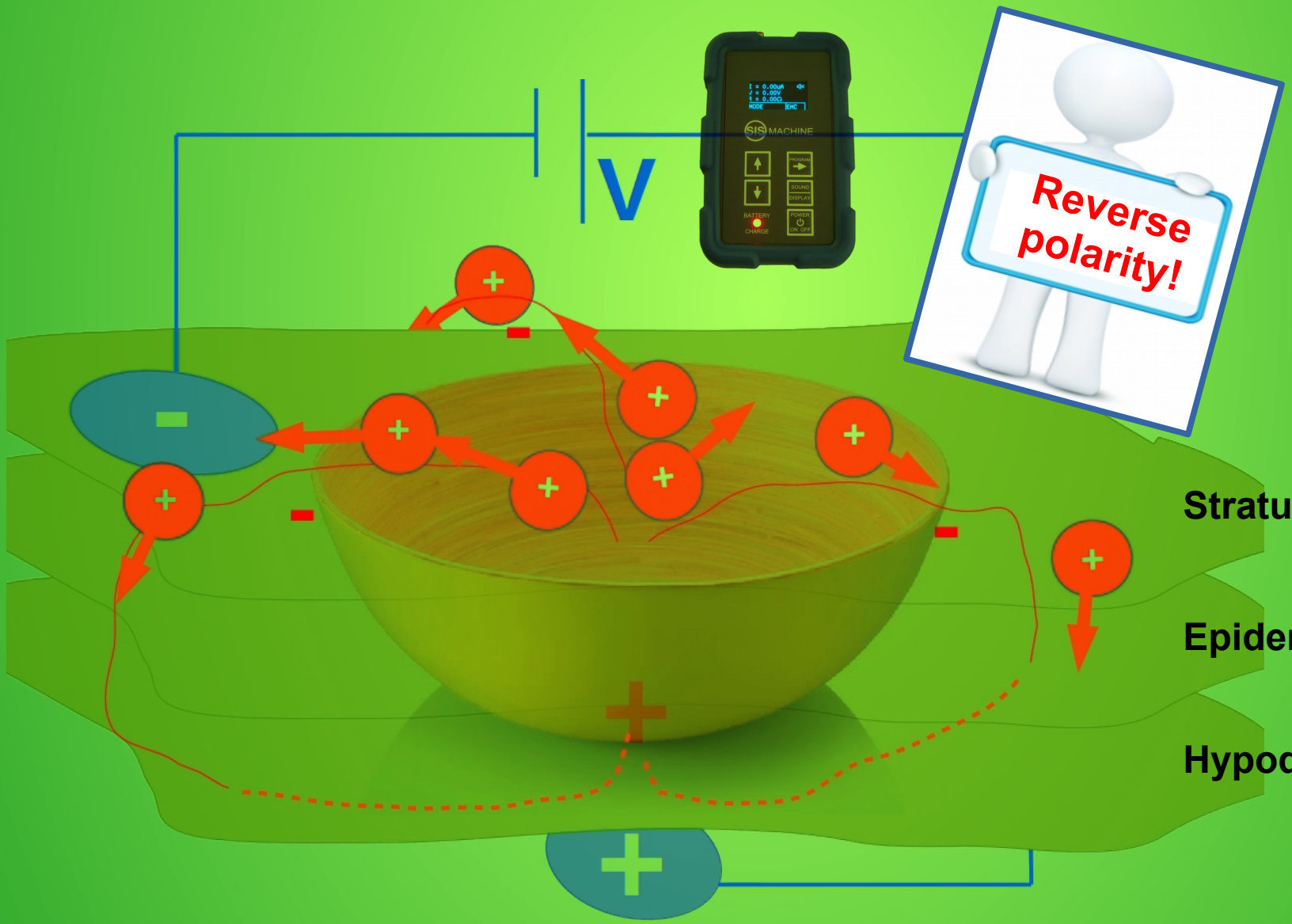
ELECTRIC FIELD GENERATED ACROSS WOUND GEOMETRY



