Diabetic Limb Salvage
&
HBO Therapy

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ACLES

Livonia, Michigan

May 4, 2017

National Diabetes Statistics

(Source: American Diabetes Assoc.)

- Prevalence of Diabetes: 25.8 million people – approx. 8.3% of population
- Age 65 yrs or older: 10.9 million (11.3% of all people in this age group have diabetes)
- New cases diagnosed per year: 1.9 million aged 20 yrs or older
- Cost of diabetes in the US: Direct medical costs - $116 B / Indirect costs - $58 B (disability, work loss, premature mortality)

Diabetic Wounds

- Wound problems affect 15%-20% of all diabetic patients
- Reason for 60% of all diabetic-related hospital admissions
- Precedes 84% of all Lower Extremity Amputations
- Result in >86,000 lower extremity amputations per year in U.S.
- Ulceration is the most common single precursor to amputation

Survival Rates After Amputation

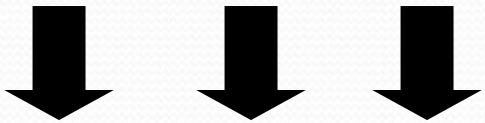
- After 1 major lower-extremity amputation
  - 3-year survival rate is 50%
  - 5-year survival rate is 40%
- Contralateral amputation
  - 42% of patients within 1 to 3 years after amputation
  - 56% of patients within 3 to 5 years after first amputation

Survival Rates After Amputation

- Larsson et. al. (Clinical Orthopedics, 1998) reported a 5-year mortality rate of 68% after lower limb amputation with lower survival rates in those patients with higher levels of amputation.

Risk Factors for Ulceration

- Peripheral sensory neuropathy
- Structural foot deformity
- Trauma and improperly fitted shoes
- History prior ulcers/amputations
- Limited joint mobility*****



PROLONGED, ELEVATED------ PRESSURE

Limited Joint Mobility

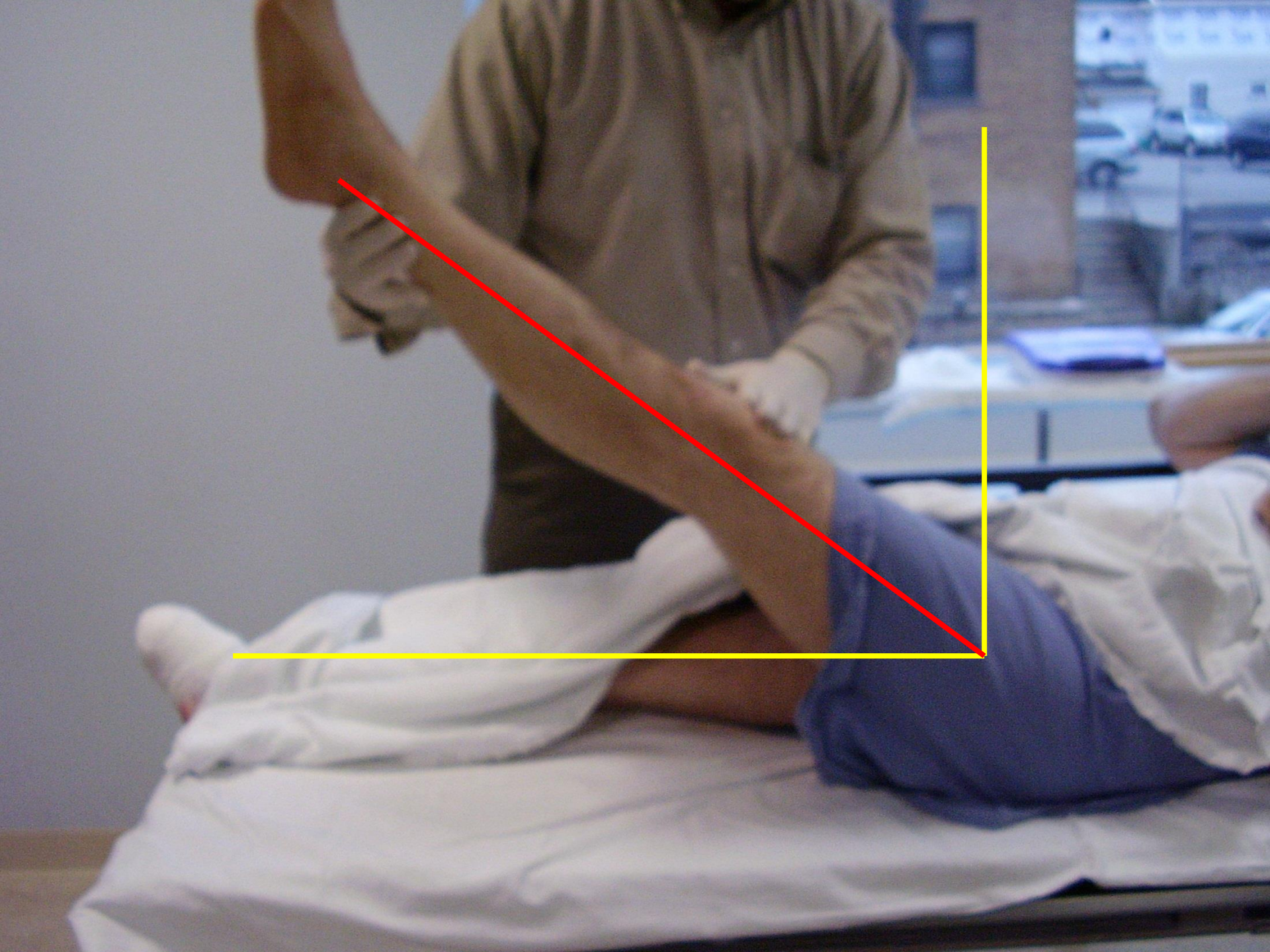
- Glycosylation of collagen-- ⬆ Blood sugar
- Physiological shortening of collagen
- EQUINUS-----Major Factor

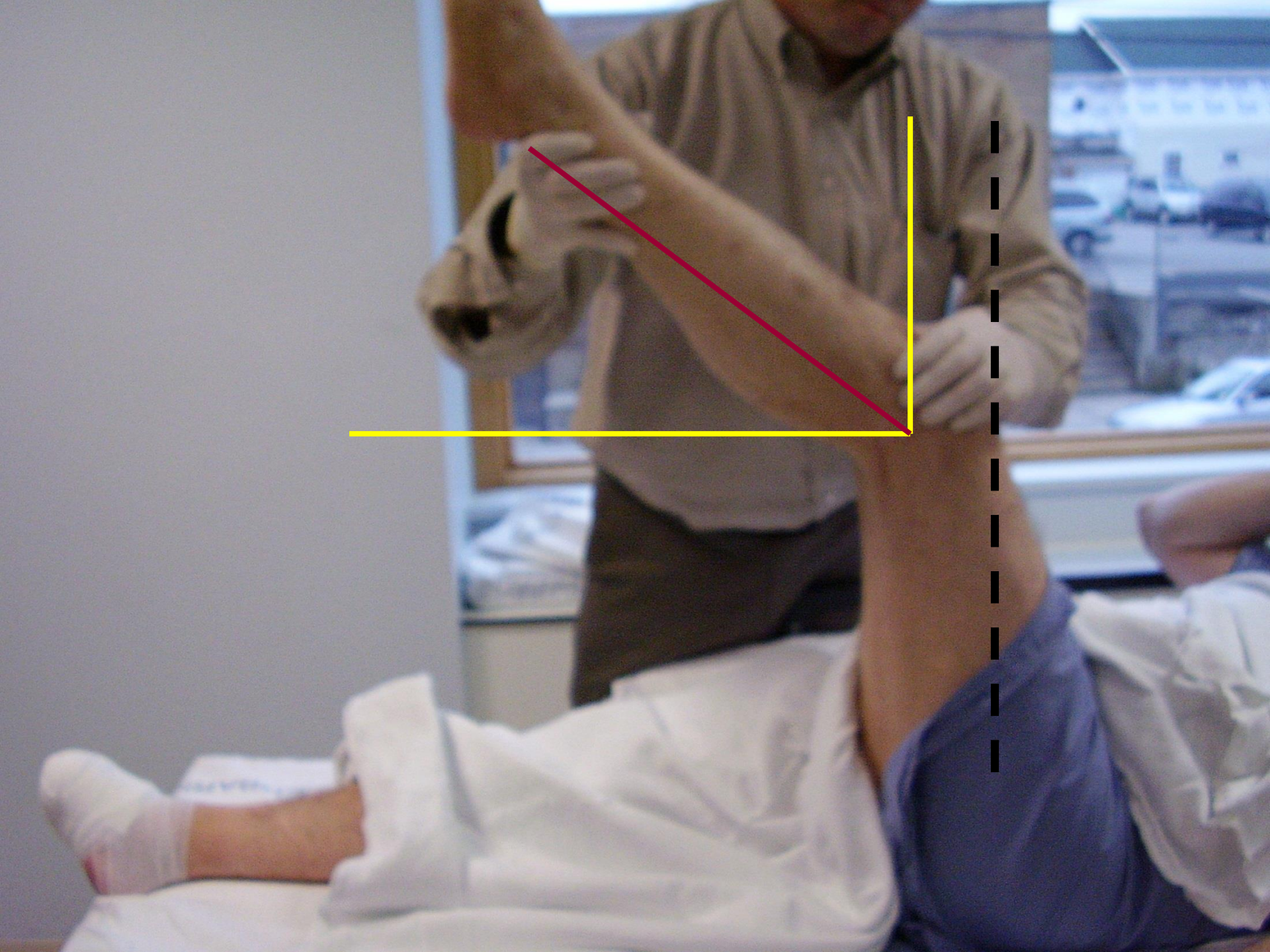
*Equinus---Limited range of normal joint function

