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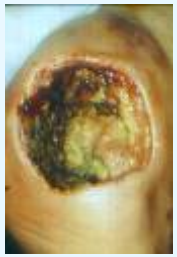
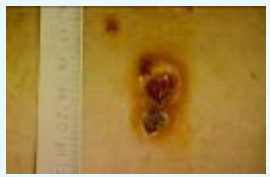
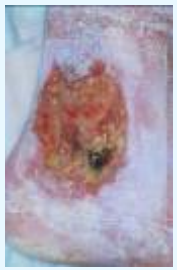
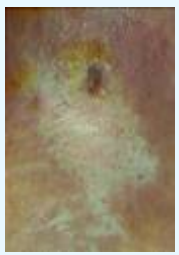
TIME

Transformation of the science of wounds into daily practice of wound assessment and treatment

Wound Bed Preparation International Advisory Board

- Elizabeth Ayello PhD, US
- Caroline Dowsett, UK
- Dr Vincent Falanga, US
- Dr Keith Harding, UK
- Dr Marco Romanelli, Italy
- Greg Schultz PhD, US
- Dr Gary Sibbald, Canada
- Dr Mike Stacey, Australia
- Dr Luc Teot, France
- Dr Wolfgang Vanscheidt, Germany

Clinical Observations		Pathophysiology		
Tissue Non-viable or deficient		**Defective matrix and cell debris impair healing**		
Infection or inflammation		↑ inflammatory cytokines ↑ protease activity ↓ growth factor activity		
Moisture imbalance		Desiccation slows epithelial cell migration Excessive fluid causes maceration of wound margin		
Edge – non advancing or undermined		Non migrating keratinocytes Non responsive wound cells and abnormalities in protease activity		

TIME-Principles

- Each time you see a wound patient
- Assess the wound according to TIME
- Then choose the appropiate methods to correct the pathophysiology
- Decide which is actually the most predominat !

TIME-Assessment of leg ulcers

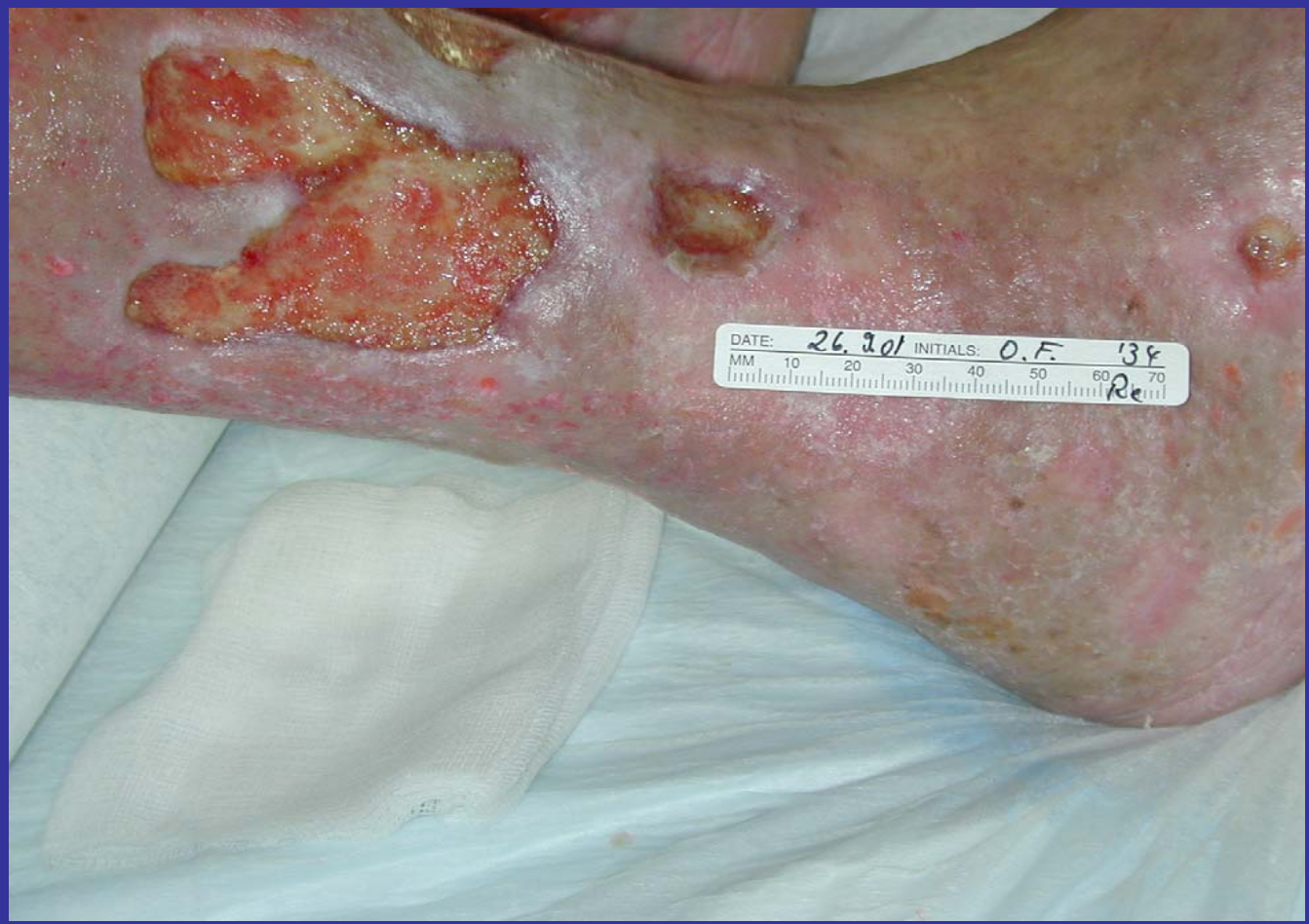
Tissue
Non-viable or deficient

Infection or inflammation

Moisture imbalance

Edge – non advancing or undermined

Tissue -deficient



TIME-Assessment of leg ulcers

Infection or inflammation

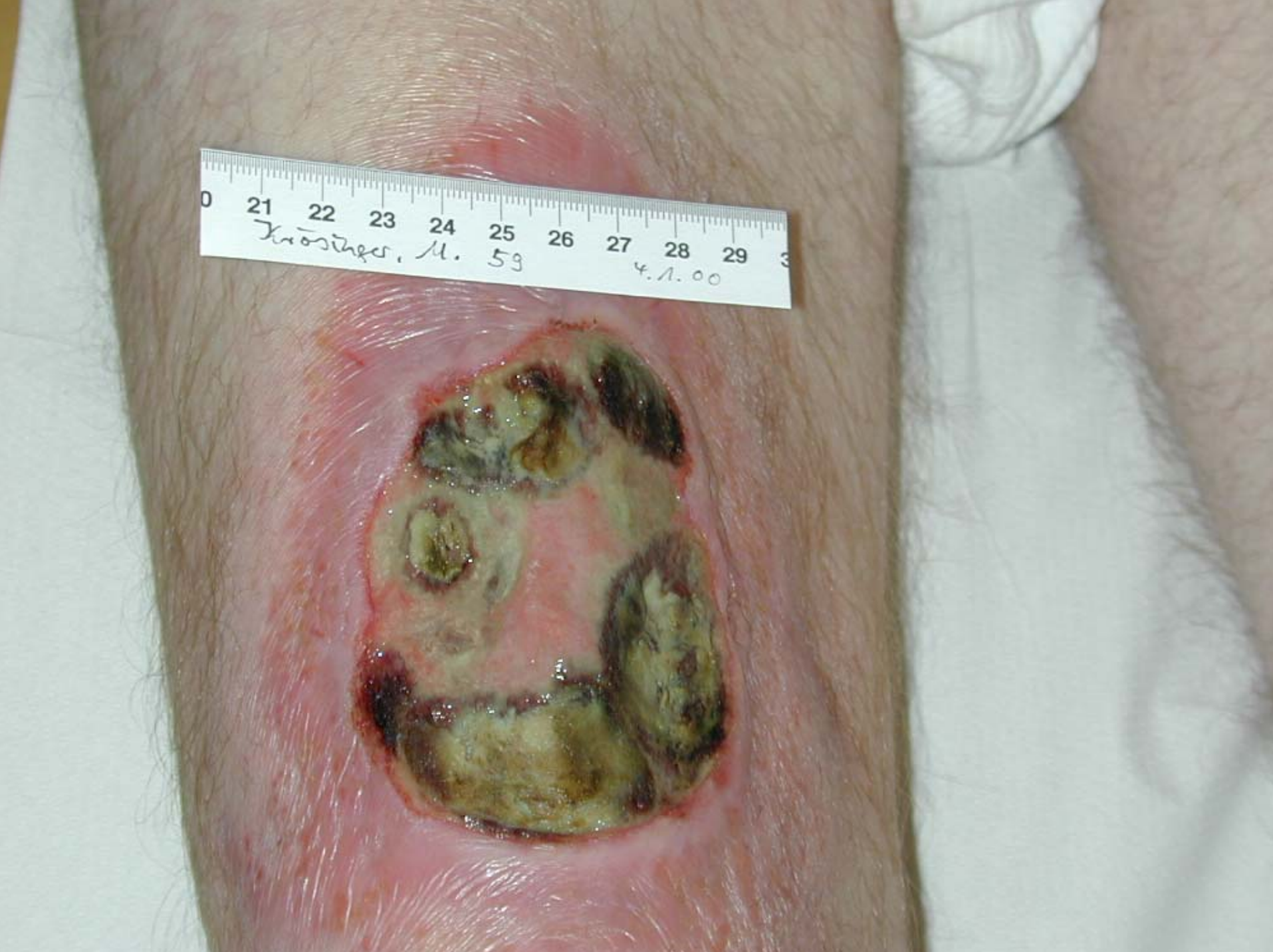
Swabs from the wound surface are usually not senseful

They tell more about the bacteriology of your clinic than about the patient

TIME-Assessment of leg ulcers

Infection or inflammation

Therefore swabs are to be used for epidemiologic purposes rather than for the treatment of the patient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TIME assessment - moisture

Moisture imbalance

TIME assessment - moisture

The most important diagnostic tool is the dressing itself

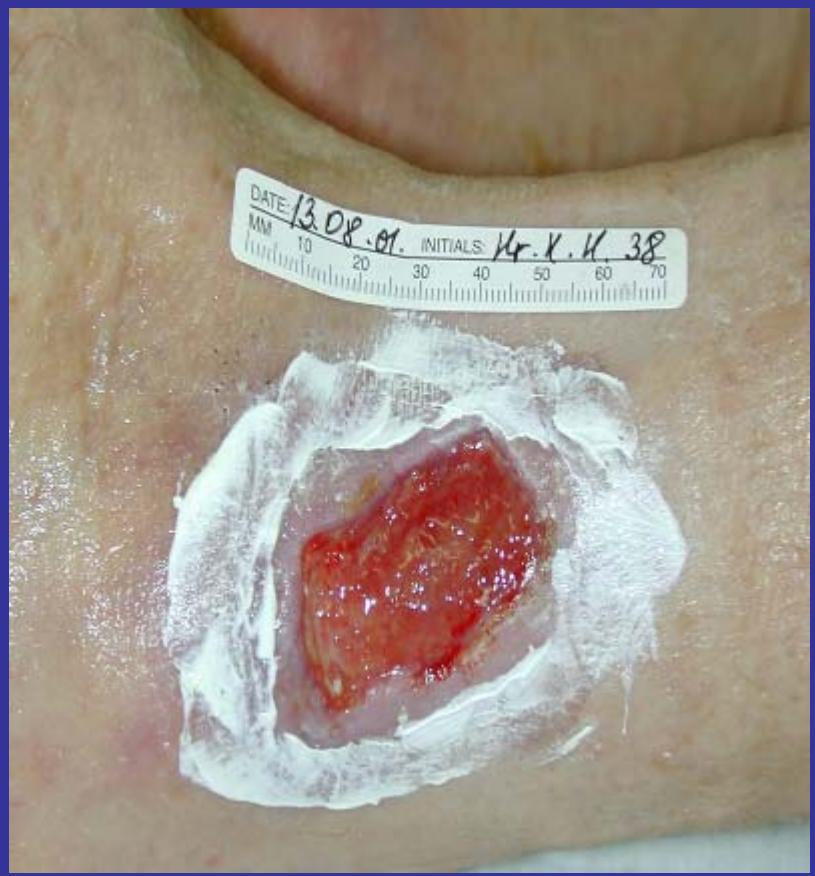
TIME assessment - moisture

If it is thrown away before the clinical visit, you loose the most precious information about the history of the wound

TIME assessment - moisture

- Inspect the wound edge for maceration

Excessive moisture

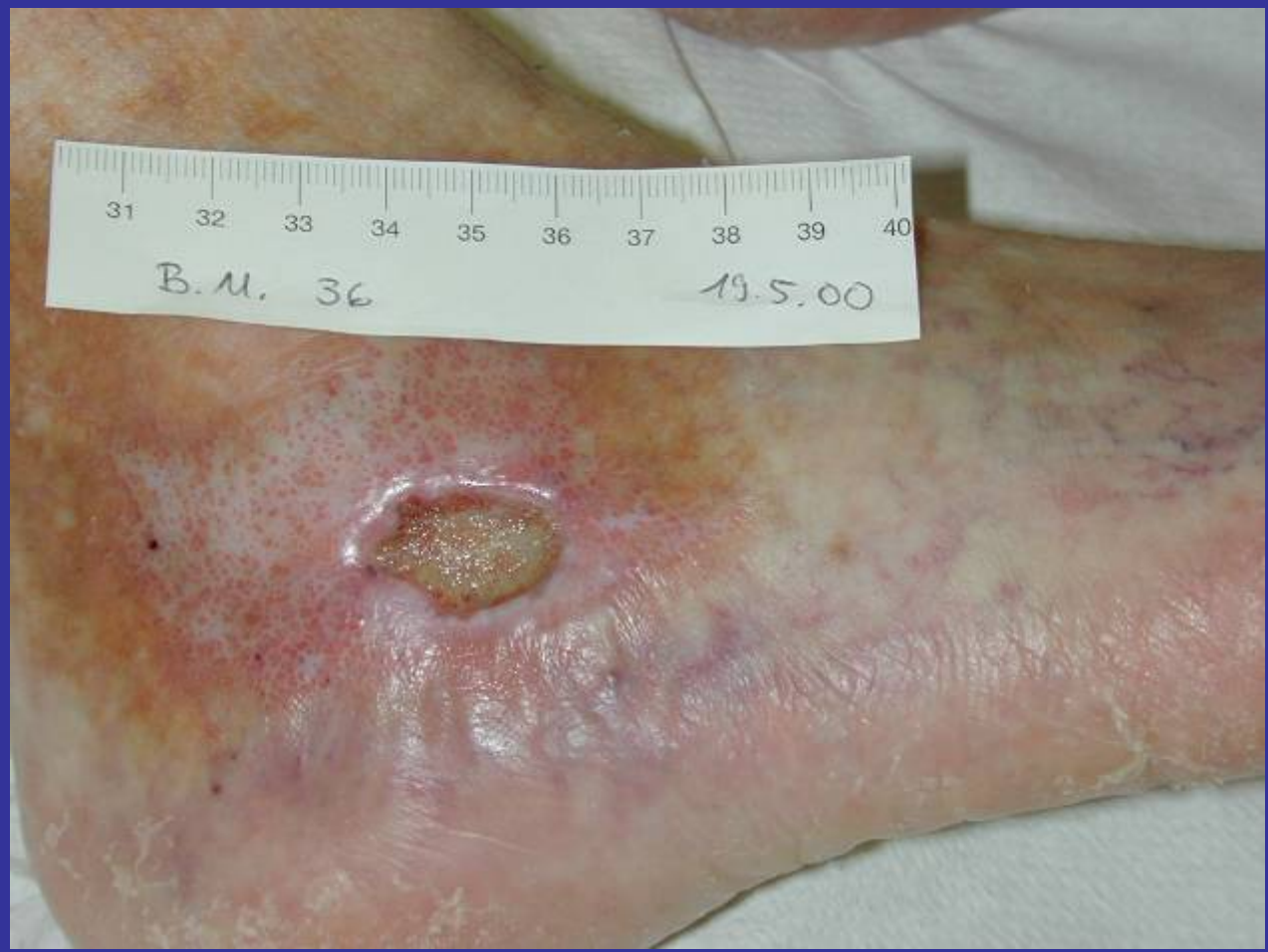


TIME – Assessment -Edge

- Edge

- non advancing or undermined
- Measurement by planimetry

White atrophy



TIME- Bed-side score

- Tissue ?
- Infection/Inflammation ?
- Moisture ?
- Edge ?
- 0=healthy
- 1=slightly disturbed
- 2=severe problem
- 3=main problem

Therapeutic Options in TIME

- Be prepared to change your options according to your TIME-assessment at each dressing change
- Redefine your options !