VOLTAGE SUPPLEMENTATION: INCREASING E-FIELD AND COI THROUGH WOUND

Superficial Wound COI

VOLTAGE SUPPLEMENTATION: ELECTRODE POSITIONING



Deeper Wound COI

SUPPLEMENTATION VOLTAGE: ELECTRODE POSITIONING

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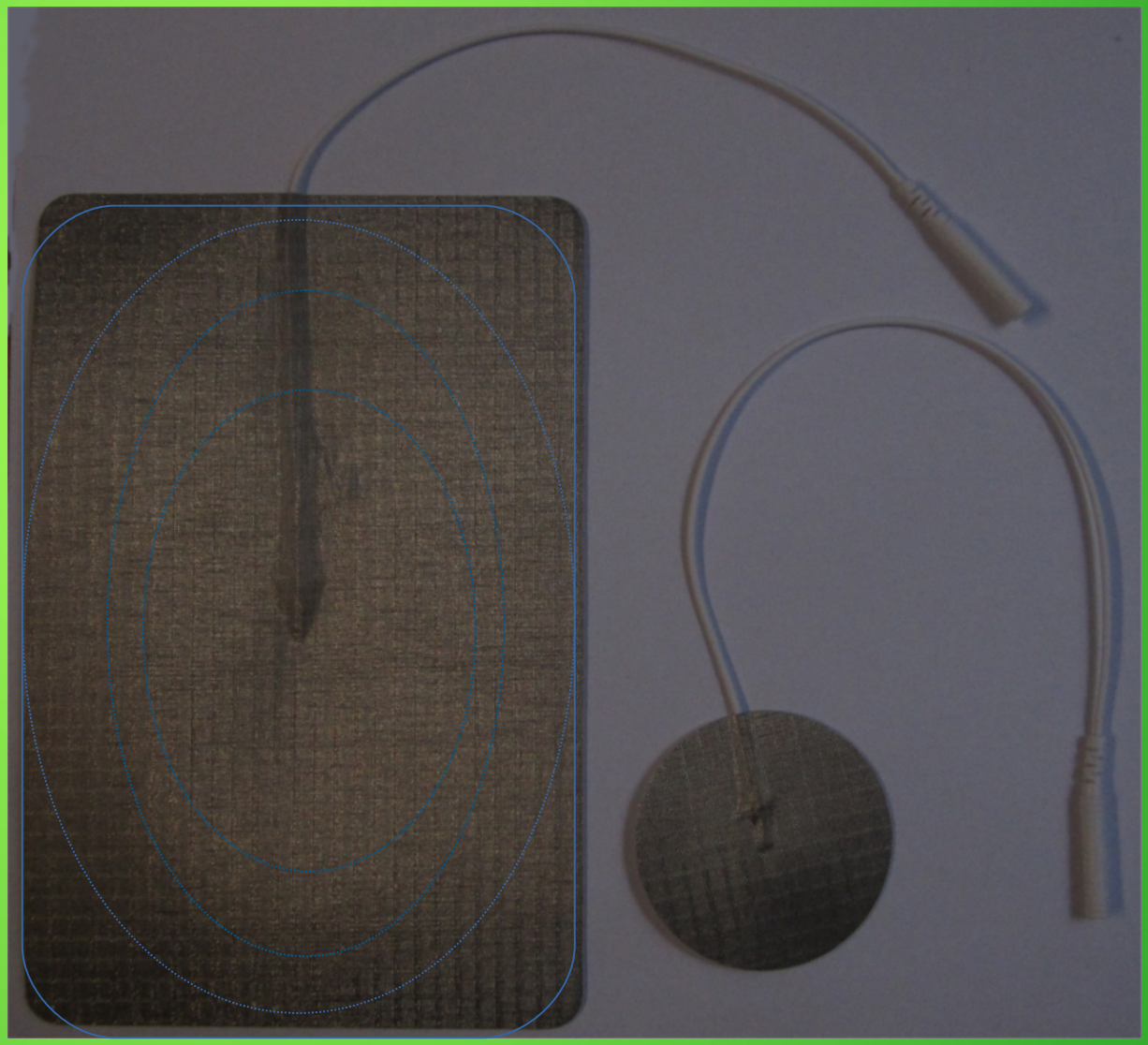
Operation regardless of 'infection' status