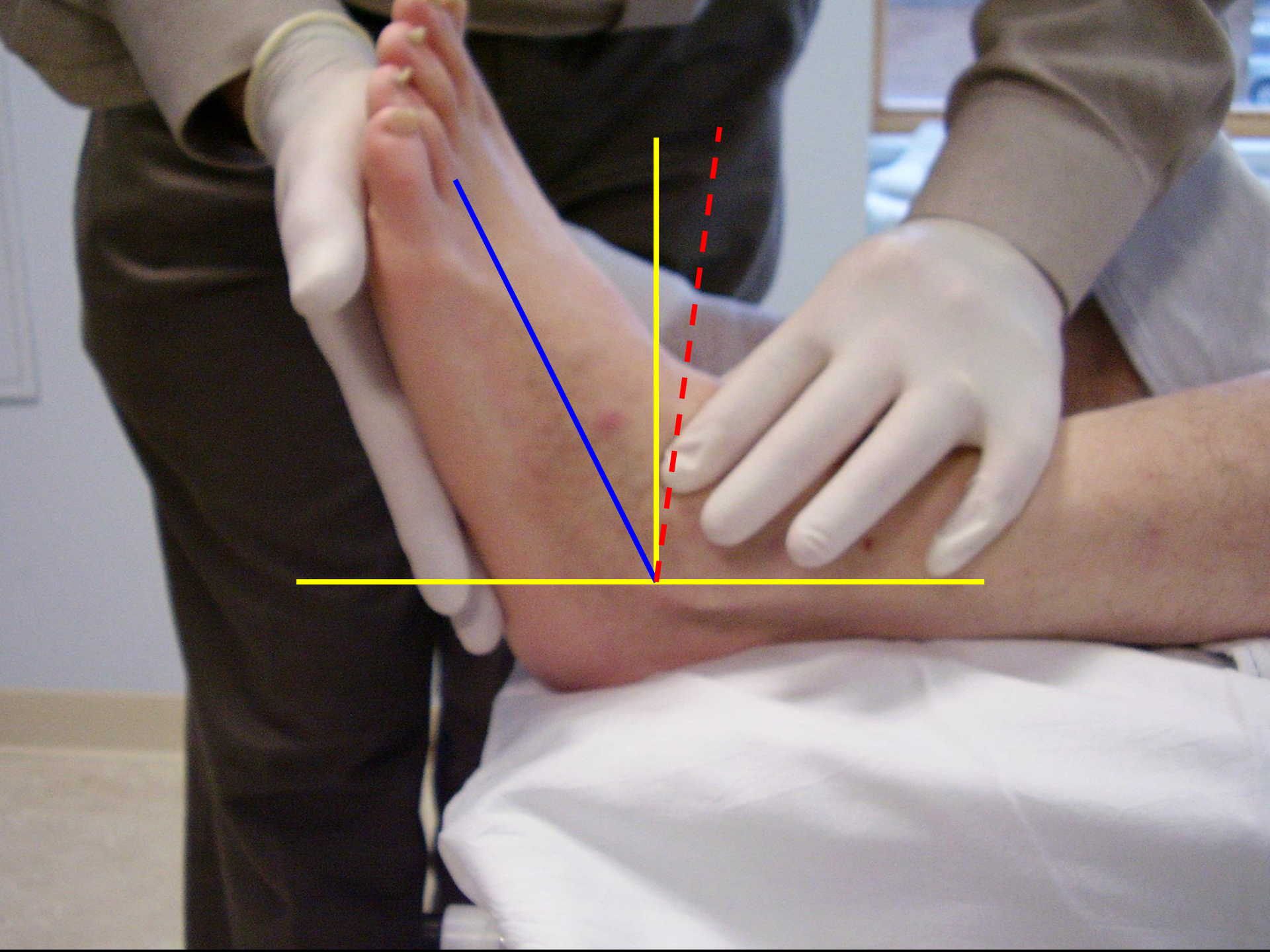
Lavery et. al., JAPMA, vol. 92, No. 9, Oct. 2002

***Patients with EQUINUS deformities had Significantly higher peak plantar pressures Than those patients without the deformity.

(92.7 +/- 23.1 N/cm2 *versus* 85.7 +/- 27.7 N/cm2)