What are the therapeutic options in daily wound care

- With

- TIME

Tissue

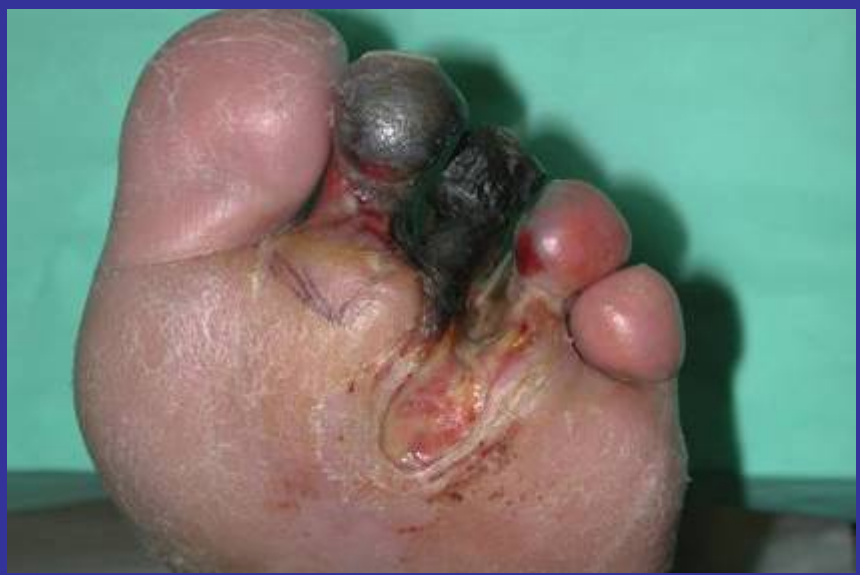


Fig A. Necrotic toes with dry gangrene as the end result of ischaemia and deep tissue infection

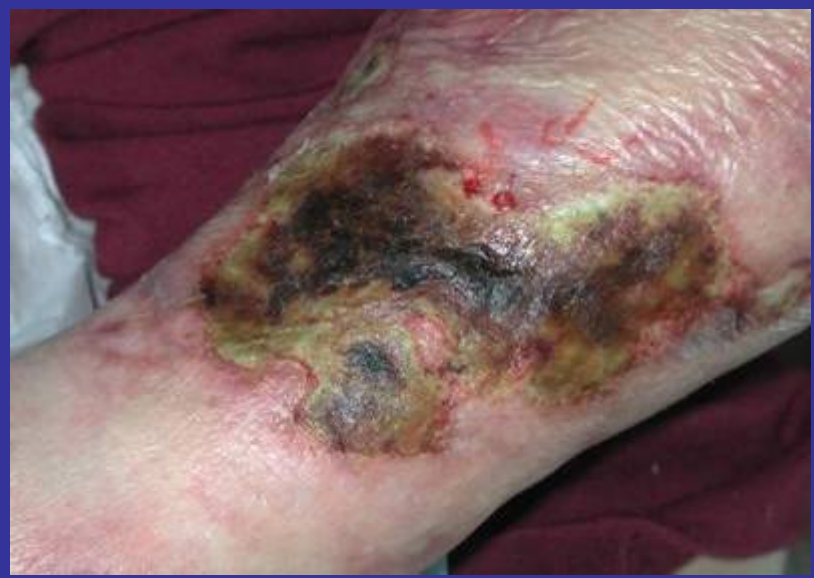


Fig B. Leg ulcer with hemorrhagic necrosis

Debridement

- Efficient debridement is essential in treating all wounds
- Debridement has to be a repetitive process
- Since necrotic tissue is continually produced in chronic wounds

Debridement

- Debridement will allow healthy granulation tissue to form
- Debridement reduces wound contamination and reduces further tissue destruction
- Debridement reduces dead spaces that harbour bacterial growth

Types of debridement

- Autolytic debridement
- Surgical/sharp debridement
- Enzymatic debridement
- Mechanical debridement
- Biological therapy

Autolytic debridement

- Occurs spontaneously in all wounds
- Enzymes spontaneously separate necrotic tissue from healthy tissue
- Moist dressings can enhance the environment for debridement
- Eschar can contribute to the delay in autolysis

Autolytic debridement

- If it does not work within 3 weeks
- Change to another mode of debridement

Surgical/sharp debridement

- Fastest and most effective way to remove debris and necrotic tissue
- Can leave a bleeding base which is known to increase the healing rate of neurotropic foot ulcers

Surgical Debridement

Debridement of buttock ulcer

Fig A. Interoperative

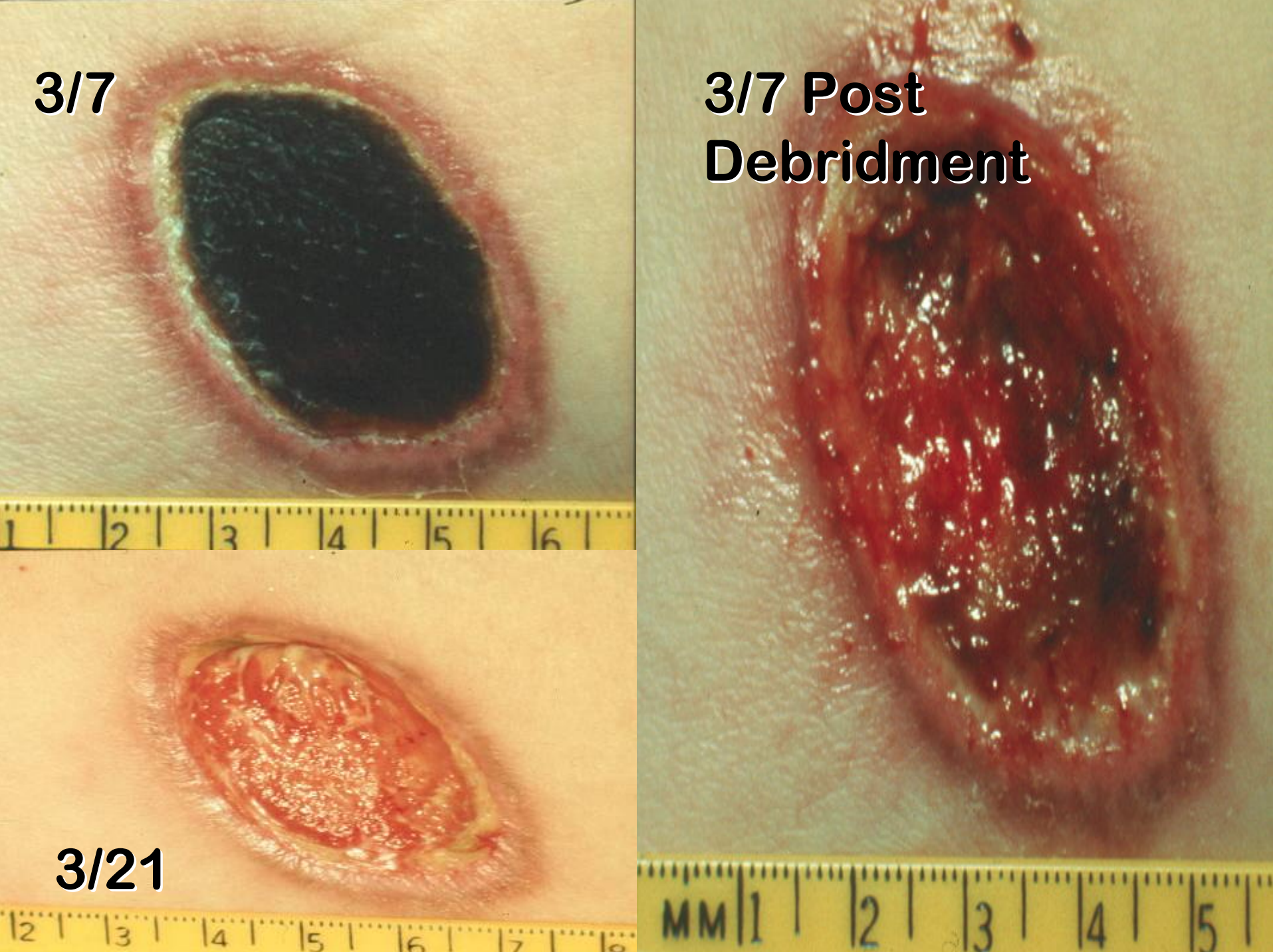
Fig B. Post-surgical debridement

Surgical/sharp debridement

- Surgical debridement is normally performed:
  - Where there is a wide wound area
  - Where there is widespread infection
  - Where bone and infected tissue must be removed
  - Where the patient is septic

Surgical/sharp debridement

- Myth I
- Do not touch black necrosis
- Why ?


3/7
3/7 Post Debridment
3/21

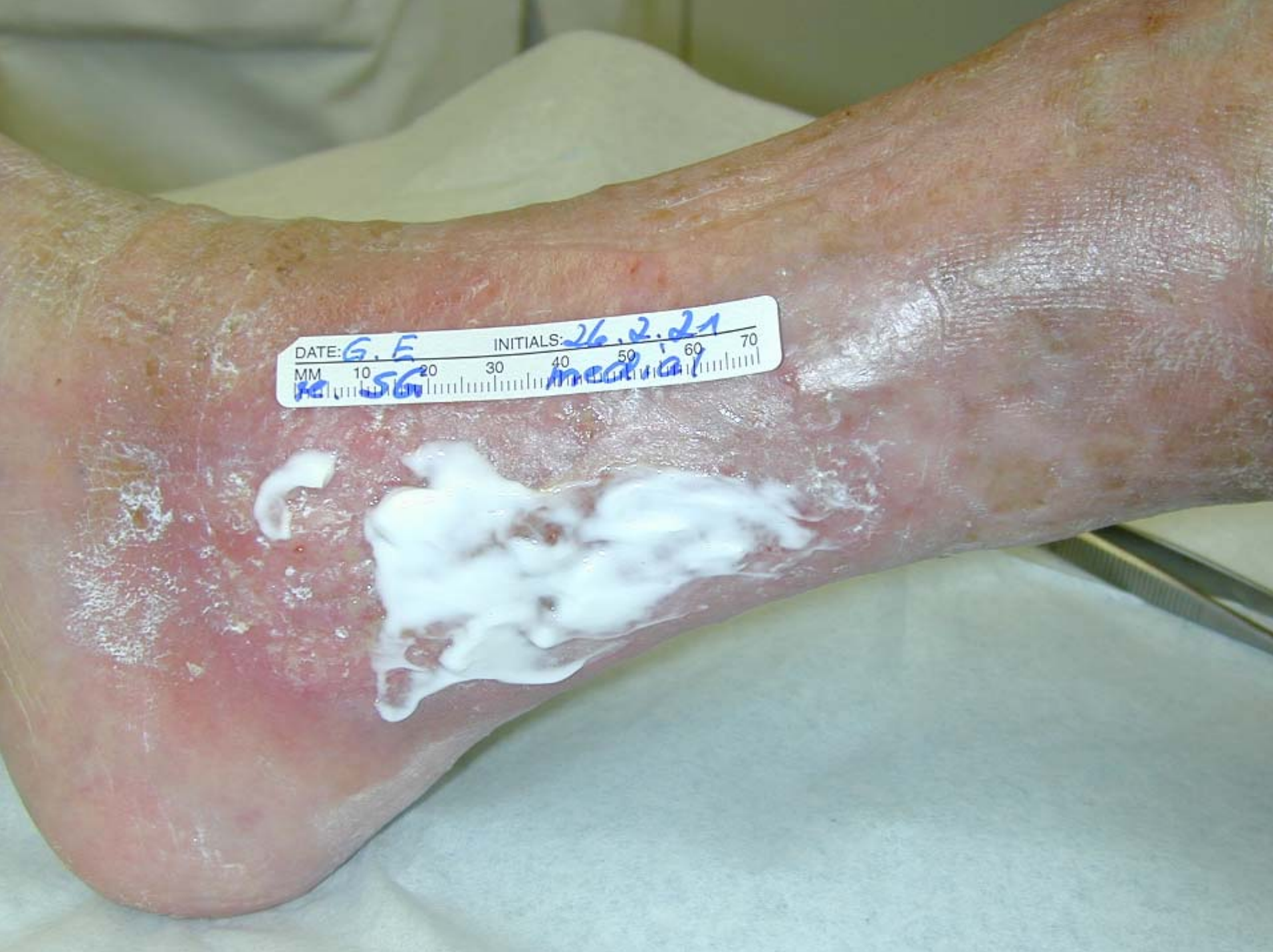
Surgical/sharp debridement

- Myth II

- Sharp debridement is dangerous in the patient under cumarines
- Why ?