Bioelectric & Electronics: Basic Solutions

- **Delivery along pathway of least resistance**
  - Anatomical cross-sectioning with electrodes
  - Low voltage ‘gated’ sweat gland ion channels
- **Microcontroller regulated self-adaptive circuitry:**
  - Nanoampere accuracy constant ultra-low microcurrent
  - Real-time measurements of electrical skin/wound resistance (Ω)
  - Voltage producing & switching
  - Self-adaptive temperature calibration
  - Electrode stimulation efficiency (ESE) smart software

ELECTRODES: FDA 510(K)/EU(CE)
Class I conformity Ag-nylon material



DEMONSTRATION OF CLINICAL EFFICACY:

Illustrative Case Studies

1. Acute Periodontitis

2-3 days continuous near 24 hour use

- Asymptomatic:
  - No pain
  - No swelling

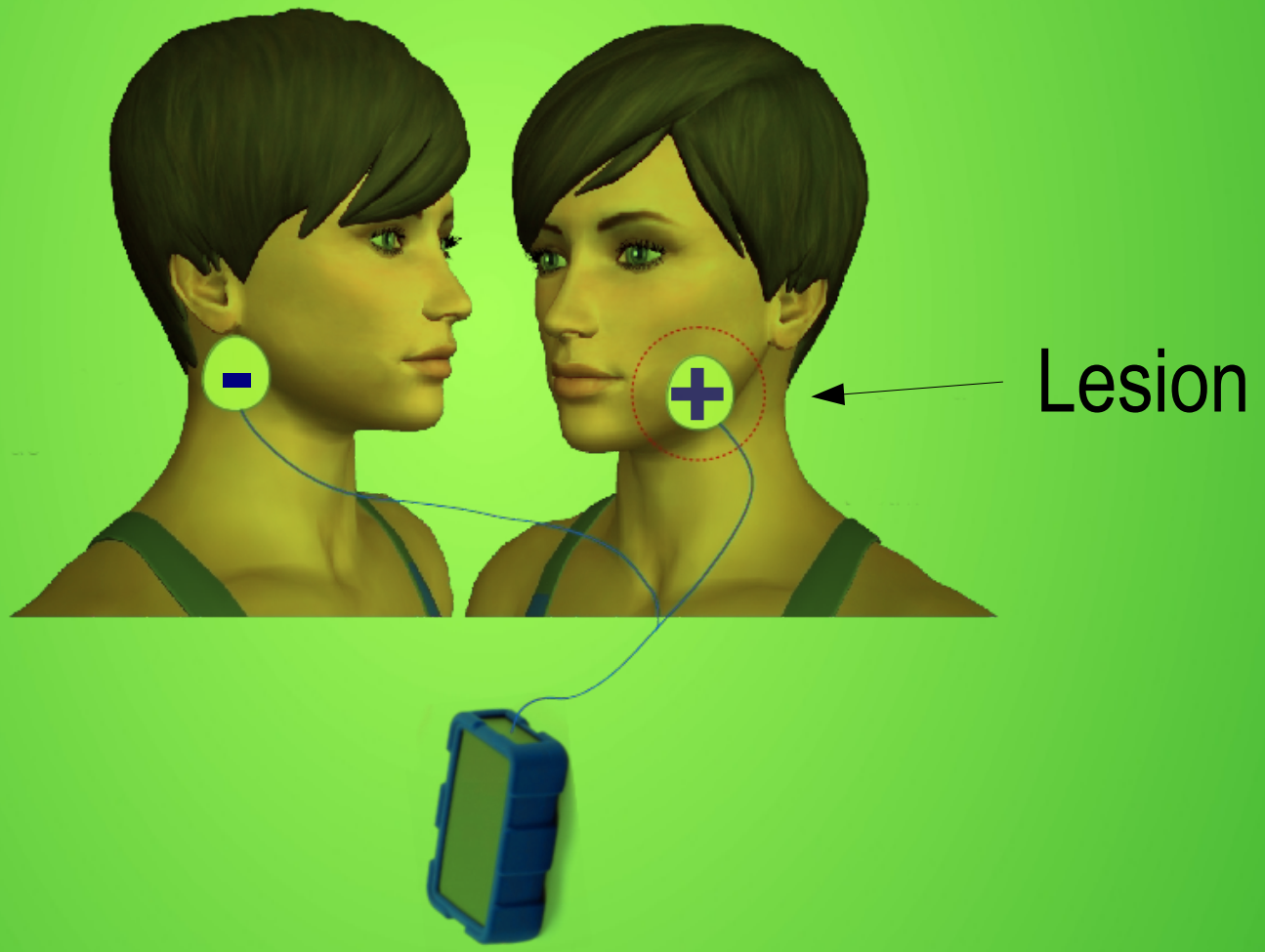
- No antibiotics nor painkillers

- Coincidental gum regeneration
  (Becker's stem cell 'trick'?)

Apple-sized lesion

ZygoteBody® image source

1-1. Jaw electrode placement



ZygoteBody® image source

2. Symptomatic H. Pylori