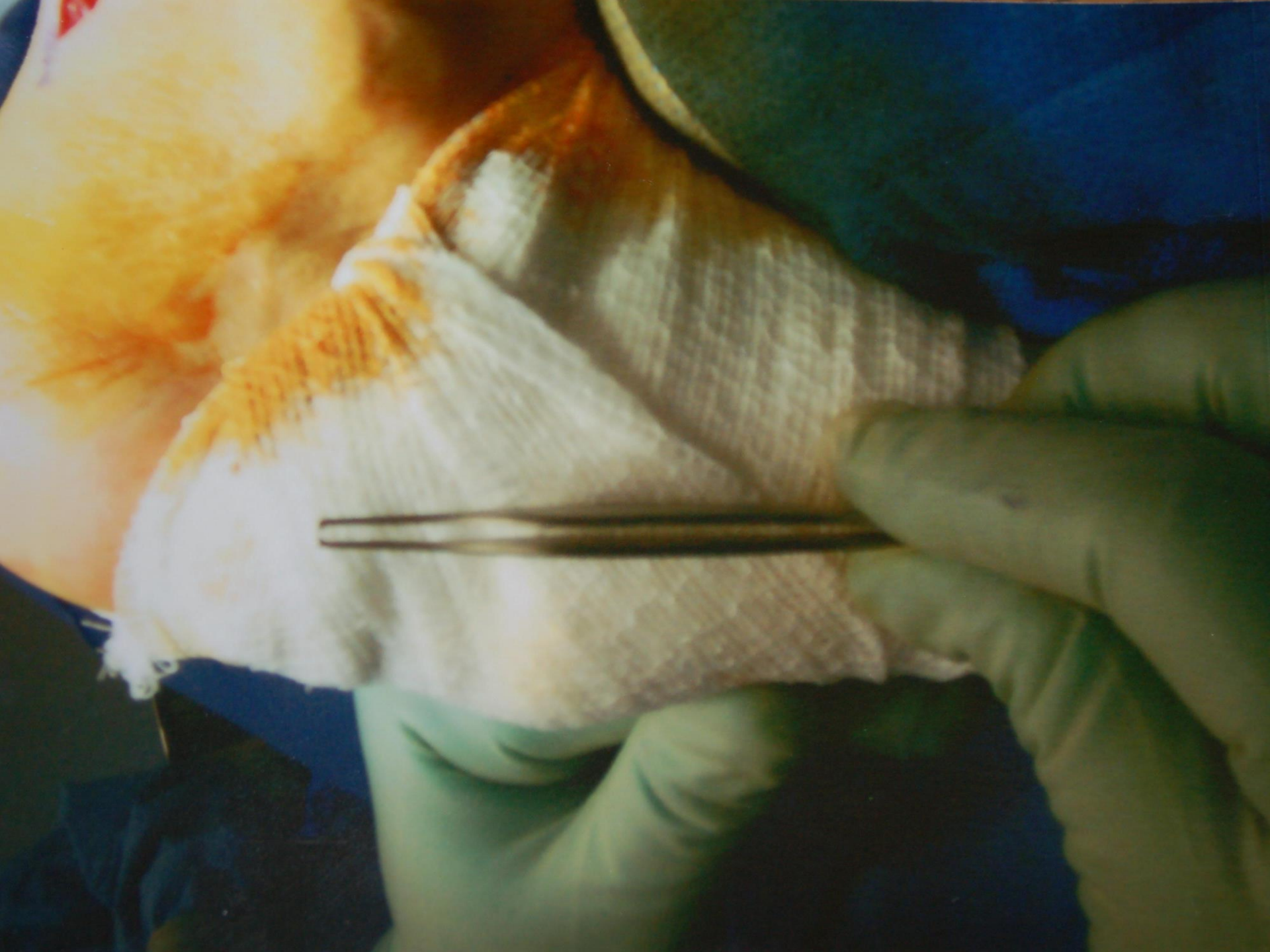
Equinus Treatment

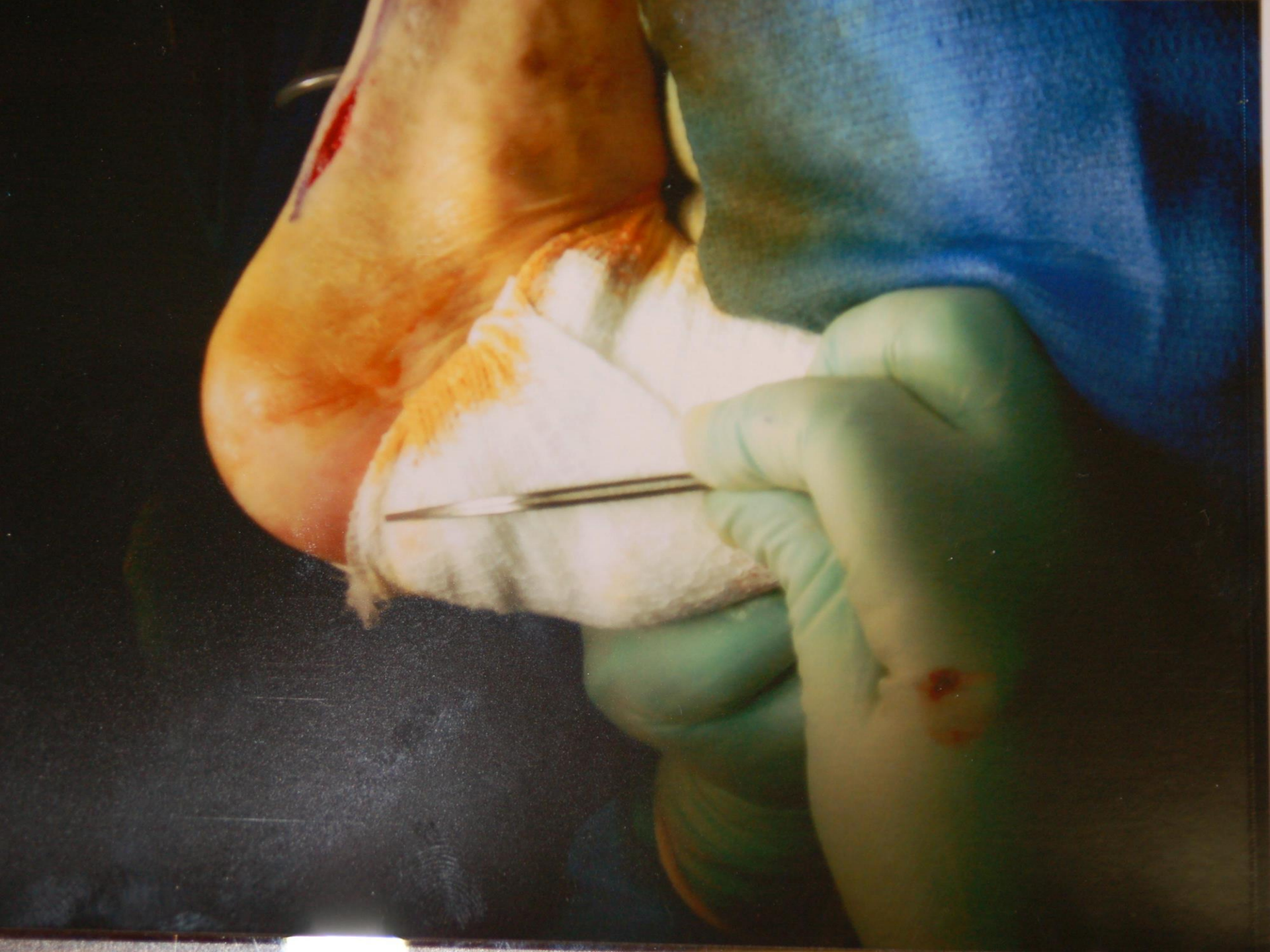
- Aggressive Physical Therapy

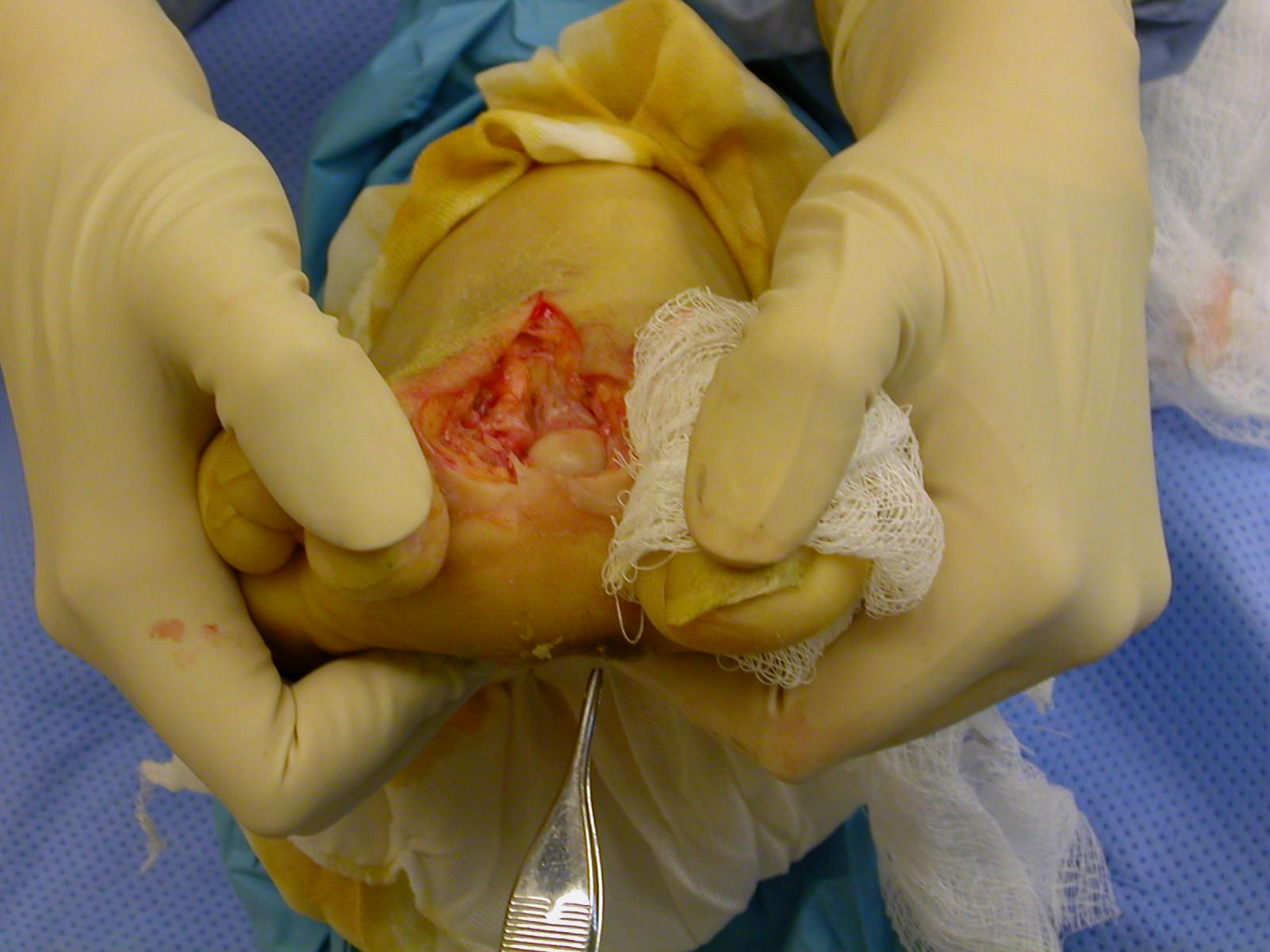
  Range of Motion (ROM)/Stretching exercises with Home Therapy Program