Sharp Debridement

- Topical Anaesthesia (EMLA ^{R})
- Application 45 min before treatment
- Under occlusion
- Risk of allergic reaction minimal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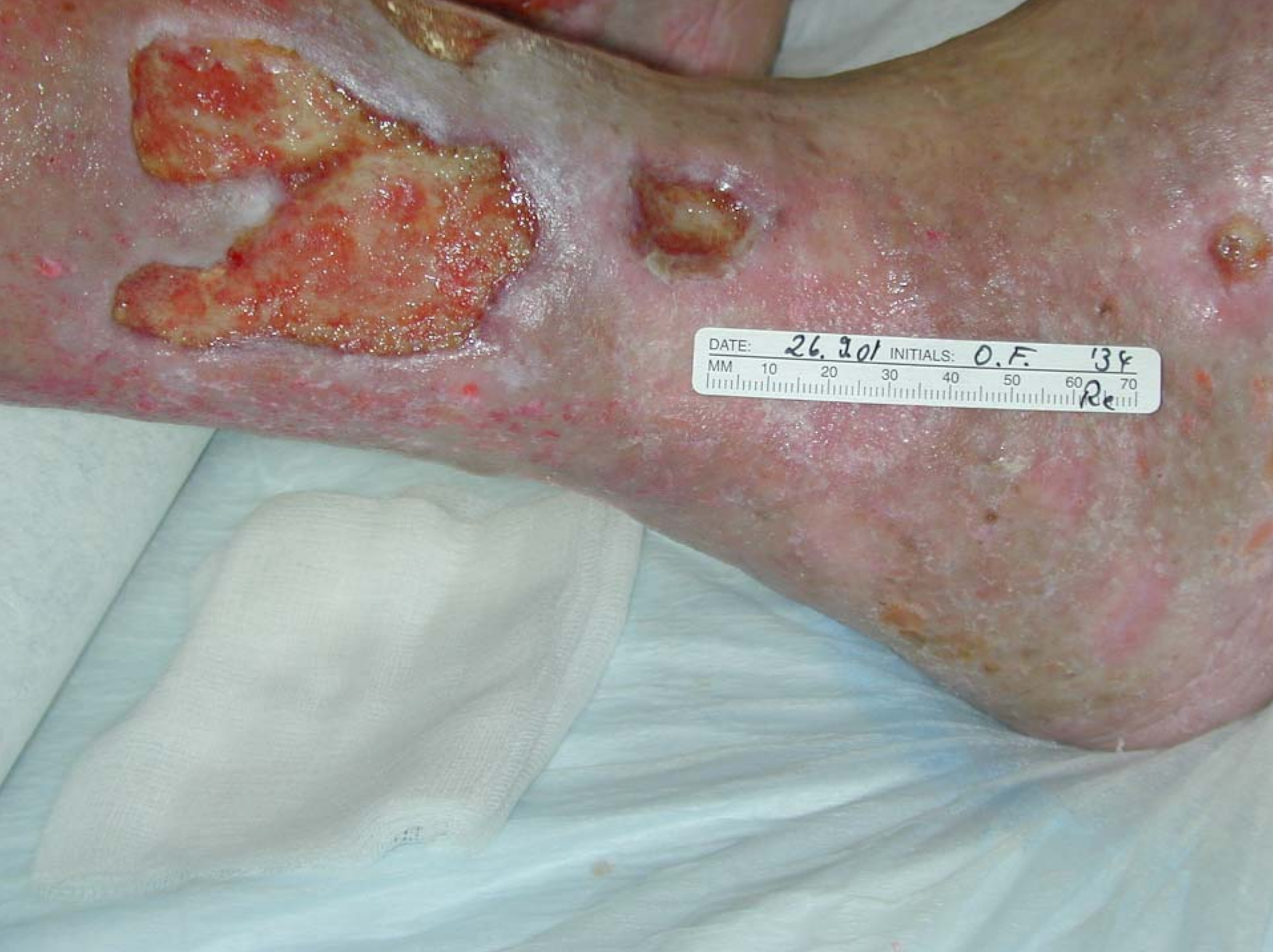
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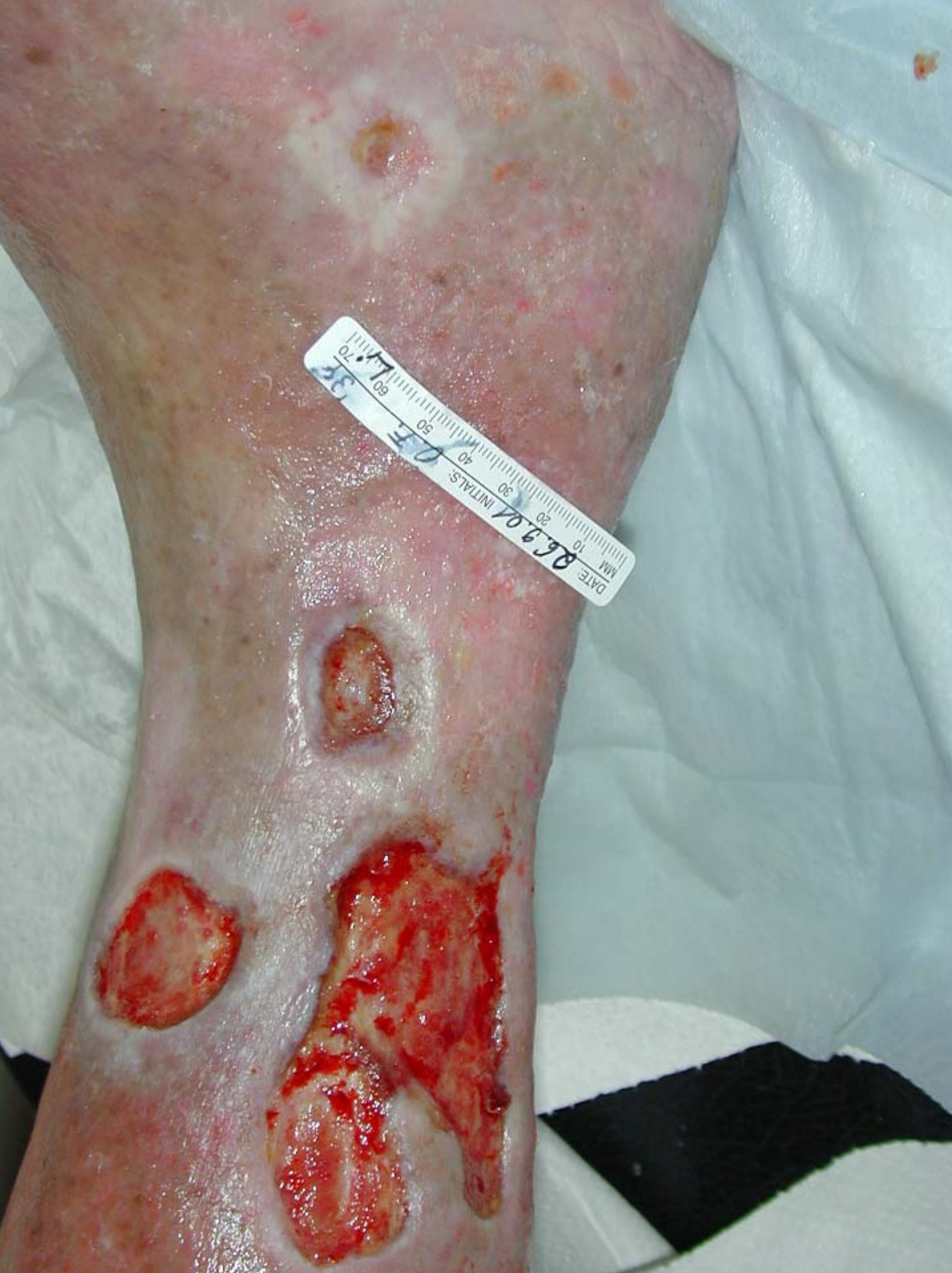
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Enzymatic debridement

- Uses topical application of exogenous enzymes to the wound surface
- Useful in removing eschar from large wounds where surgery has failed
- Excess exudate may be produced with these agents:
- Available agents include:
  - Bacterial collagenase
  - DNase/fibrinolysin
  - Papain/urea
  - Trypsin

Enzymatic debridement

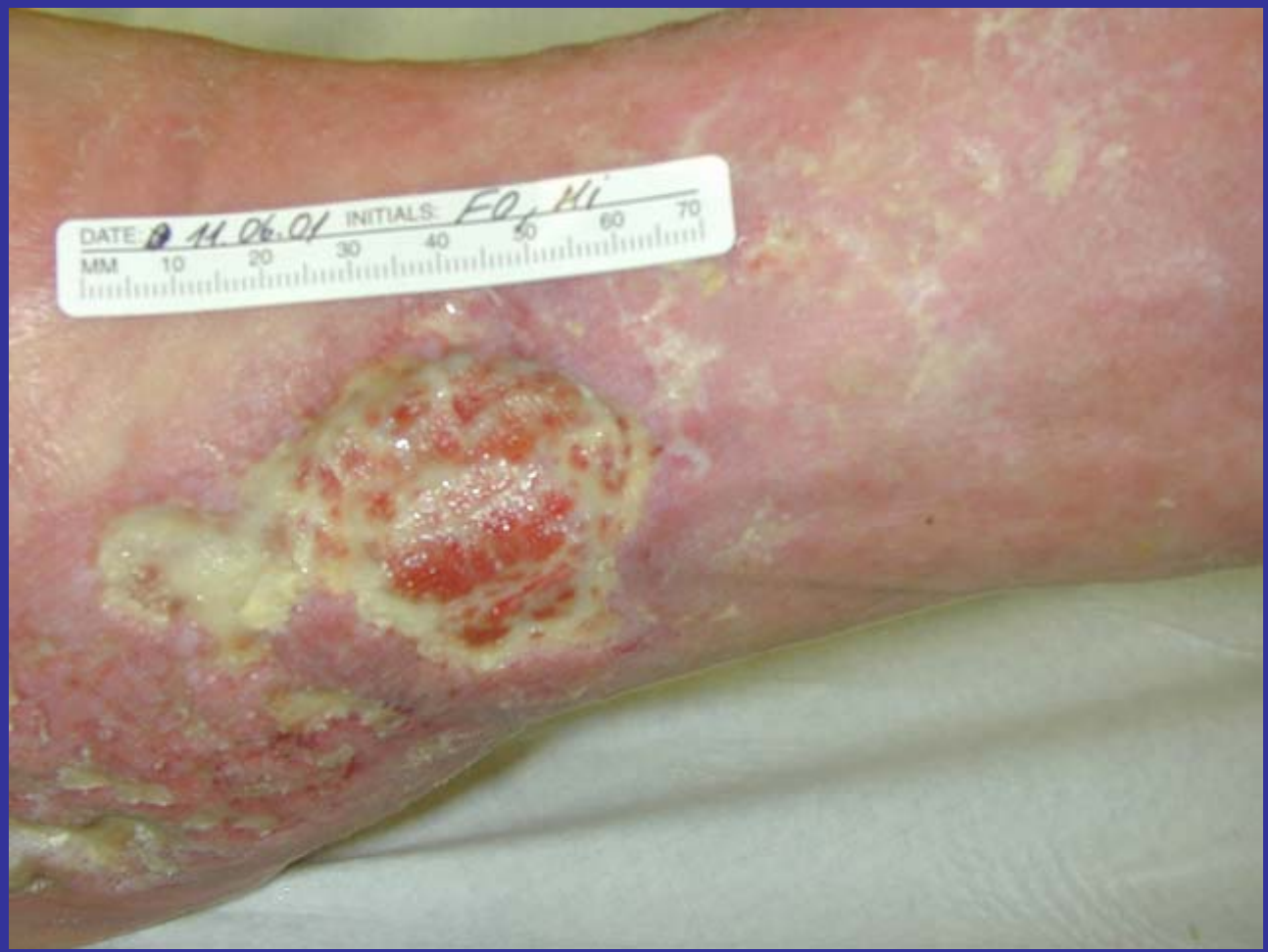
- Temperature

- Enzymes are temperature-dependent to work
- (not out of the refrigerator on a cool wound)

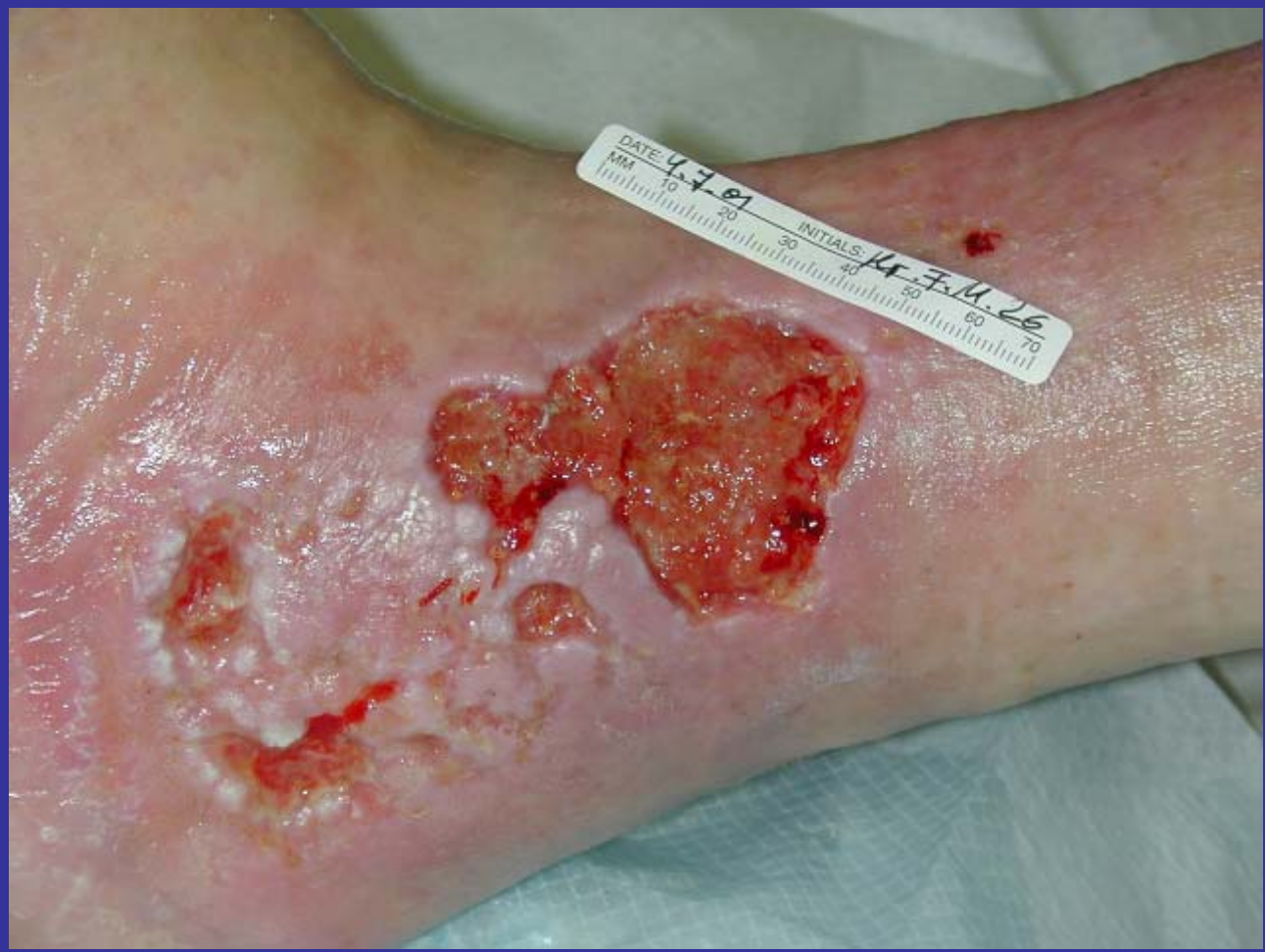
Enzymatic debridement

- Is the substrate of the enzyme in the wound ?