16 days continuous near 24 hour use (prototype SIS equipment)

- C14 Urea Breath Test positive

- No antibiotics, painkillers, proton pump inhibitors

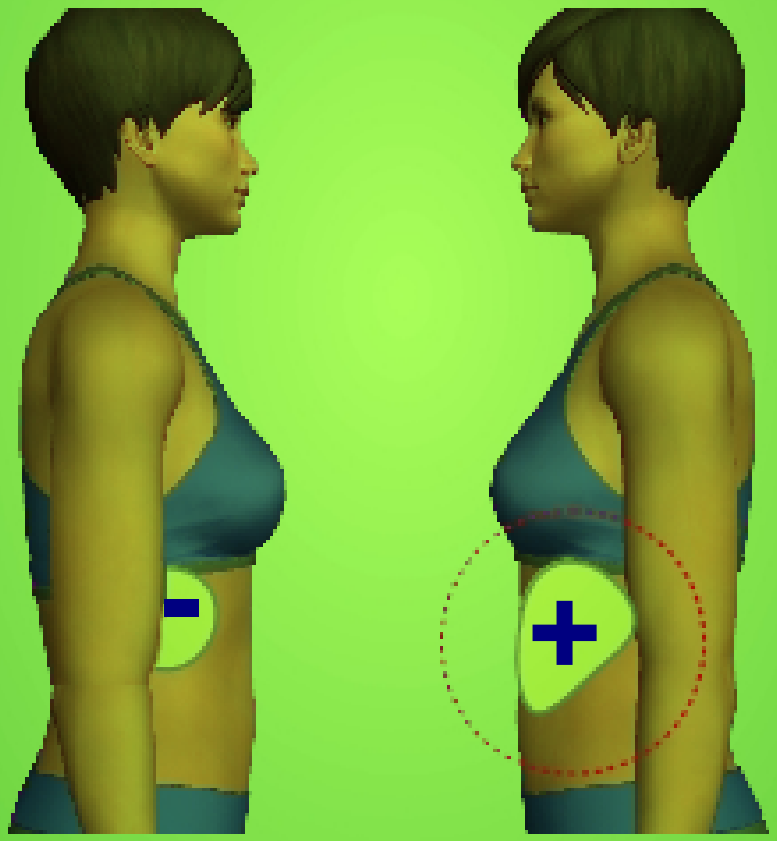
- BDORT negative

- 90% reduction of symptoms

- C14 Urea Breath Test negative

ZygoteBody® image source

2-2. H Pylori electrode placement



ZygoteBody® image source

3. Infected oozing antibiotic-resistant Cesarean section surgical scar

Positive Electrode placement directly on wound

- 7 days: no signs of infection or swelling (prototype SIS equipment)

- Complete healing, not requiring any further treatment

- No pain/painkillers

4. Symptomatic cervical Human Papiloma Virus (HPV) infection

10-12 days of continuous near 24 hour use

- Asymptomatic

- Pathology testing not obtained/unavailable

- BDORT negative

4-1. Cervical electrode placement

ZygoteBody® image source

5. Symptomatic ear infection in 7yo child

12 hours of near continuous use

- Asymptomatic

- Recurrence after several weeks and repeat treatment; again asymptomatic.