- Ankle Equinus----Tendo-Achilles Lengthening

  {TAL}





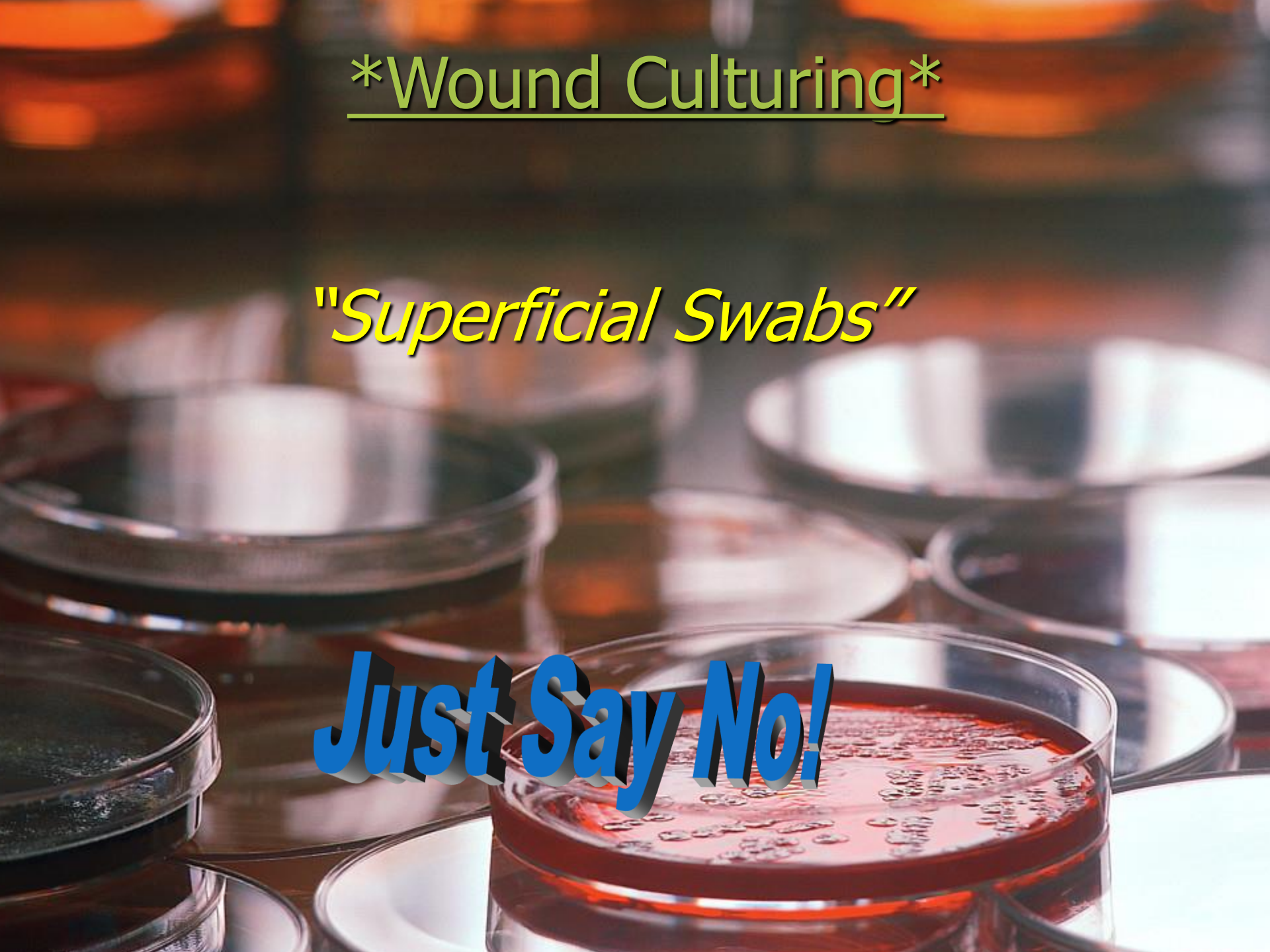



Two Days Post Op

Ulcer Comparison Pre and Post Operatively

Wound Culturing

"Superficial Swabs"



Wound Culturing (continued)

Slater, et.al.-----Diabetic Medicine, 2004

- Cultured 60 ***infected*** Diabetic Foot Wounds
- All wounds were cultured via ***superficial swab*** before ***debridement***
- All wounds were subsequently cultured to obtain a deep specimen via curretage **Post Debridement**

Culture Study Results

- **Superficial Swabs** identified a mean of *2.7* isolates
- **Deep Tissue Culture** identified a mean of *2.5* isolates

*Results were identical in only 62% of Patients

Culture Study Results (cont.)

- Additional organism on superficial swab vs. deep swab in ***25%*** of cases
- Superficial swab missed an organism present in deep tissue culture in ***18%*** of cases
- Superficial swabs only recovered ***55%*** of all isolates in wounds penetrating to bone

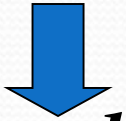
Culture Study Results (cont.)

Study outcome

Wrong Cultures

Wrong Antibiotic Choices

Inappropriate treatment of True Pathogens



Increase in healthcare cost

Culture Technique

1. Debride Wound

2. Cleanse with 0.9% Normal Saline

3. Culture Deep To Wound Surface

   *Curettage with tissue Specimen

4. Aerobic and Anaerobic Cultures


Starswab™ Anaerobic System
For Transport of Anaerobic, Facultative and Aerobic Specimens / Pour le prélevèment et le transport d'échantillons anaérobie, aérobie et facultatifs
NAME/NOM:
S120-D
LOT 6E29A

Surgical Approaches

Surgical Approach Planning

Identify area of abscess origination

"Sub Met"

One----------MEDIAL SPACE

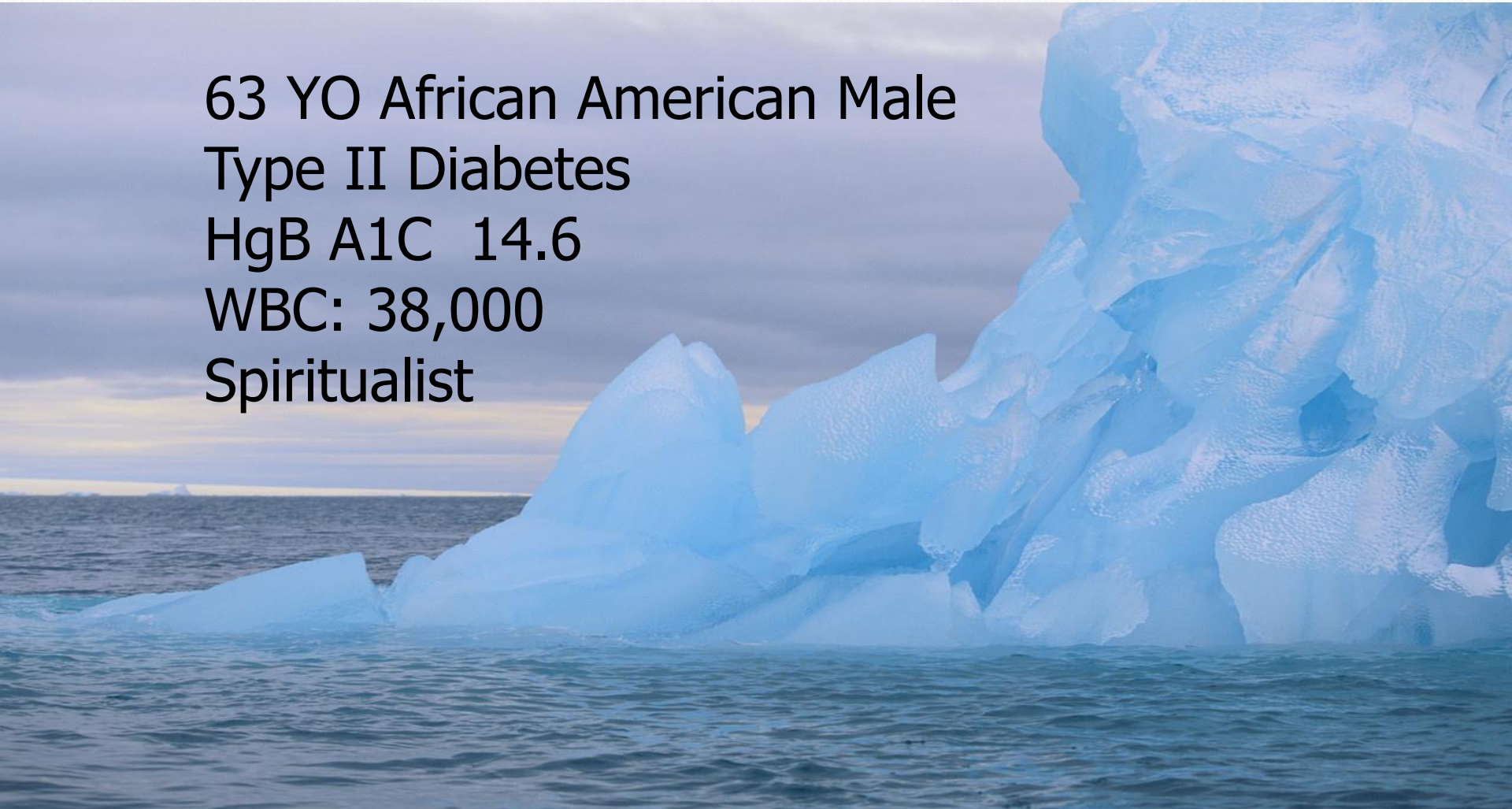
Two, Three & Four---CENTRAL SPACE

Five----------LATERAL SPACE

"Attack and Explore"

Exposure is Mandatory
“Think Iceberg”

Iceberg Effect



63 YO African American Male
Type II Diabetes
HgB A1C 14.6
WBC: 38,000
Spiritualist

Post Limb Salvage

Wound Management

Wound Debridement

- Surgical Wound Debridement…the most critical yet fundamental technology of Wound Bed PreparationWhen properly performed, surgical wound debridement removes:•devascularized tissue•necrotic material•eliminates dead space•reduces wound contamination

General Principles of Surgical Debridement

- •Complete removal of undesirable tissue
- •Maximum preservation of collateral tissue
- •Wound closure

Classic Principles of Surgical Debridement and Limb Salvage

Insightful and Aggressive Decision Making

Radical excision

Removal of necrotic tissue

Preservation of viable skin

Planned incisions to

- facilitate reconstruction
- Inspect deep fascia and muscle

Staged Surgical Procedures

Pack wound

The Clinical Benefits of Debridement

Removes necrotic tissue that impairs wound healing

Creates bacterial balance in the wound

Results in controlled bleeding that stimulates the production of blood-borne growth factors

Removes the senescent fibroblasts –leaving younger, more viable cells

Removes the hyper-proliferative, non-migratory wound edge that slows healing

Thorough debridement is essential for the wound repair process.