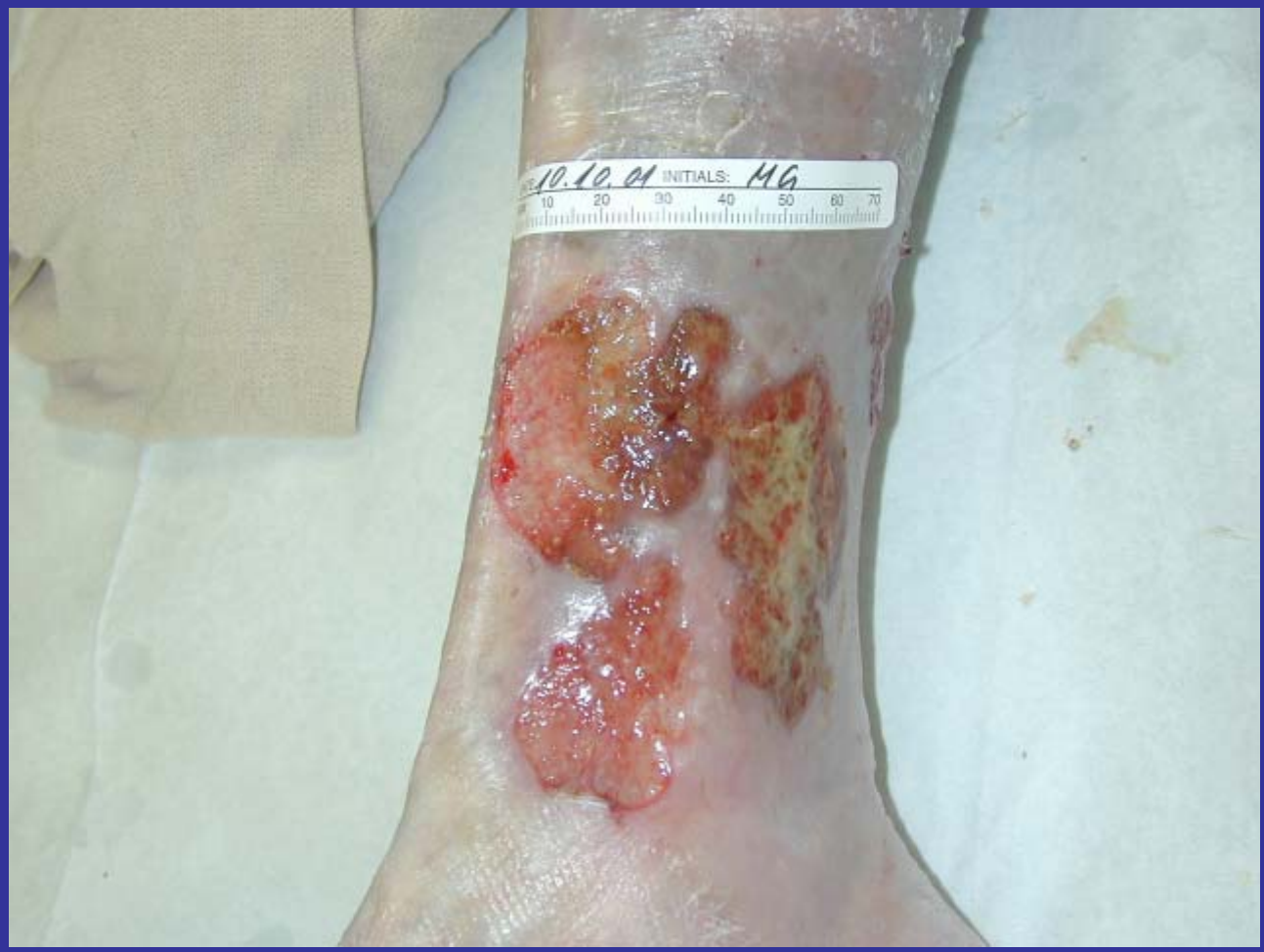
Arterial leg ulcer with denaturated collagen



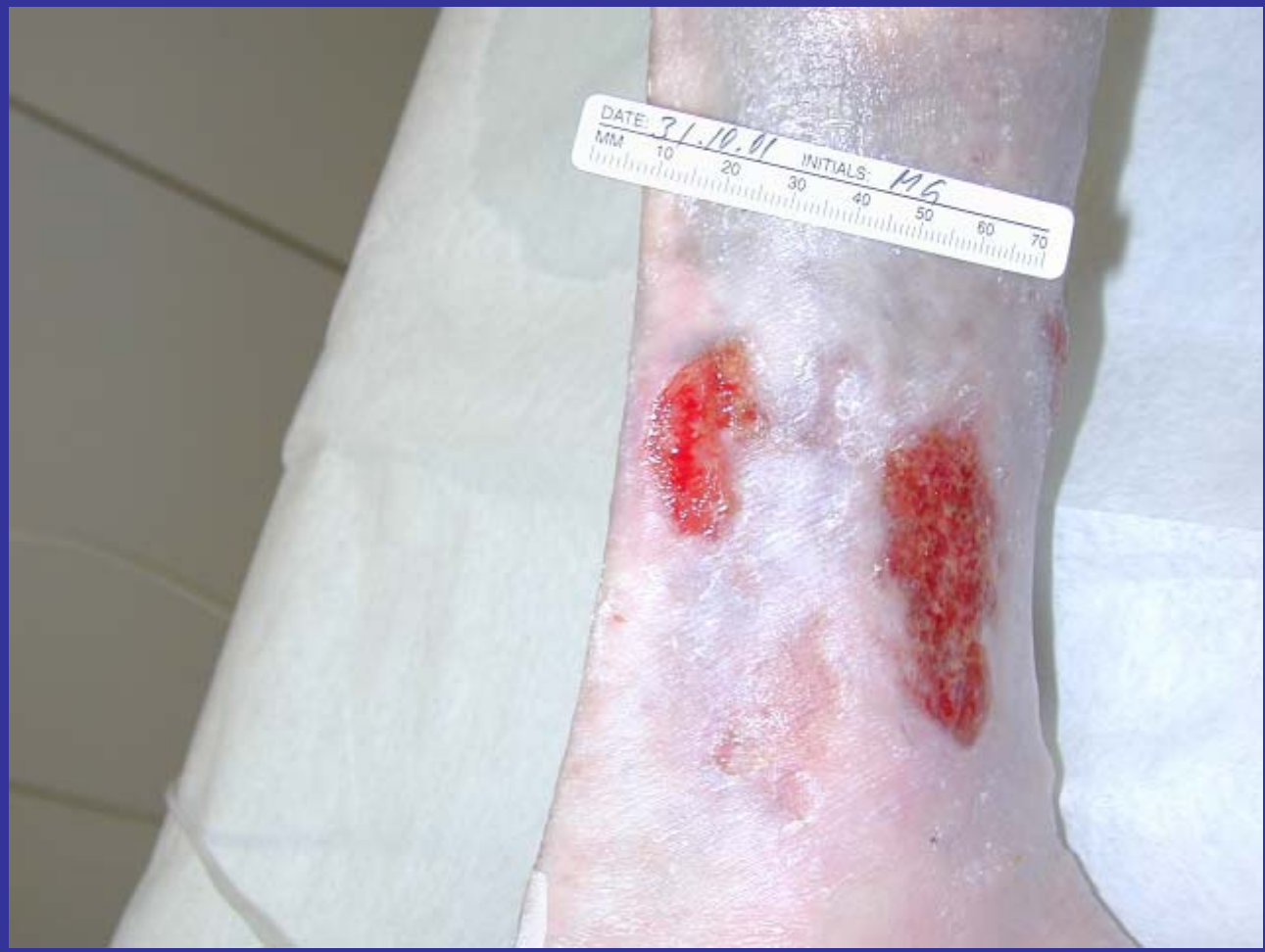
4 weeks after therapy with Iruxol mono + Allevyn



Before therapy



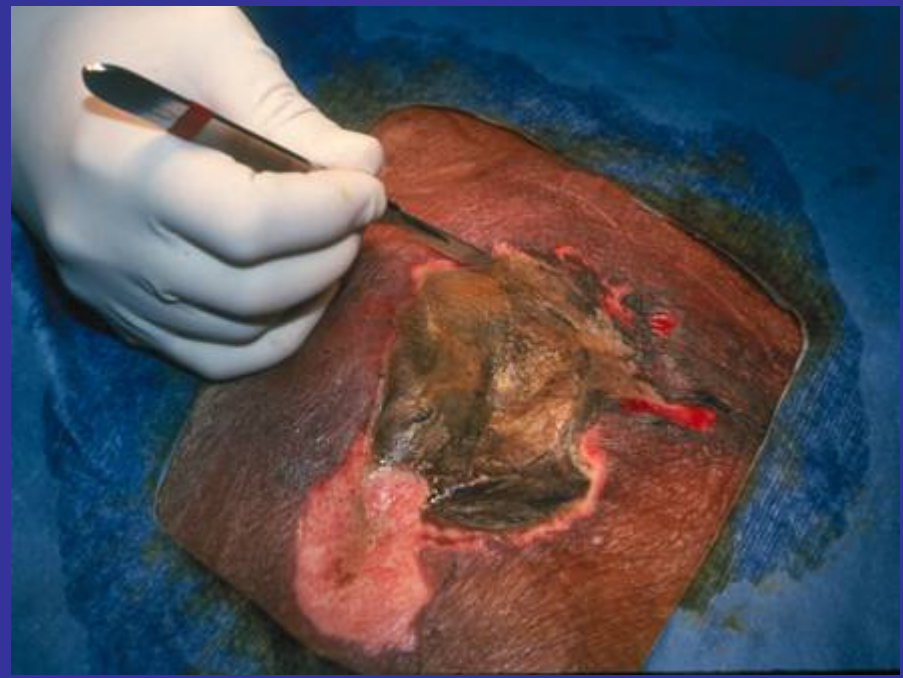
3 weeks after therapy with Collagenase+ Allevyn

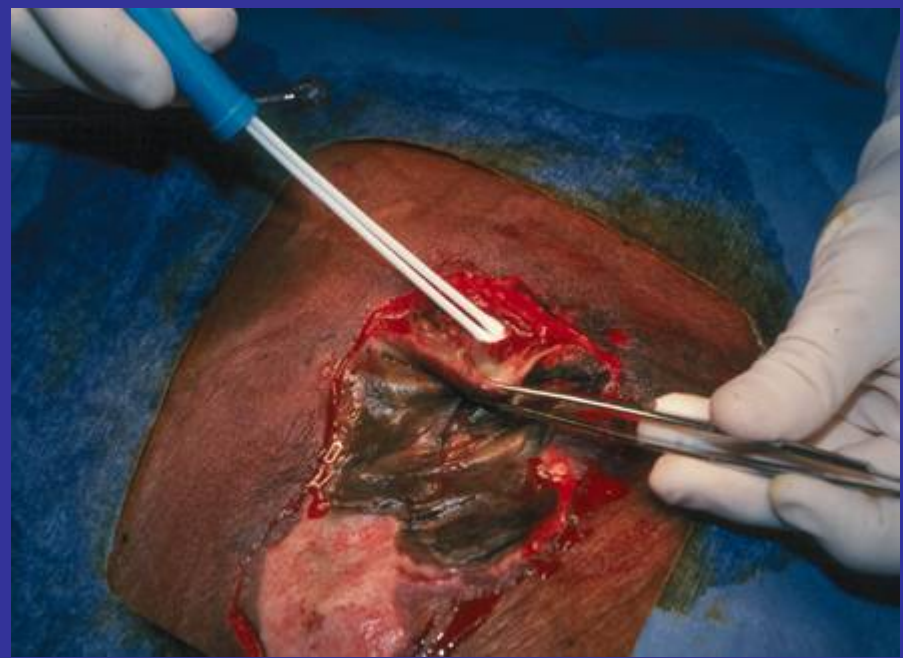


Mechanical debridement

- Used to physically remove debris from a wound
  - Wet-to-dry dressings
  - Wound irrigation
  - Whirlpool techniques
- Can be uncomfortable and damage newly formed tissue
- Also used to remove bacteria through water pressure

Versajet





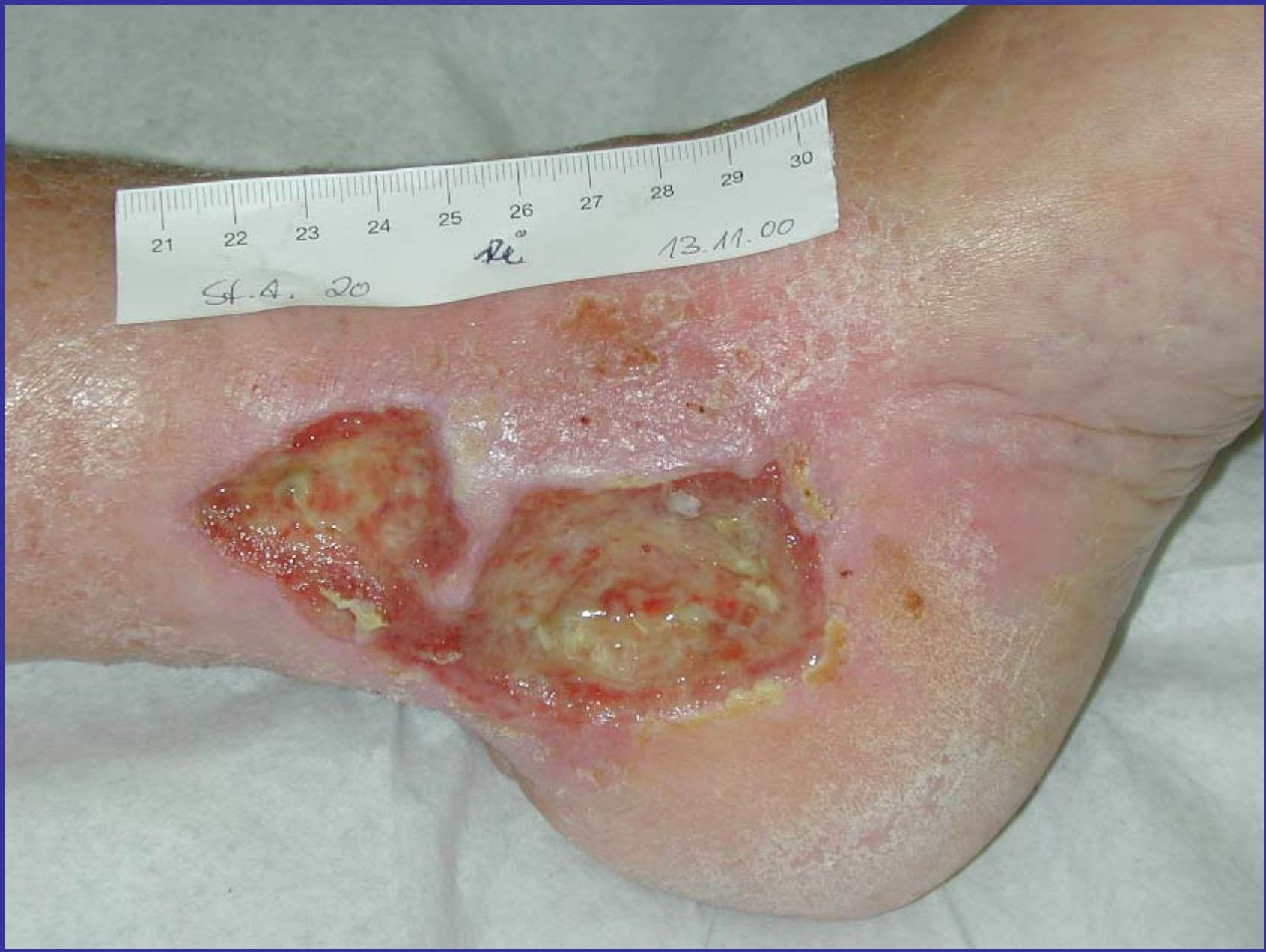
Courtesy of G. Schultz

Biological therapy

- Larval therapy is re-emerging
- Sterile larvae of the Lucilia sericata fly is used
- Produce powerful enzymes which break down dead tissue without harming healthy granulation tissue
- Also appear to combat clinical infection
- Moisture content needs to be at correct level