5-1. Ear electrode placement

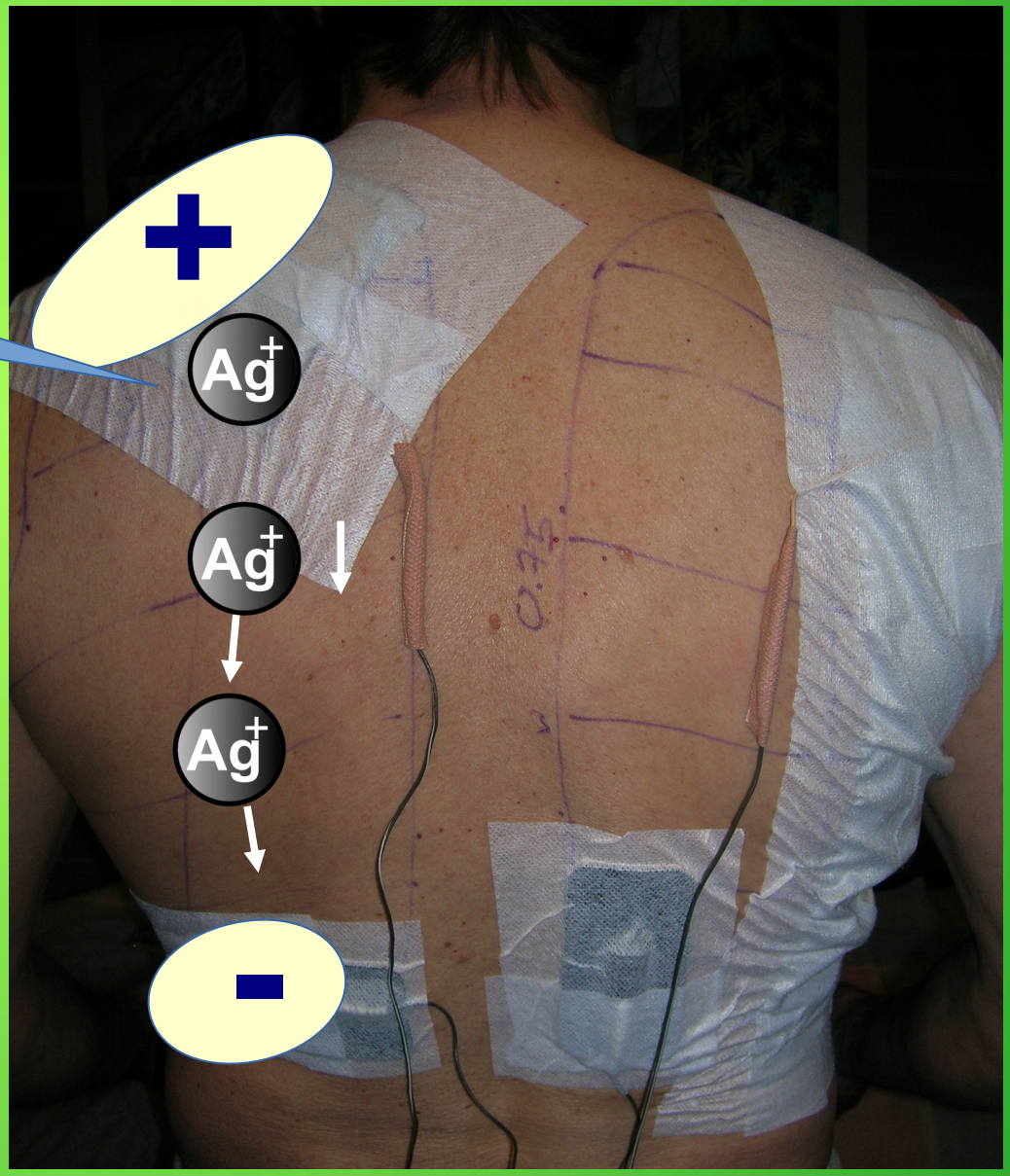
ZygoteBody® image source

6. Internal chronic scar tissue reversal: Decades of Mycobacterium tuberculosis induced lung scarring:

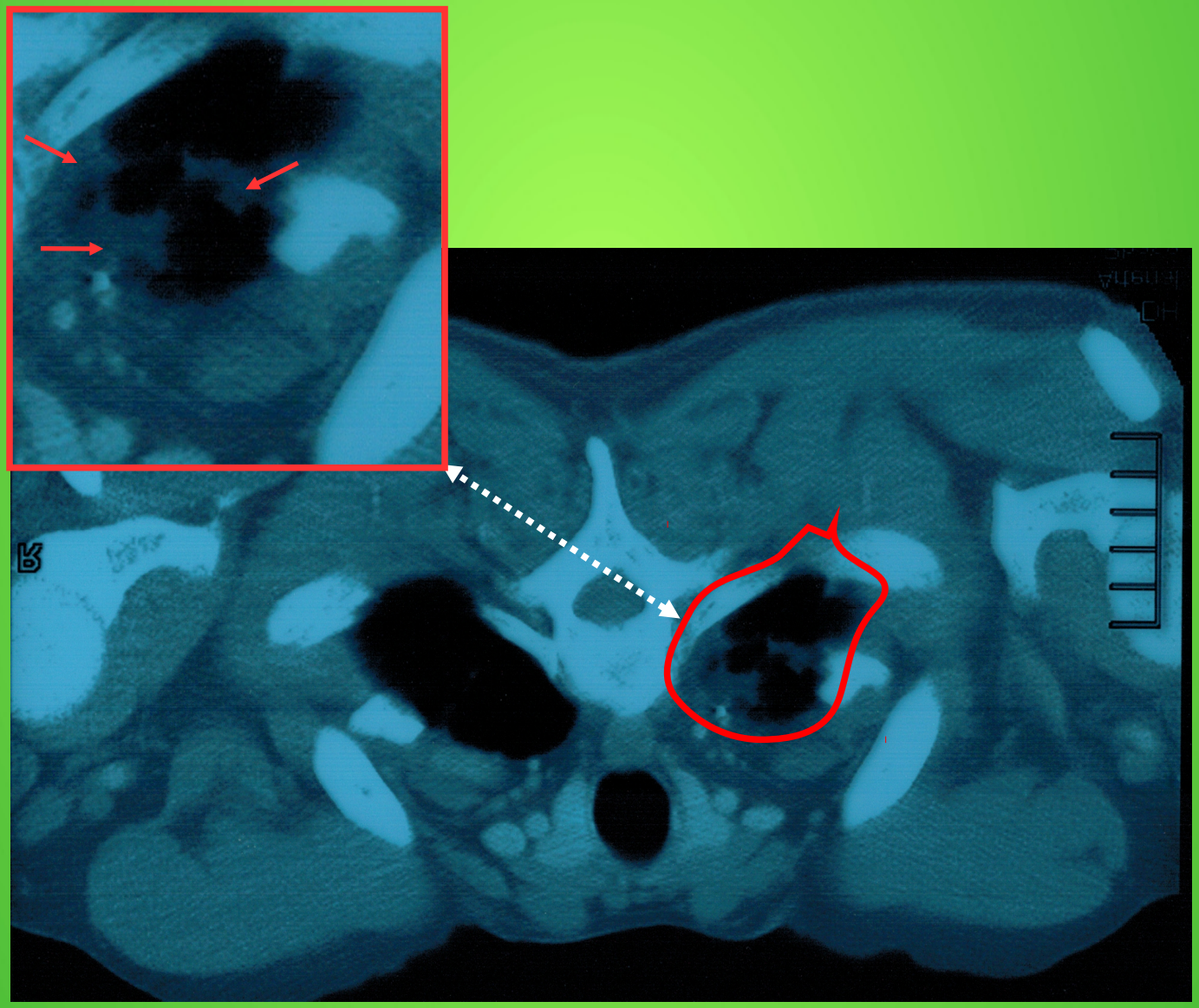
Several weeks continuous treatment

6-1. Lung electrode placement

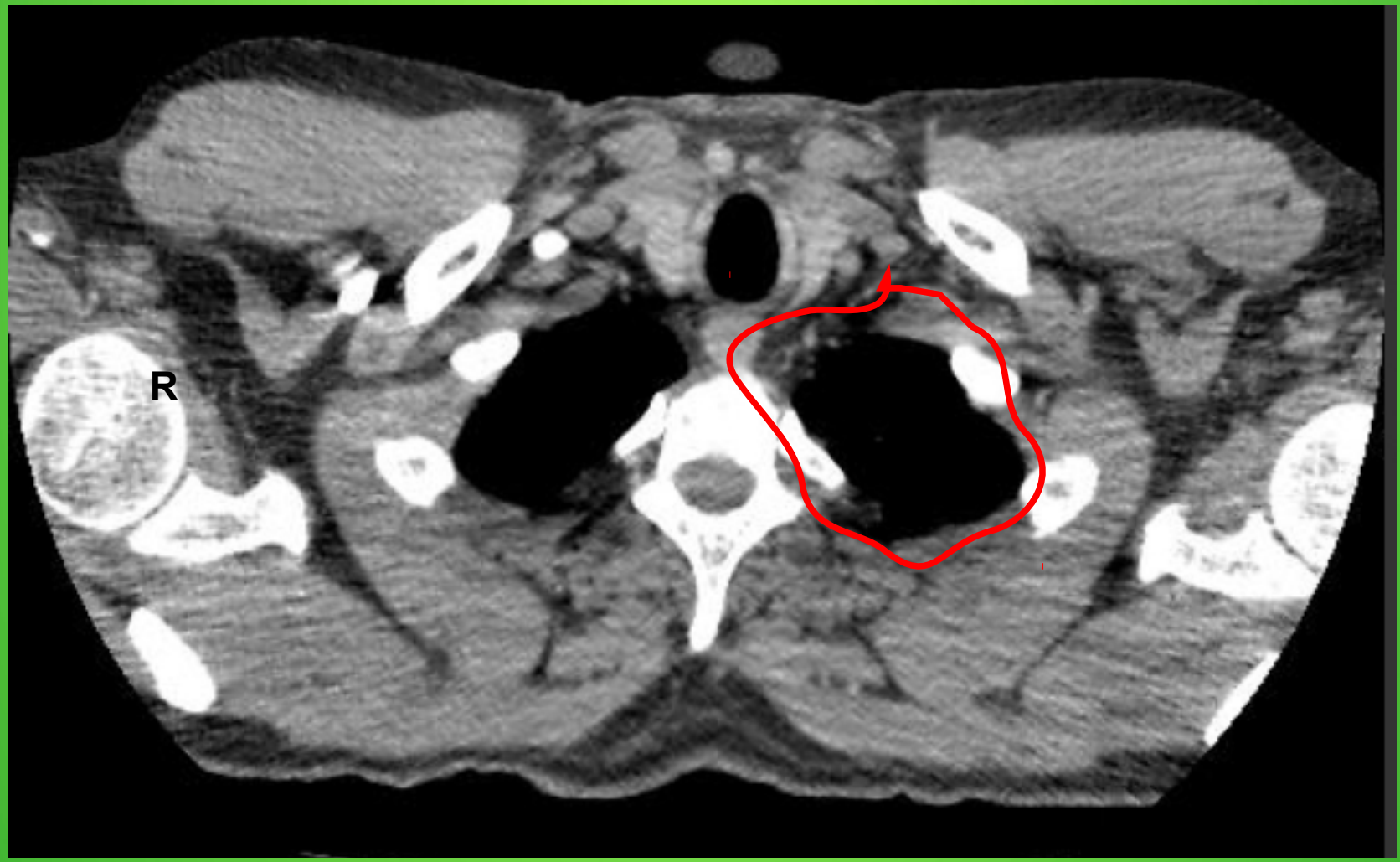
Major effect proximal to +ve electrode



6-1. CAT SCAN IMAGE:
APICAL SCARRING



6-2. CAT SCAN IMAGE COMPARISON: NO SCARRING



Medical Need Fulfilment

- Iontophoresis precedences established for surface and internal tissue targets
- Data based development
- Ag+ iontophoresis via low amperage direct current
- Delivery through variable:
  - Distance
  - Tissue type: varying electrical impedances
  - Time-frames
- Supported by case study results

SIS machines

- Dedicated and portable silver iontophoresis stimulators (SIS) and electrode system
- RCM, FCC, CE electronics conformity tested
- **Bacterial & viral infections**
- **Wound protection & healing**
- **Tissue healing & regeneration**
- Patent pending devices and technology.

SIS

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