Debridement Options

Mechanical

Autolytic

Biologic

Enzymatic

Surgical

Curette, Scissor, Scalpel

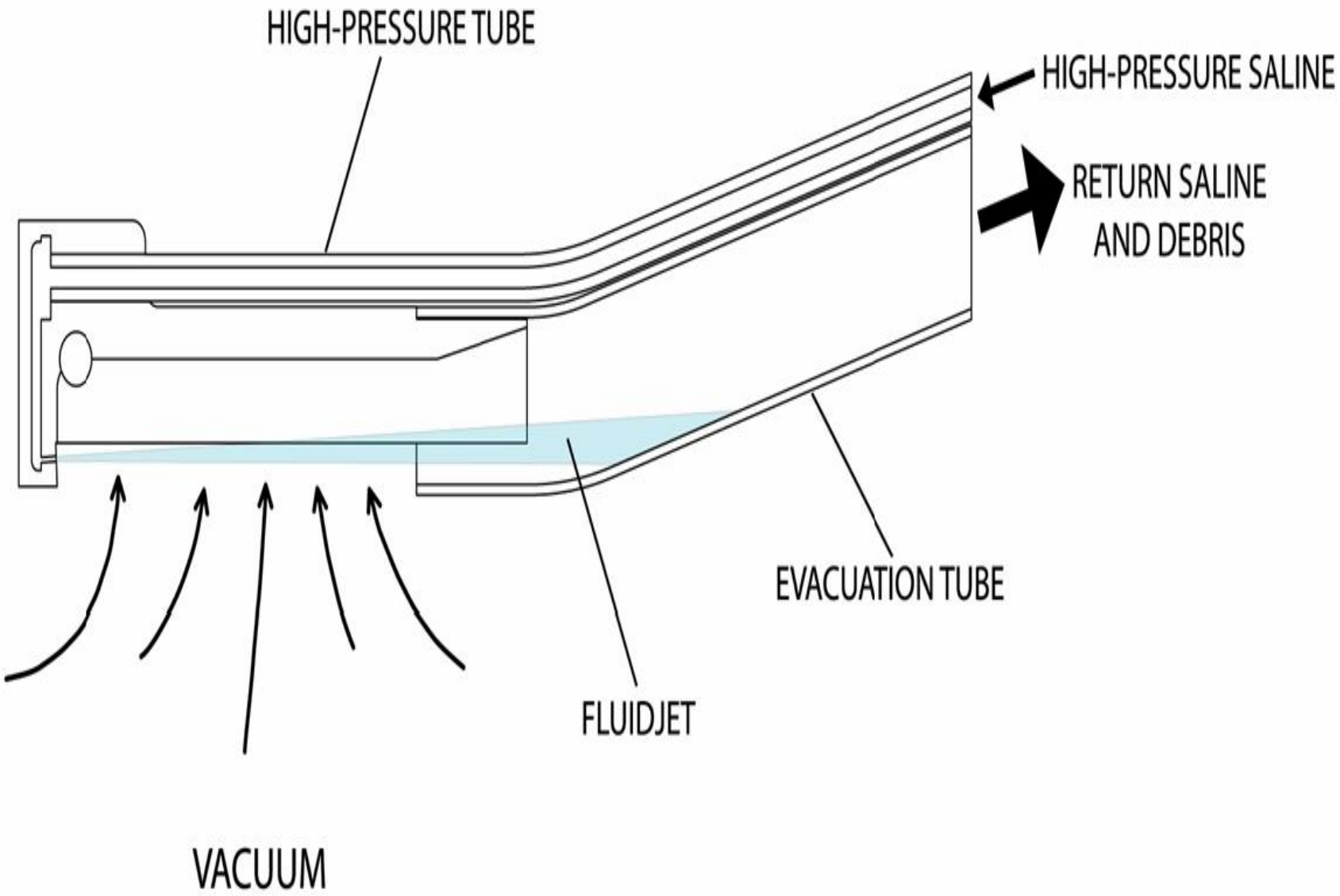
Hydrosurgery

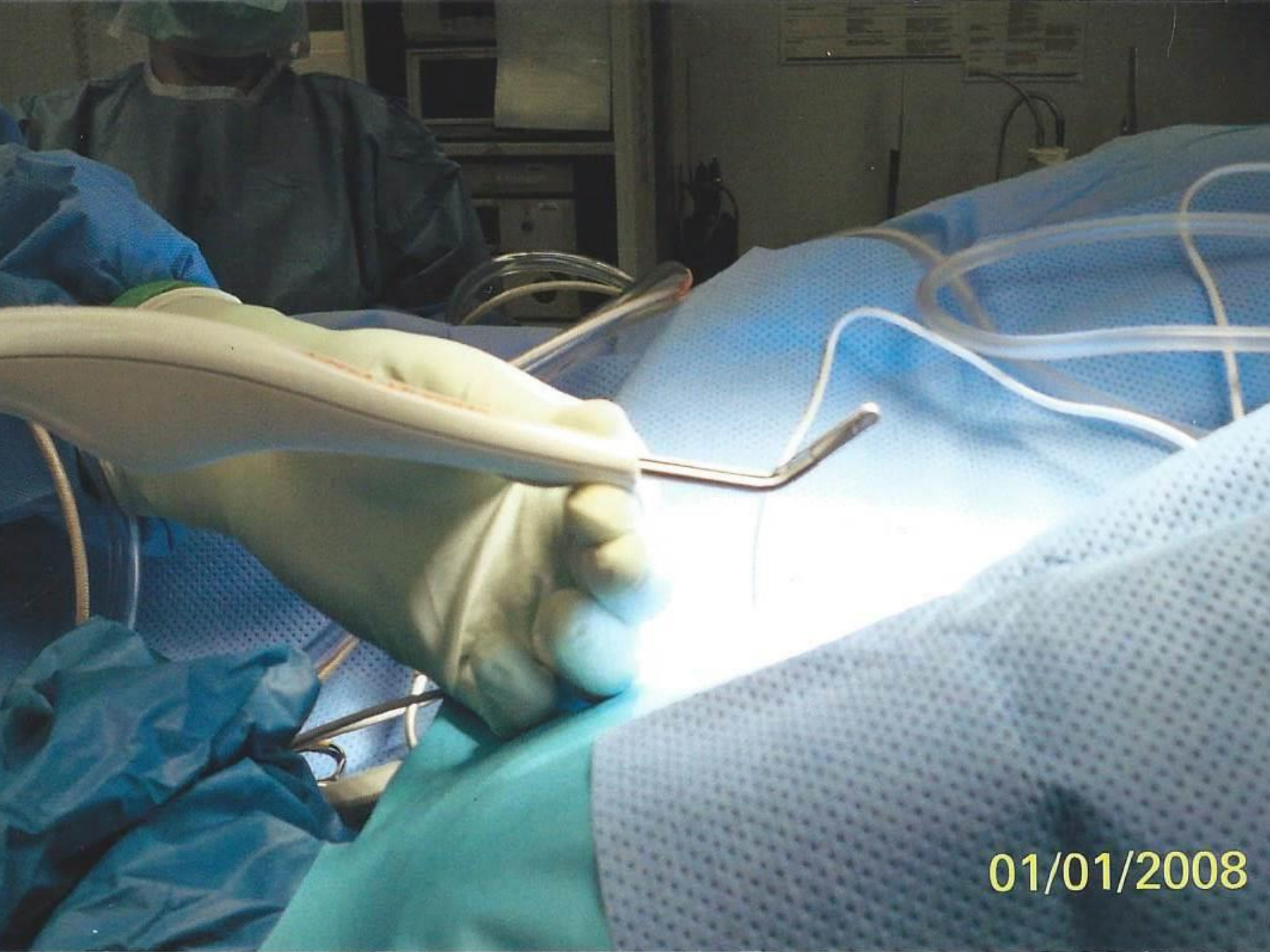
VERSAJET

High pressure stream of saline

- –.005 of an inch in diameter
- –Various power settings
- –Multiple tip options
- –Creates a Venturi effect