Larval therapy

- Not suitable for black necrosis
- Care for enough moisture within the wound
- Put saline on the dressing
- Mind Pseudomonas-Infection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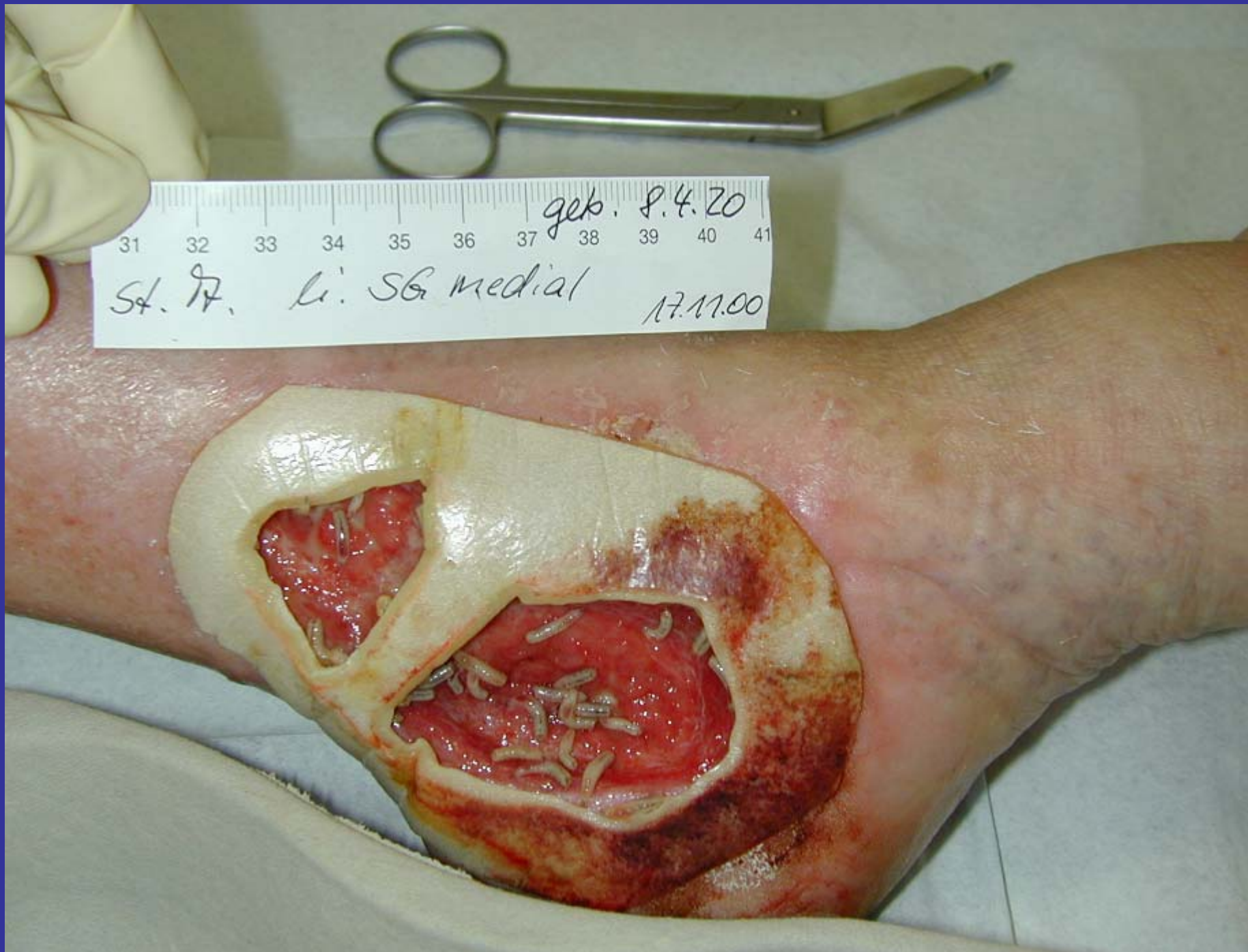
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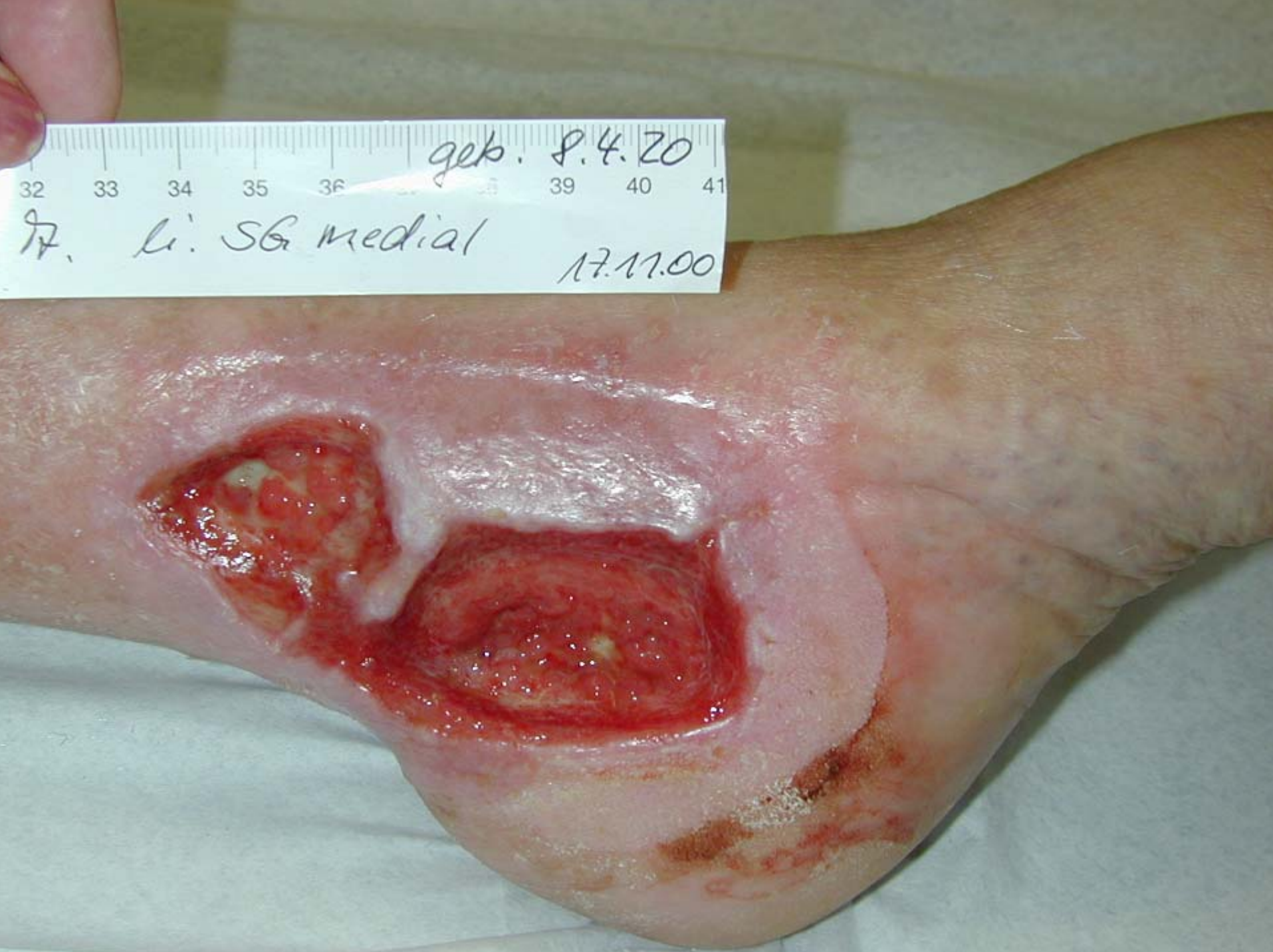
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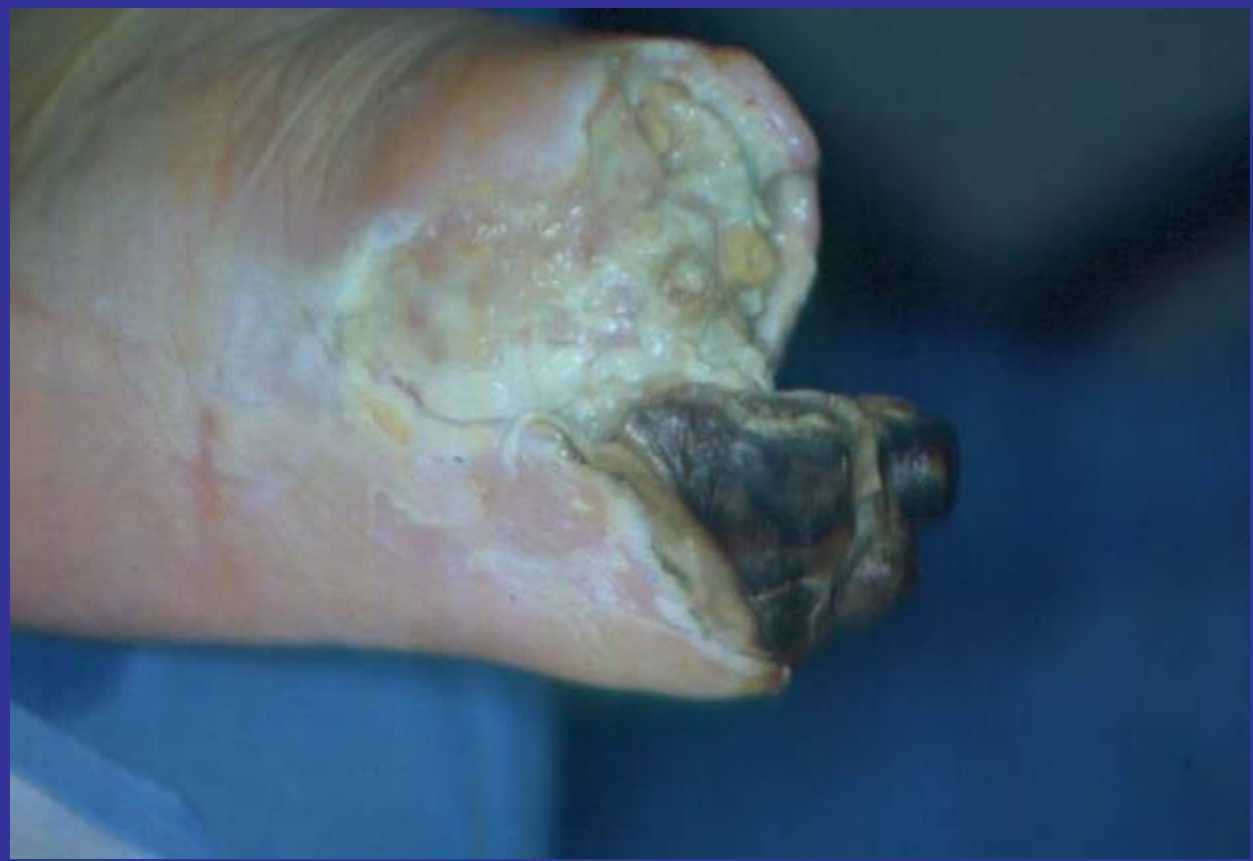
Larval Therapy

- Painful in venous leg ulcers
- Inefficient for black necrosis
- Optimal indication neuropathic foot ulcer
- (no pain, difficult clinical separation between healthy and necrotic tissue)

Diabetic foot ulcer



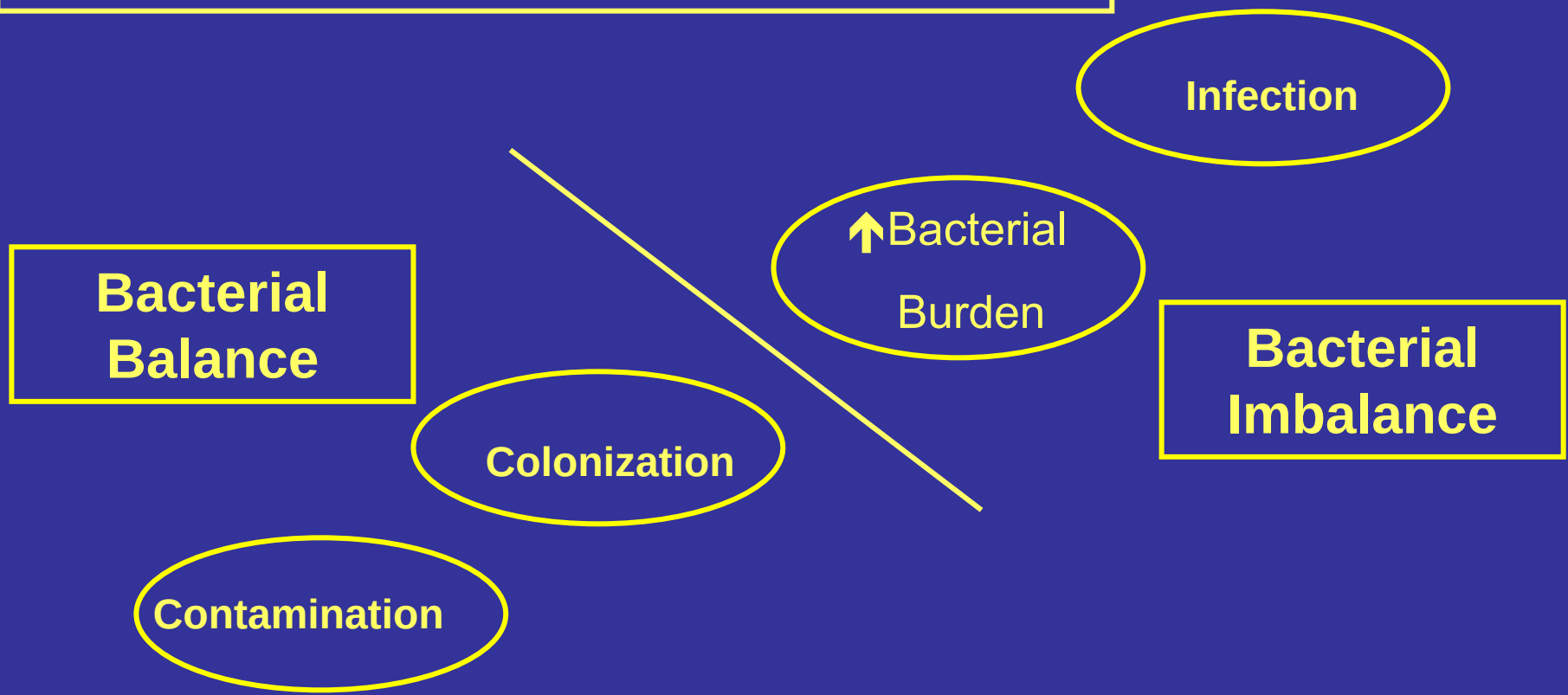
Clinical Observations	Proposed Pathophysiology	WBP Clinical Actions	Effect of WBP Actions	Clinical Outcome
Tissue **Non-viable or deficient**	Defective matrix and cell debris impair healing	Debridement (episodic or continuous) ▪Autolytic, sharp surgical, enzymatic, mechanical ▪Biological agents	Restoration of wound base and functional extra-cellular matrix proteins	Viable wound base