- •The stream of saline allow surgeons to:
- –Select tissue
- –Excise tissue “layer by layer”
- –Evacuate waste


HIGH-PRESSURE TUBE
HIGH-PRESSURE SALINE
RETURN SALINE
AND DEBRIS
EVACUATION TUBE
FLUIDJET
VACUUM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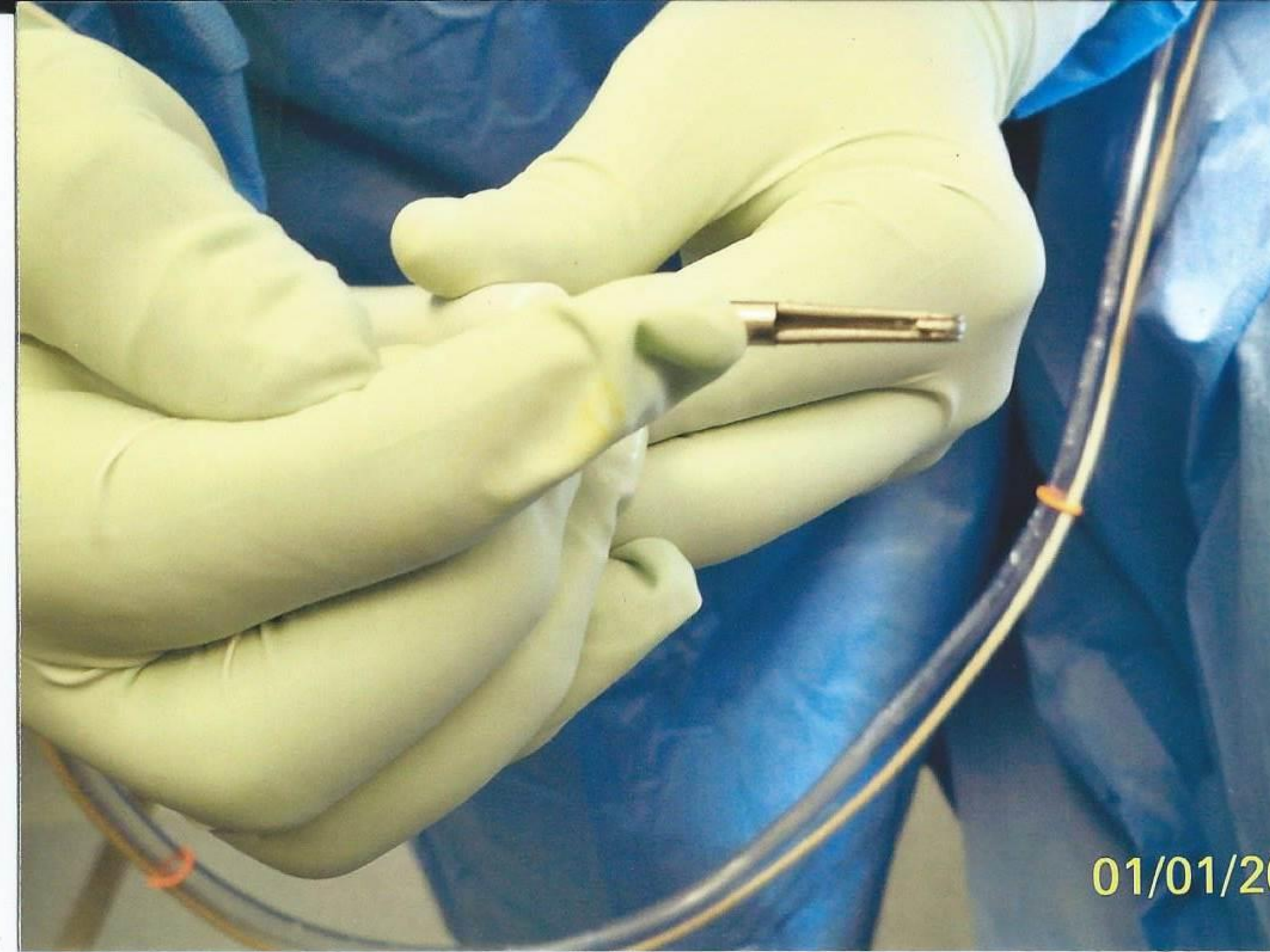
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CE 0086 Rx only

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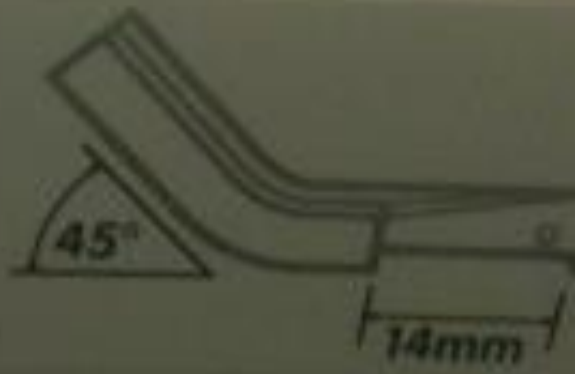

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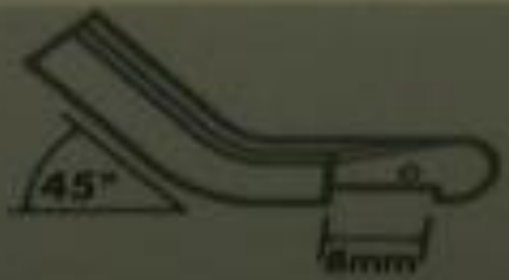



VersaJet
Hydrosurgery System
Door
Pedal
Error
10
Power Level
APR


01/01/20


01/01/200


01/01/2008


One Week Post
Debridement

Debriding Agents

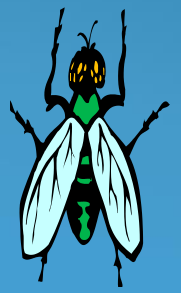
Santyl Collagenase

Derived from fermentation by Clostridium Histolyticum

** Will ***NOT*** harm Non necrotic tissue **

Maggot Therapy

- Little controlled evidence support outcomes
- Phaenicia sericata {Green Blow Fly}
- 5-8 Larvae to each Cm2 of wound surface
- Cover with porous dressing glued to surrounding wound surface
- Change every 2-3 days



Advanced Technologies for Wound Closure

Stem Cell Therapy

Biologic Therapy

Topical Therapy

Stem cell definition/potential

- Stem Cells are cells characterized by the ability to renew themselves through mitotic cell divisions and **differentiate into a diverse range of specialized cell types.**
- Two types of Stem Cells:
- Embryonic and Adult
- ****Arteriocyte is an adult stem cell research company**

2 Types of Adult Stem Cells:

- Hematopoietic
- Mesenchymal

Nonhealing Wounds

- Addition of Stem Cells is a potentially powerful tool to enhance the healing potential of chronic wounds
  - Diabetes
  - Renal failure
  - Circulatory impairment

Who is Using cBMA?

- Foot and Ankle Fusions
- Spinal fusions
- Non-unions of long bones, Coupled w/ microfracture
- Large bone grafting procedures
- Tendonitis and tendon repair
- Wound healing

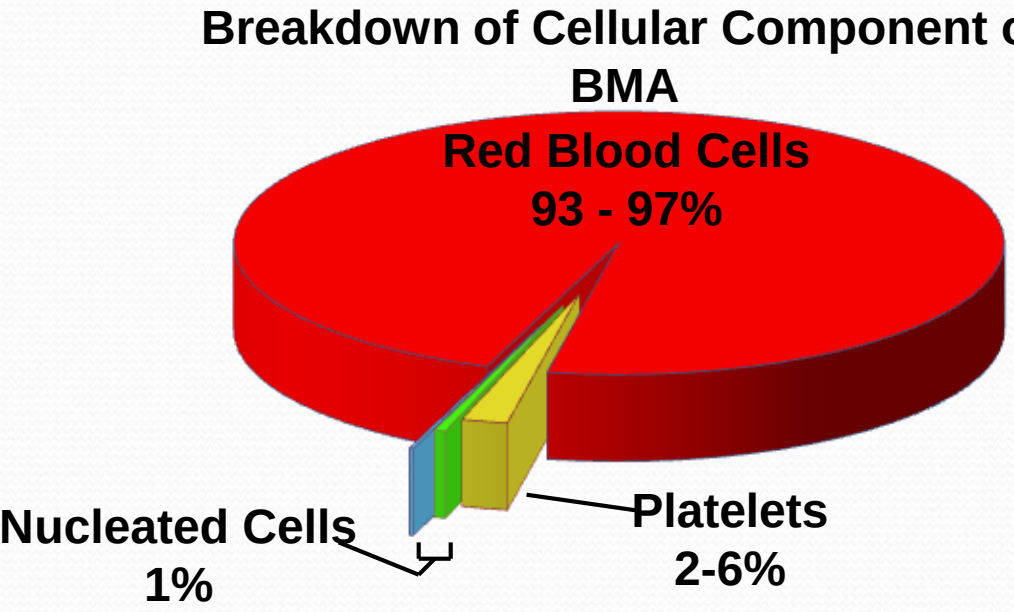
Bone Marrow Harvest Sites

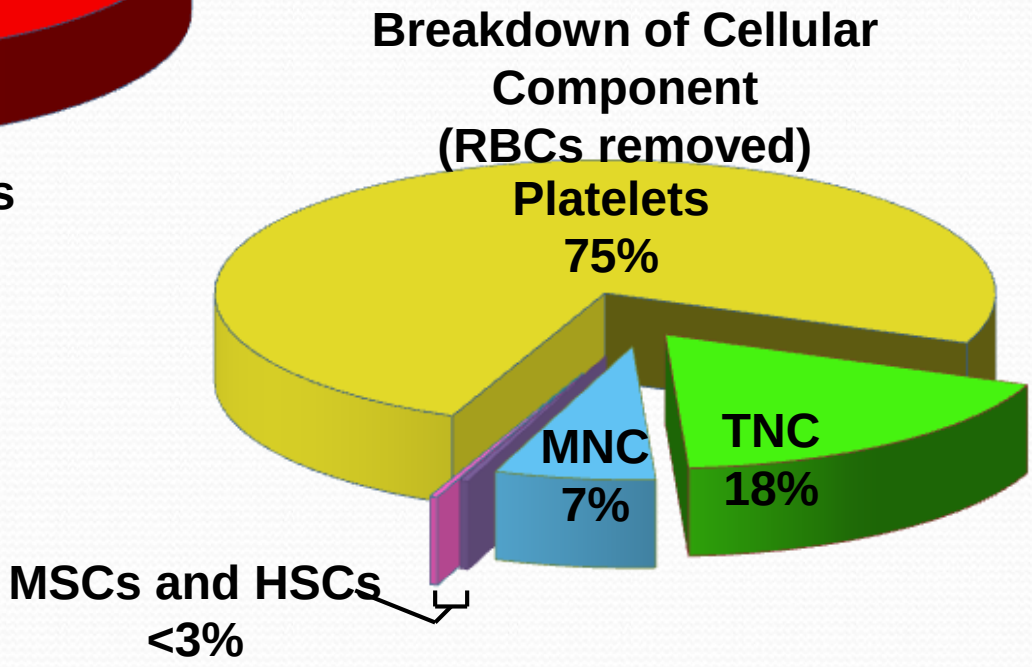
- Posterior or Anterior Iliac Crest, vertebral bodies
- Intermedulary canal of long bones(proximal or distal tibia, femur, humerus)
- Calcaneus

Calcaneous


Procedure Pearl
Do Not Use
Tourniquet

Cellular Content of Bone Marrow





ARTERIOCYTE
MEDICAL SYSTEMS

- **Platelet-Rich Plasma (PRP)**
  - Platelets
  - WBC
  - Growth Factors
- **Bone Marrow Concentrate**
  - Stem Cells (HSC and MSC)
  - Platelets
  - WBC
  - Growth Factors
- **Platelet-Poor Plasma (PPP)**
  - Matrix Proteins
  - Platelets (0.5-2 X BL)

Thank you

Diabetic Limb Salvage
&
HBO Therapy

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ACLES

Livonia, Michigan

May 4, 2017

ADVANCED TECHNOLOGIES
BIOLOGIC THERAPIES

Apligraf

- Human Skin Equilvalent
- Contain both Fibroblasts and Keratinocytes

**Fibroblasts secrete: Human dermal Collagen, Fibronectin,Glycosamino Glycans,Growth Factors

**Keratinocytes secrete: Substances that stimulate target genes controlling the cellular activation cycle that promotes wound healing

Apligraf® Science

- Cell Therapy
  - Growth Factors, cytokines, natural antibiotics, matrix proteins, proteoglycans
- Barrier Function
  - Physical – epithelial coverage
  - Biologic – microbial penetration, fluid loss
- Dermal Matrix
  - Matrix for cell migration
  - Substrate to quench proteolytic enzymes

Apligraf® — Product Description

- Apligraf is a living bi-layered cell therapy
- It consists of 4 components:
  - **Cornified layer** – basket-weave keratinocytes
  - **Epidermal layer** – human keratinocytes
  - **Dermal layer** – human fibroblasts
  - **Extracellular collagen matrix (ECM)** – bovine and human collagen with additional ECM proteins
- It does not contain melanocytes, macrophages, lymphocytes, Langerhans' cells, blood vessels, hair follicles or sweat glands

Apligraf® FDA Indications

- Indicated for the treatment of noninfected partial- and full-thickness **venous leg ulcers** with standard therapeutic compression
  - Ulcers that have not adequately responded to at least **4 weeks** of conventional therapy

- Indicated for the treatment of full-thickness neuropathic **diabetic foot ulcers** when used with standard diabetic foot ulcer care
  - Ulcers that have not adequately responded to at least **3 weeks** of conventional therapy

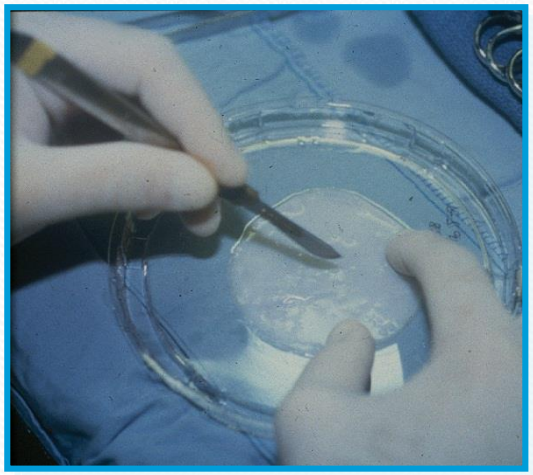
Apligraf® Application: Open and Inspect Package

Apligraf® Application: Remove Apligraf From Storage Dish

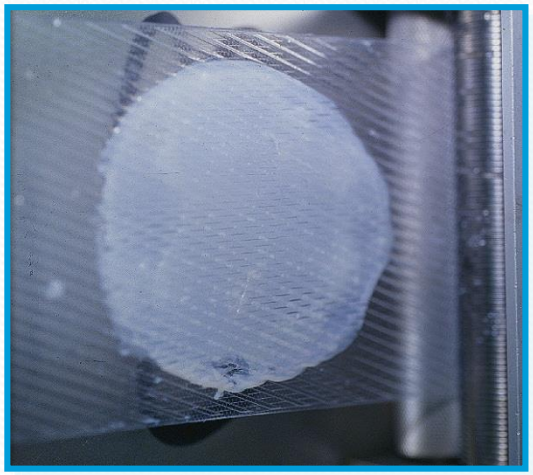
Photographs courtesy of John S. Steinberg, DPM.