Infection/Inflammation

- Every chronic wound is contaminated
- A lot of them are colonized
- Less are infected

Host Bacterial Relationship

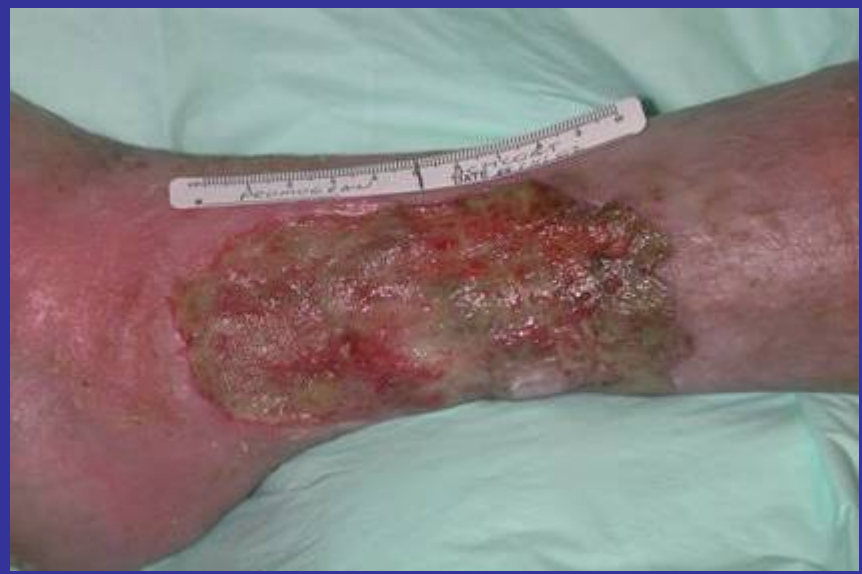
Infection = Organism number x virulence / Host resistance



Sibbald et al OWM OCT 2001
Sibbald RSM supp 2001

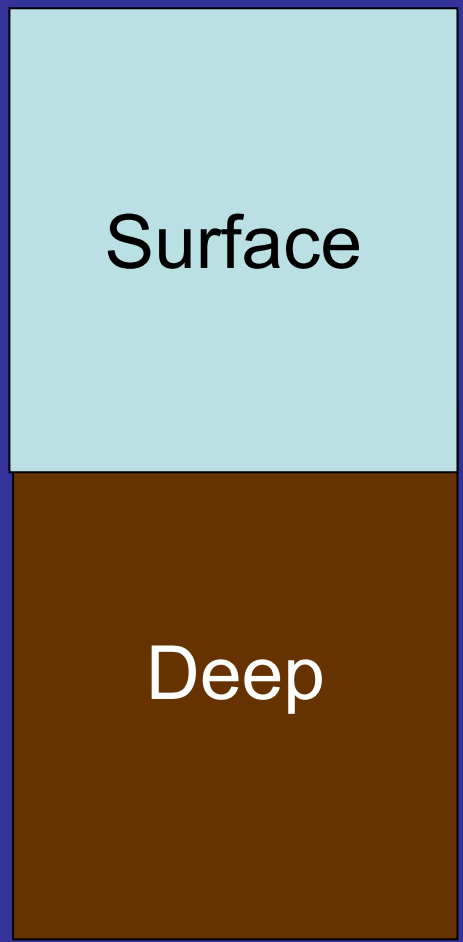
Inflammation

- Often a symptom of infection
- Part of the acute wound healing process
- Some chronic wounds are stuck in the inflammatory phase, ie venous and foot ulcers



Leg ulcer stuck in the inflammatory phase. Note yellow slough on the surface

Bacterial Wound Interaction



Infection

- Classical signs of infections like
- Rubor
- Calor
- Dolor
- Functio lesa
- Do not apply to chronic wounds

INFECTION

- Pain
- Increased wound size
- New areas of breakdown
- Odour

Gardner/Frantz/Doebbeling WWR 2001

- Friable bright red granulation
- Exuberant granulation.
- Increased discharge
- Devitalized tissue(slough)

Cutting and Harding J Wound care 94

Treatment options

- Systemic antibiotics (beware bacterial resistance)
- Enhance host defense mechanisms
- Debridement
- Wound cleaning
- Topical antimicrobials

Topical Antimicrobials

- Unproved belief not knowledge

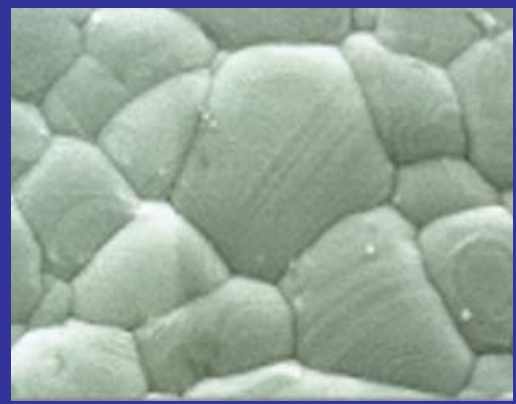
- Topical Antimicrobials inhibit healing of chronic wounds
- Literature ??

Topical Antimicrobials - Silver

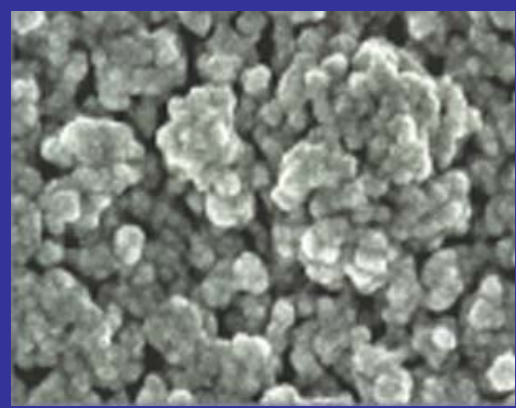
- Centuries of proven antimicrobial activity
- Cytotoxicity concerns associated with carriers, not silver - eg. Silver nitrate, Silver sulfadiazine
- Traditional delivery required repeated applications due to binding with chlorine and proteins
- New silver dressings allow for continued silver release - up to 7 days

Nanocrystalline Silver

- Decreased size of silver particles leads to increased proportion of surface atoms compared with internal atoms
- It is believed that the nanocrystalline structure is responsible for the rapid and long lasting action



Magnification of normal silver



Magnification of Nanocrystalline Silver (<1 micron)

Demling and DeSanti (2001)

Clinical Observations	Proposed Pathophysiology	WBP Clinical Actions	Effect of WBP Actions	Clinical Outcome
Tissue **Non-viable or deficient**	Defective matrix and cell debris impair healing	Debridement (episodic or continuous) ▪Autolytic, sharp surgical, enzymatic, mechanical ▪Biological agents	Restoration of wound base and functional extra-cellular matrix proteins	Viable wound base
Infection or inflammation	High bacterial counts or prolonged inflammation ↑ inflammatory cytokines ↑ protease activity ↓ growth factor activity	▪Remove infected foci Topical/systemic ▪antimicrobials ▪anti-inflammatories ▪protease inhibition	Low bacterial counts or controlled inflammation: ↓ inflammatory cytokines ↓ protease activity ↑ growth factor activity	Bacterial balance and reduced inflammation

Moisture imbalance

Moisture imbalance

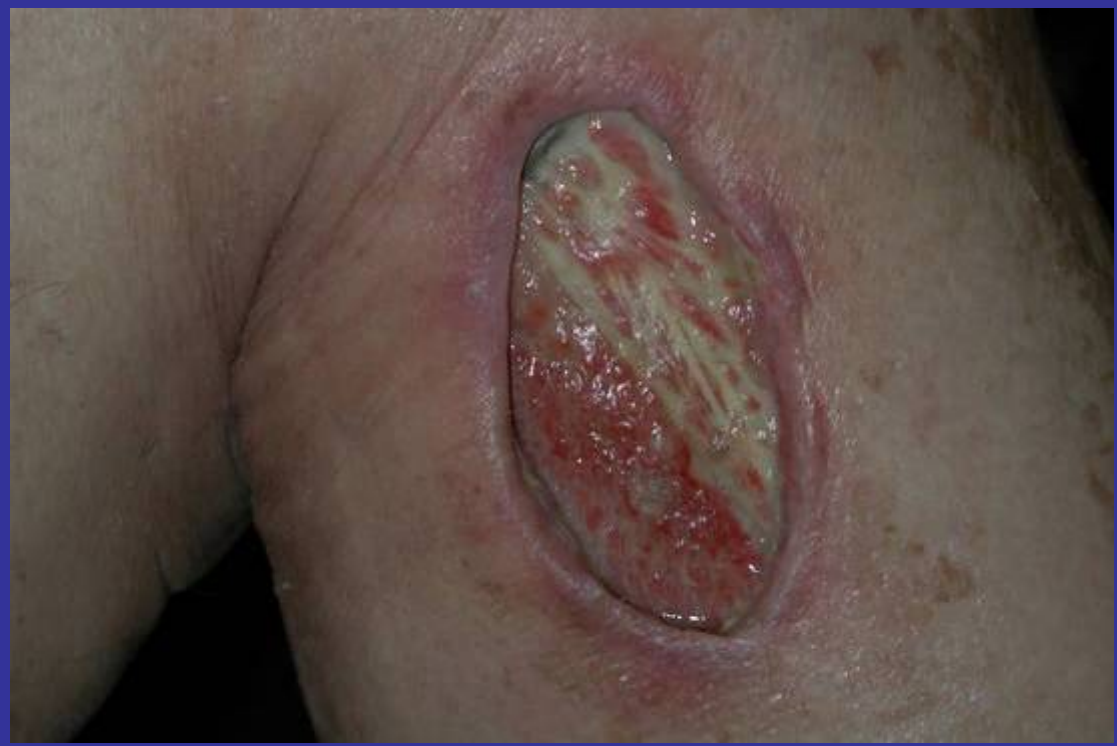


Fig A. Knee wound post drainage of an abcess

Chronic wound fluid is aggressive

- Contains elevated levels of pro-inflammatory cytokines
- Contains high levels of tissue necrosis factor alpha (TNF-α).
- Contains high levels of matrix metalloproteinases (MMPs) which degrade epidermal growth factor leading to tissue break down
- Contains macromolecules which bind albumin

Moisture Balance

- Rebalance moisture to the levels seen in acute wounds
- Not too dry – desiccation slows epithelial cell migration
- Not too wet – excessive fluid causes maceration of the wound margin

Alternative dressings to manage exudate

- Foam
  - Provide thermal insulation, high absorbency, a moist environment, gas permeable, easy to cut to shape
- Hydrofiber
  - Highly absorbent; contain fluid within the fibre and good tensile strength

Alternative dressings to manage exudate (Contd)

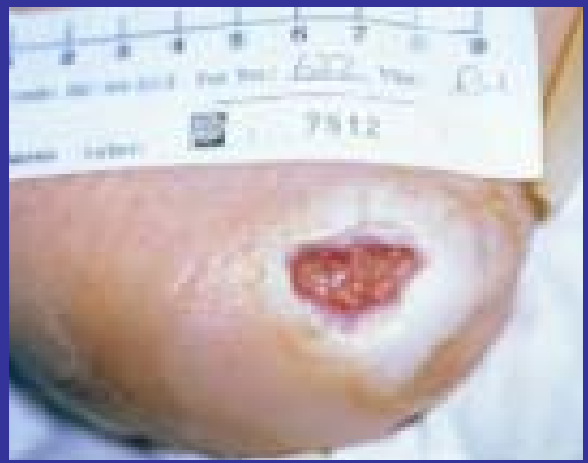
- Crystalline sodium chloride gauze
  - Used for highly exudative wounds, mechanical debridement; has antibacterial properties
- Calcium alginates
  - Form a gel upon contact, promoting moist interactive healing, ideal for exudative and infected wounds

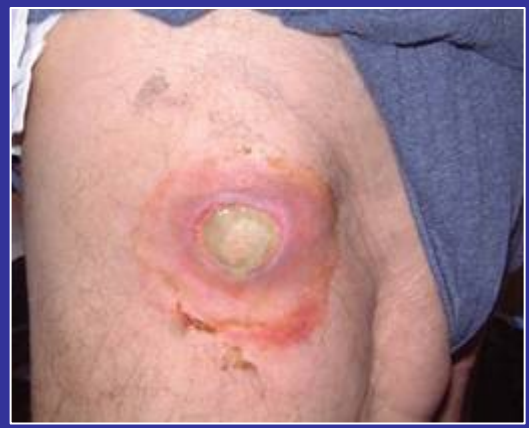
Alternative dressings to manage exudate (Contd)

- Hydrocolloids
  - Form a linked matrix gel on contact with the wound exudate; suited to autolytic debridement for mild to moderately exudating wounds
- Hydrogel
  - Best choice for dry, sloughy wounds with low level of exudate
- Films
  - Ideal at the later stages of wound healing when there is no longer significant exudate

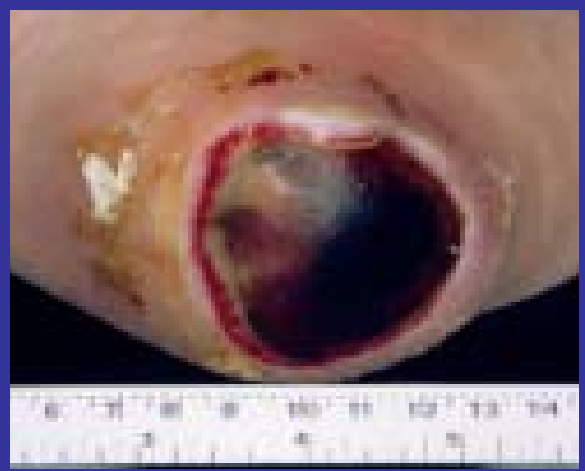
"M" Moisture imbalance

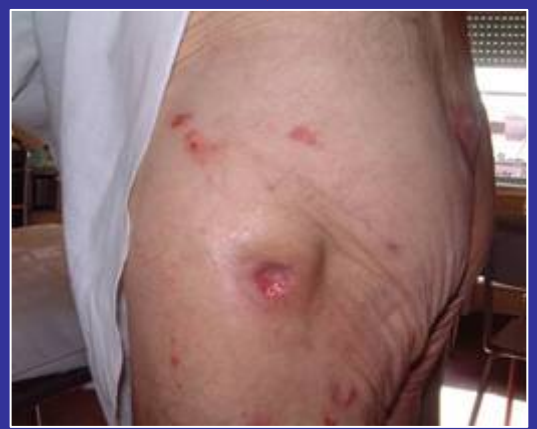
Too wet



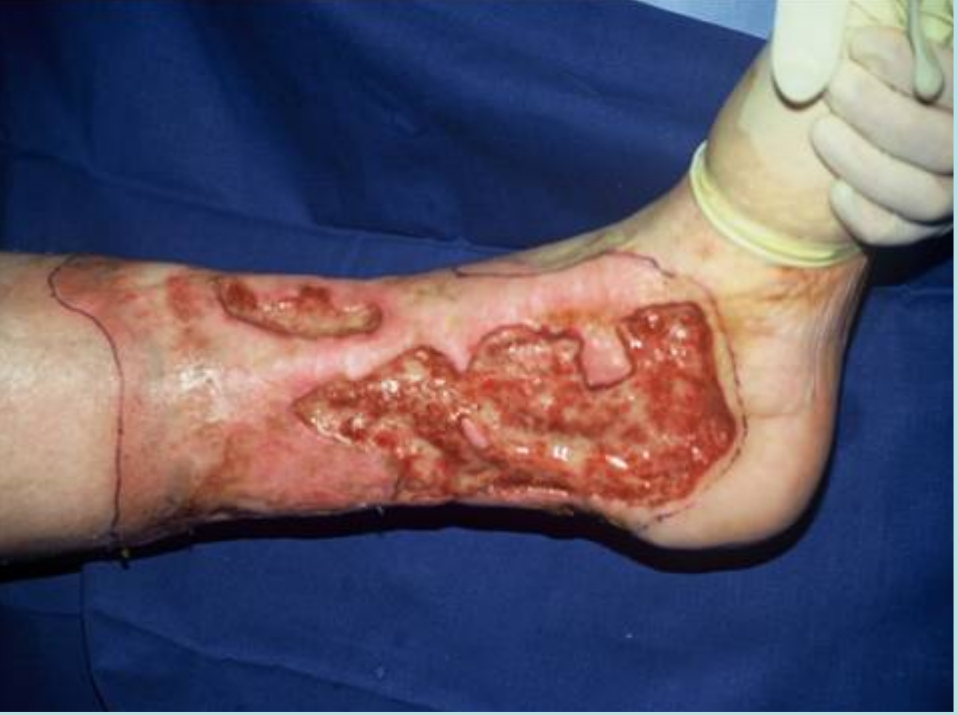
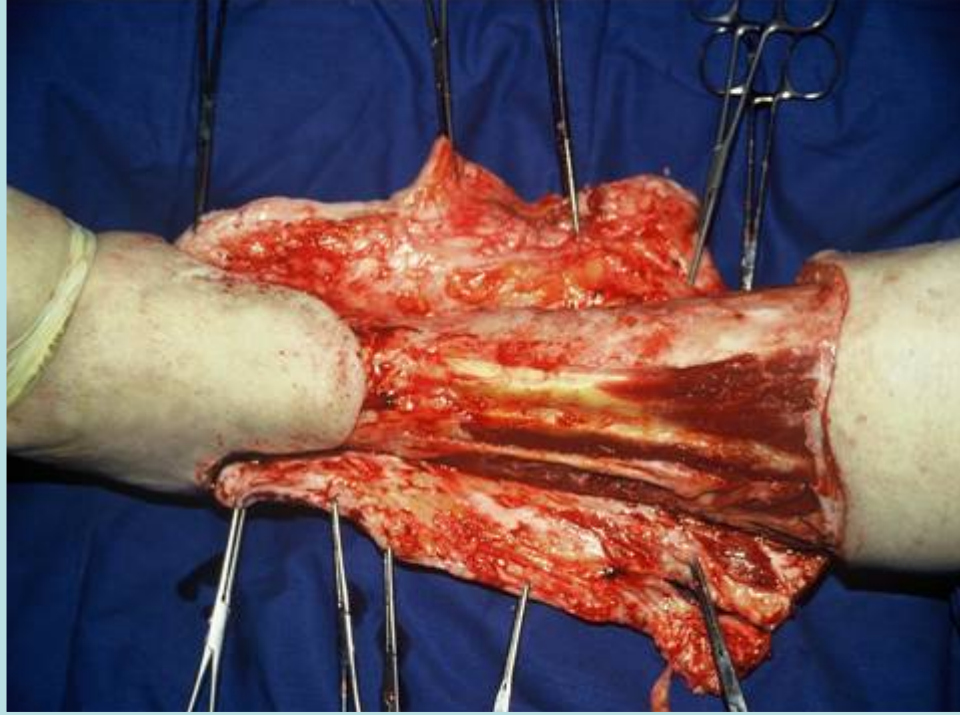
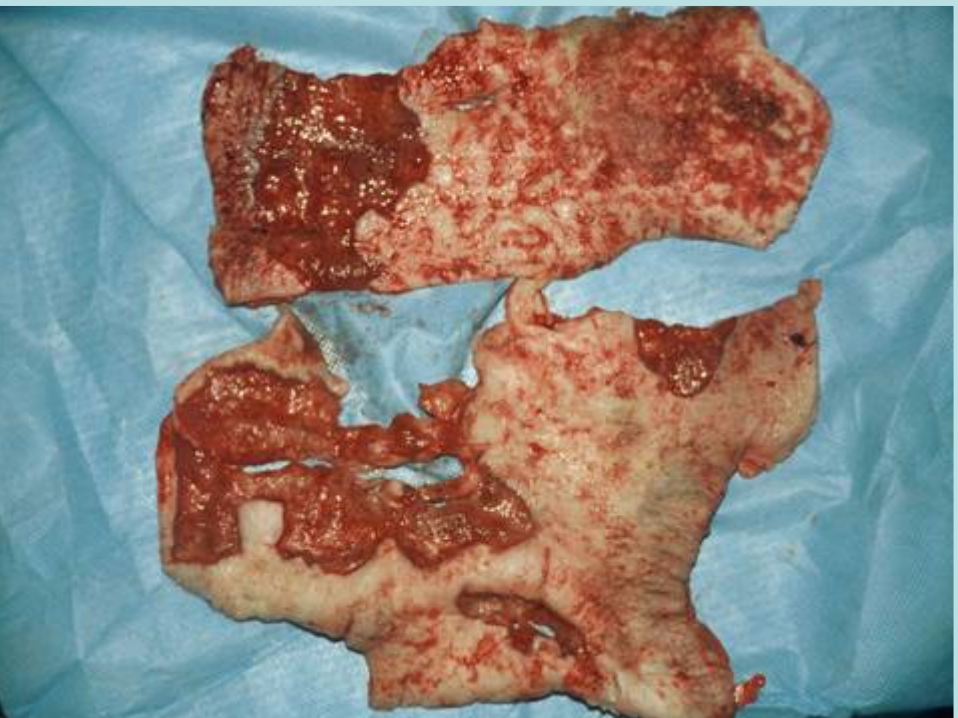
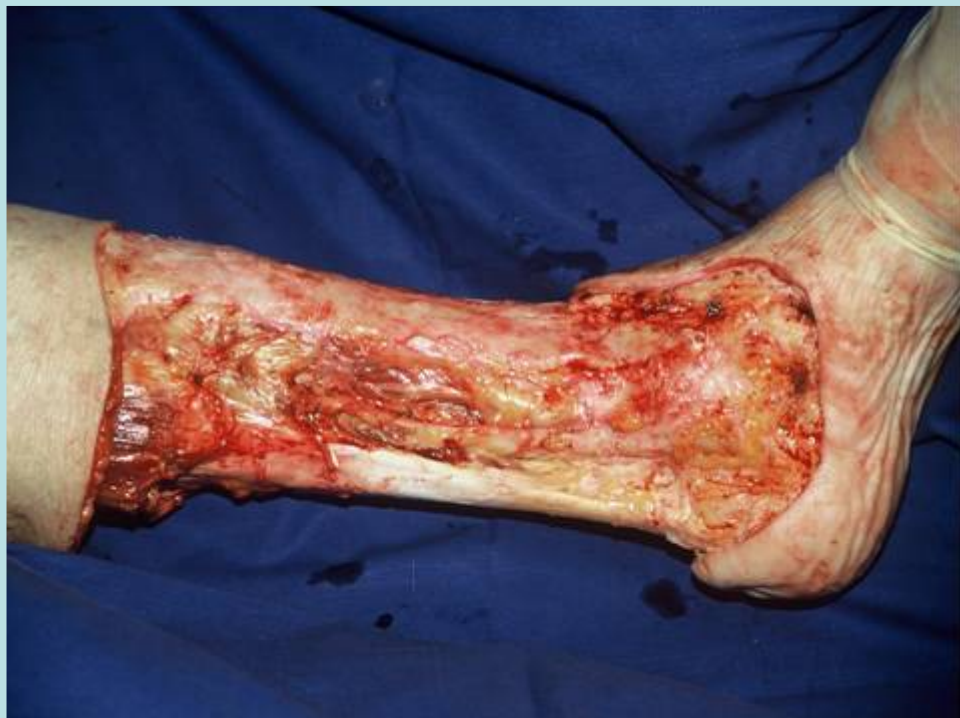


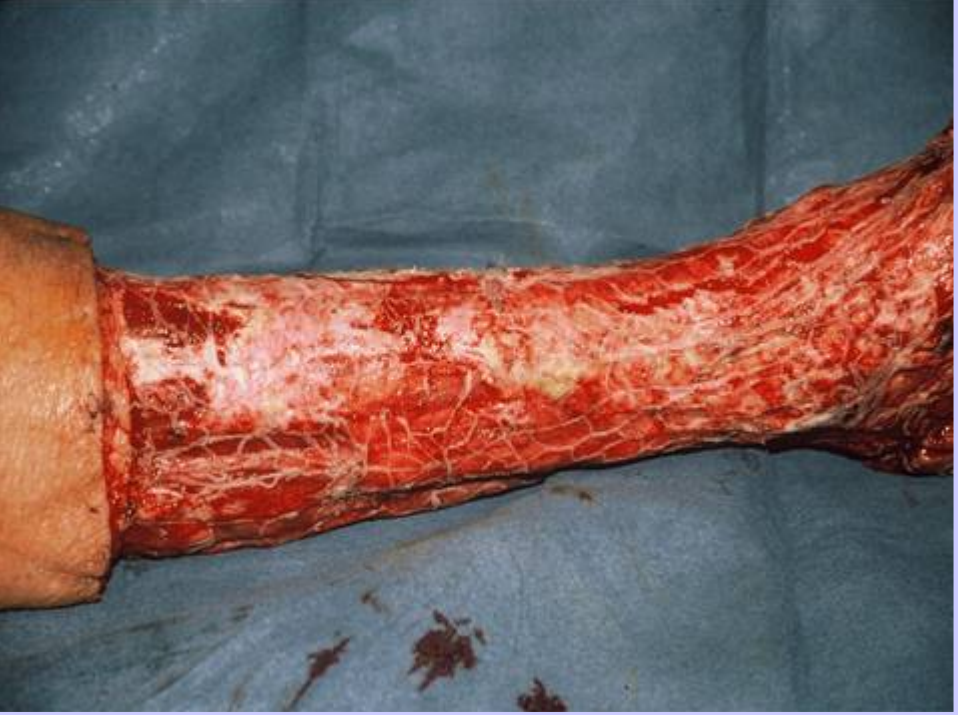
Too dry

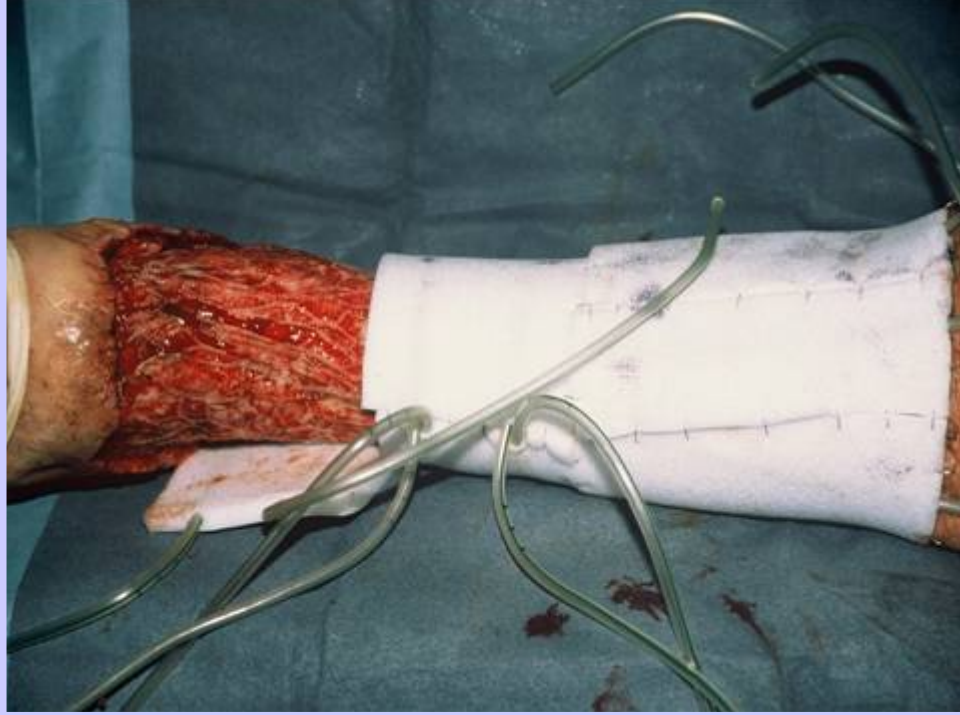


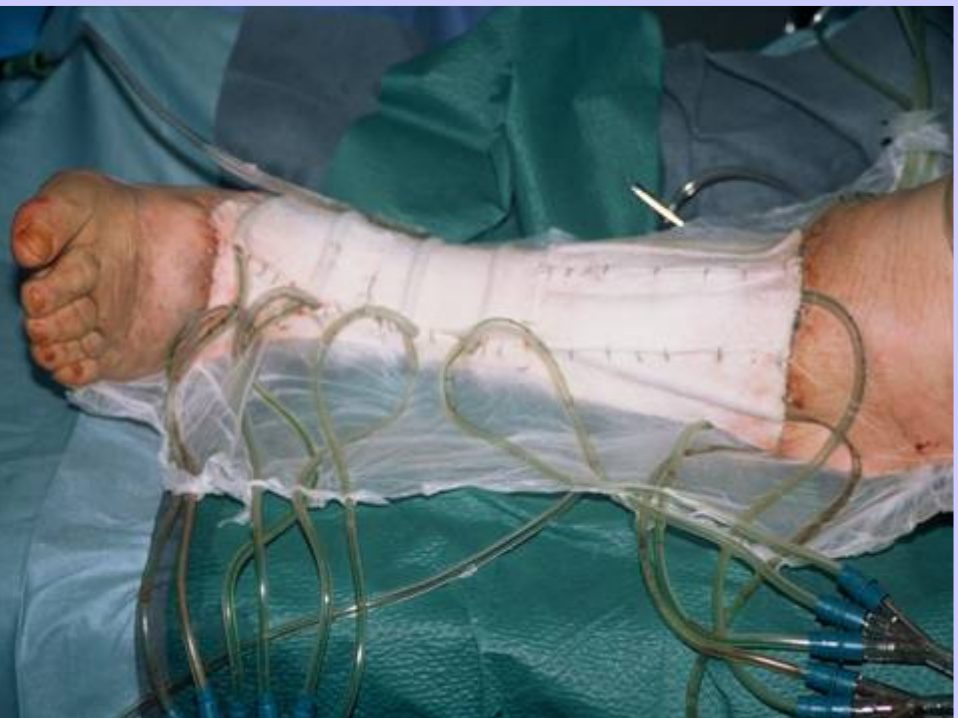


R. Romanelli

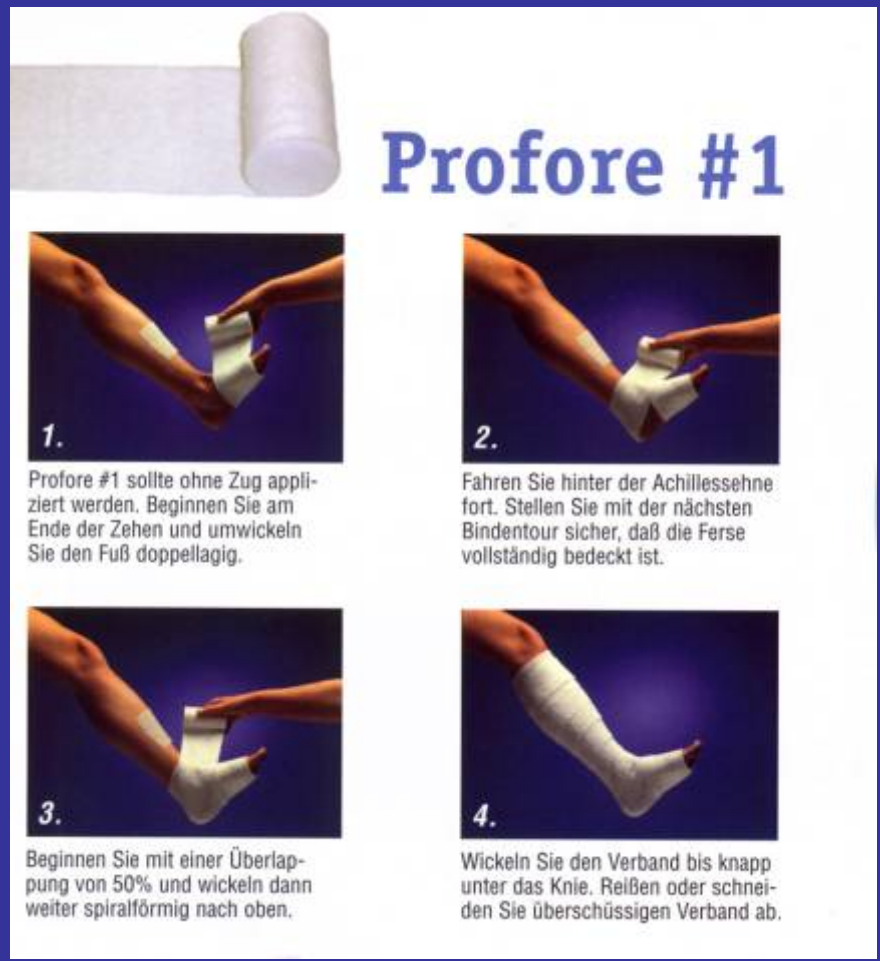


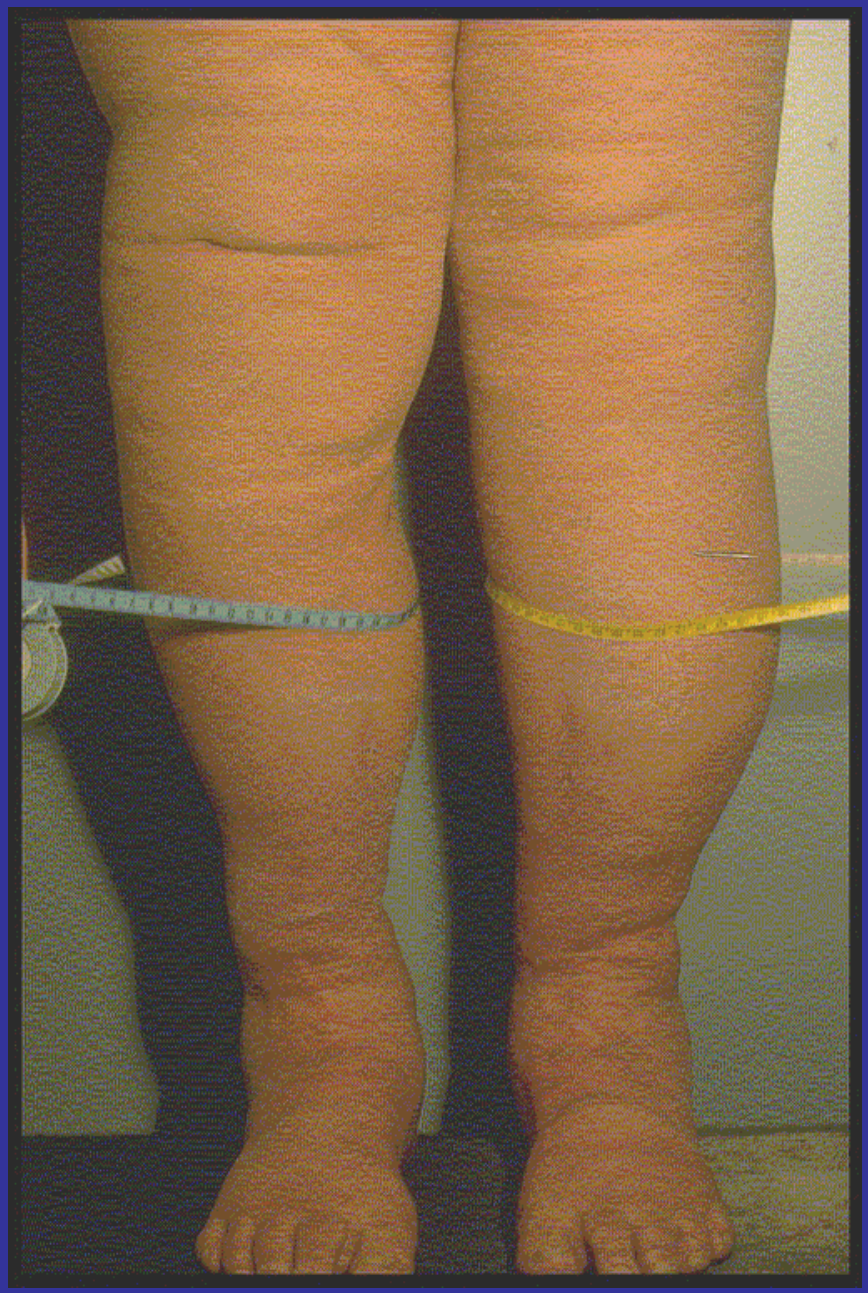




Vakuumpumpe

Four-layer-bandage (Profore R)





Before and after 6 weeks of compression

H. Partsch, Vienna

Clinical Observations	Proposed Pathophysiology	WBP Clinical Actions	Effect of WBP Actions	Clinical Outcome
Tissue **Non-viable or deficient**	Defective matrix and cell debris impair healing	Debridement (episodic or continuous) ▪Autolytic, sharp surgical, enzymatic, mechanical ▪Biological agents	Restoration of wound base and functional extra-cellular matrix proteins	Viable wound base
Infection or inflammation	High bacterial counts or prolonged inflammation ↑ inflammatory cytokines ↑ protease activity ↓ growth factor activity	▪Remove infected foci Topical/systemic ▪antimicrobials ▪anti-inflammatories ▪protease inhibition	Low bacterial counts or controlled inflammation: ↓ inflammatory cytokines ↓ protease activity ↑ growth factor activity	Bacterial balance and reduced inflammation
Moisture imbalance	Desiccation slows epithelial cell migration Excessive fluid causes maceration of wound margin	Apply moisture balancing dressings Compression, negative pressure or other methods of removing fluid	Restored epithelial cell migration, desiccation avoided Oedema, excessive fluid controlled, maceration avoided	Moisture balance

Edge
–
non advancing or undermined

Why does the edge fail to migrate?

- Failure of the epidermal margin to migrate across the wound is the most obvious sign that a wound is failing to heal
- If the margin is undermined this may be a sign of critical colonisation or infection
- At a cellular level the lack of epidermal migration is due to non responsive wound cells and abnormalities in protease activity which degrade ECM while it is formed

What if the edge fails to advance?

- Reconsider the principles of wound bed preparation and the acronym TIME:
  - Has necrotic tissue been debrided?
  - Is there a well vascularised wound bed?
  - Has infection been put under control?
  - What is the status with inflammation?
  - To what level has moisture imbalance been corrected?
  - What dressings have been applied?

The next option

Prepare the wound bed for advanced wound healing techniques

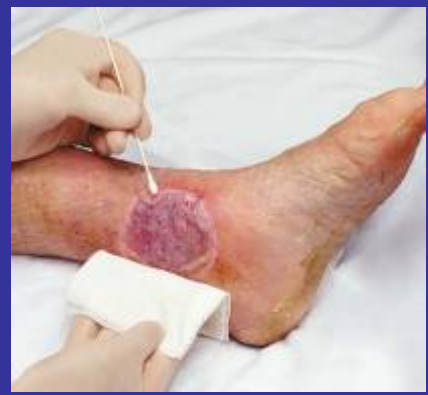
Advanced wound healing techniques

- Remember that optimal preparation of the wound bed requires complete debridement of devitalized tissue, bacterial balance and moisture balance
- Skin grafts fail if there are ≥1.0 * 106 organisms in the wound bed

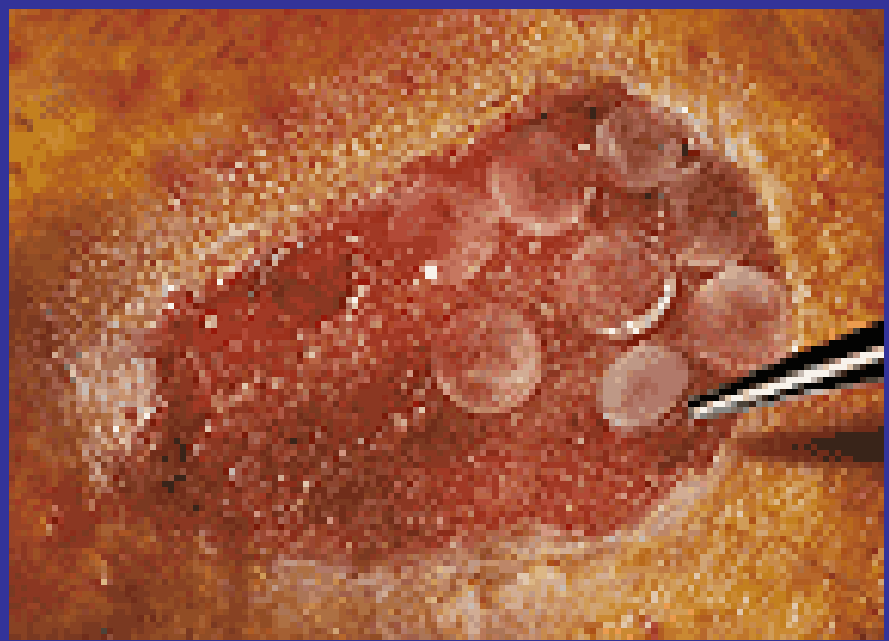
Advanced wound healing – tissue engineering

- Autologous skin grafts
- Grafting using cultured cells/keratinocytes
- Bioengineered products
- Allogenic, bilayered tissue
- Artificial skin

Apligraf ®



Epidex ®



Autologous Keratinozytes in Fibrin-Sealant (BioSeed ^{S})

Clinical Observations	Proposed Pathophysiology	WBP Clinical Actions	Effect of WBP Actions	Clinical Outcome
Tissue **Non-viable or deficient**	Defective matrix and cell debris impair healing	Debridement (episodic or continuous) ▪Autolytic, sharp surgical, enzymatic, mechanical ▪Biological agents	Restoration of wound base and functional extra-cellular matrix proteins	Viable wound base
Infection or inflammation	<u>High bacterial counts or prolonged inflammation</u> ↑ inflammatory cytokines ↑ protease activity ↓ growth factor activity	▪Remove infected foci <u>Topical/systemic</u> ▪antimicrobials ▪anti-inflammatories ▪protease inhibition	<u>Low bacterial counts or controlled inflammation:</u> ↓ inflammatory cytokines ↓ protease activity ↑ growth factor activity	Bacterial balance and reduced inflammation
Moisture imbalance	Desiccation slows epithelial cell migration Excessive fluid causes maceration of wound margin	Apply moisture balancing dressings Compression, negative pressure or other methods of removing fluid	Restored epithelial cell migration, desiccation avoided Oedema, excessive fluid controlled, maceration avoided	Moisture balance
Egde – non advancing or undermined	Non migrating keratinocytes Non responsive wound cells and abnormalities in protease activity	Re-assess cause or consider corrective therapies ▪Debridement ▪skin grafts ▪Biological agents ▪Adjunctive therapies	Migrating keratinocytes and responsive wound cells. Restoration of appropriate protease profile	Advancing epidermal margin

It is TIME

- For a consequent and systematic transformation of
- Scientific knowledge into
- Daily practice of wound care

It is TIME

- For GCP-guided clinical trials
- With the TIME-concept which are unfortunately still missing

It is TIME

- To leave the myths

- „ I have made good experience with“
- „Experts have made good experience with“

It is TIME

- To start Clinical Wound Pharmacology
- With the help of the TIME-concept
- To come from belief to knowledge !