Photograph courtesy of John S. Steinberg, DPM

Apligraf® Application:
Perforating Apligraf: Fenestrate or Mesh



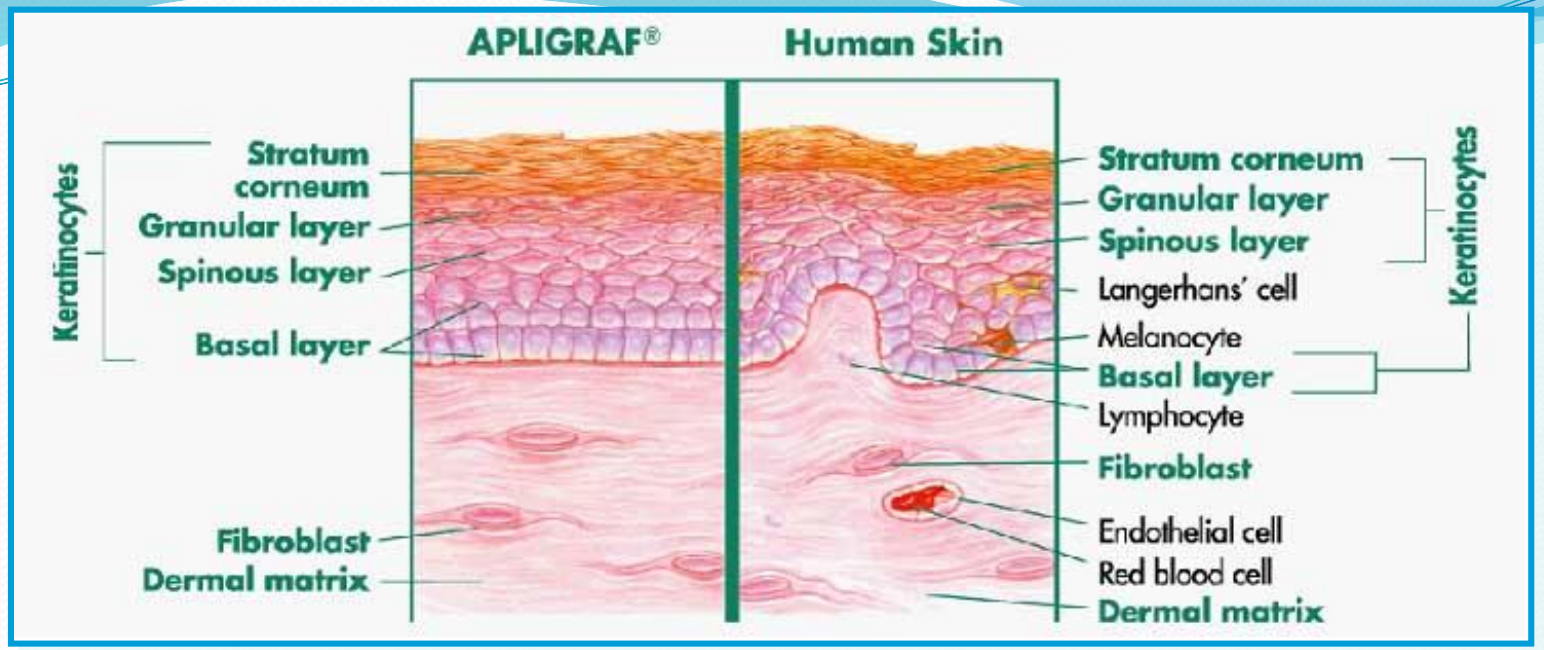
Fenestrate with #10 Blade

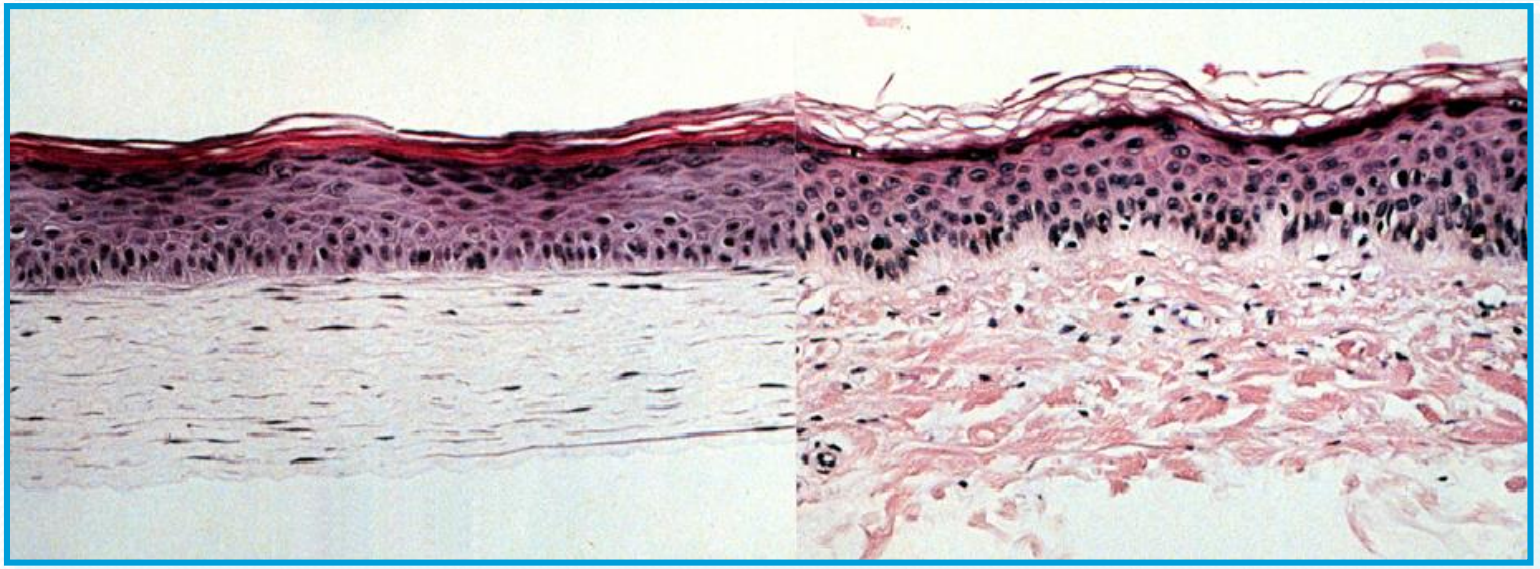


Meshed 1.5 : 1

Wounding of Apligraf has been demonstrated to stimulate keratinocytes & fibroblasts to release growth factors. This technique also allows for drainage.

Apligraf®





Data on file, Organogenesis, Inc., Canton, MA.

Parentau NL, et al. *J Cell Biochem*. 1991;45:245-251.

Table 1
Partial list of cytokines and growth factors produced from human keratinocytes and fibroblasts

Keratinocytes	Fibroblasts
• IL-1α and IL-1β [23,24]	• KGF-1, -2 (FGF-7, -10) [25–27]
• IL-1ra [24]	• TGF-β1, -2, -3 [28–30]
• IL-1, -3, -6, -8, -10, -18 [24,31–35]	• CTGF [36,37]
• G-CSF, M-CSF, and GM-CSF [24]	• FGF-2 (basic) [38]
• TGF-α, -β1 [24,39–43]	• PDGF-A [25,44]
• PDGF [24,27,45]	• IGF-1 [25]
• VEGF [27,46–48]	• VEGF [25,47]
• TNF-α and -β [24,30]	• HGF [25]
• INF-γ [24]	• IL-6, -8 [25]
• IGF-1 [27]	• TNF-α [25]
• b-FGF [24], FGF-22 [42]	• GM-CSF and G-CSF [25,33,34]
	• FGF-22 [42]
	• IGF-1 [27]

b-FGF = basic fibroblast growth factor; CTGF = connective tissue growth factor; FGF = fibroblast growth factor; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte/monocyte colony-stimulating factor; HGF = hepatocyte growth factor; IGF = insulinlike growth factor; IL = interleukin; INF = interferon; KGF = keratinocyte growth factor; M-CSF = monocyte colony-stimulating factor; PDGF = platelet-derived growth factor; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

Topical Growth Factors

Regranex®

- Made via recombinant DNA Technique---- Insertion of gene for Platelet Derived Growth Factor (PDGF) into B-Chain of the Yeast--- Saccharomyces

- Super Expensive------$$$$$$$$

Topical Growth Factors (Cont.)

Regranex® (Continued)

- Only Recombinant DNA Product approved for Treatment of Wounds
- **Biologic Activity of Regranex is to deliver PDGF to wound thus promoting chemotactic recruitment and proliferation of cells involved in wound repair


NDC 0045-0810-15
REGRANEX® GEL 0.01%
(becaplermin)
Contains: becaplermin 0.01%, sodium carboxymethylcellulose, sodium chloride, sodium acetate trihydrate, glacial acetic acid, L-lysine hydrochloride, and water for injection,
DIN 02239405
NET WT. 15g
For Topical Use Only
Multi-dose tube
See crimp end for lot number and expiration date.
ORTHO-McNEIL
Distributed by:
OMP DIVISION
ORTHO-McNEIL
PHARMACEUTICAL, INC.

Dressing Selection in Wound Care

Moist Environment Promotes:

Increased

1. ***Keratinocyte and Fibroblast Proliferation***
2. ***Keratinocyte Migration***
3. ***Collagen Synthesis***
4. ***Angiogenesis***
5. ***Wound Contraction***
6. ***Autolytic Debridement***

Wound Closure

Dressing selection (cont.)

*Hutchinson &McGuckin reviewed 100 studies comparing infection rates in more than 4000 wounds

- Moist environment: 2.6% infection rate
- Dry environment: 7.1% infection rate

{Hutchinson and McGuckin, Occlusive Dressings a Microbiological and Clinical Review: Am J. Infect. Contr. 18:257, 1990}

Ideal Dressing Characteristics

- Maintains a moist wound environment
- Absorbs excess exudate
- Elimates dead Space (packing)
- Does not harm wound
- Provides Thermal Insulation
- Provides Bacterial Barrier

*Wet to Dry Dressings----Bad News!

Dressing Catagories

- **Transparent films**
- **Hydrocolloids**
- **Foams**
- **Absorptive Wound Fillers**
- **Hydrogels**
- **Collagens**
- **Gauze**
- **Antimicrobials**
- **Contact Layers**

Table 2. Common Wound Healing Products

Product	Company
Transparent Films	
BLISTERFILM	Kendall
CarraSmart Film	Carrington Laboratories
Comfeel Film	Coloplast
Cutifilm	Beiersdorf-Jobst
mefilm	Mölnlycke
OpSite	Smith + Nephew
POLYSKIN	Kendall
ProCyte	Bard Medical
Tegaderm	3M
TRANSEAL	DeRoyal
Hydrocolloids	
CarraSmart	Carrington Laboratories
Comfeel Plus	Coloplast
Cutinova Hydro	Beiersdorf-Jobst
DuoDERM	ConvaTec
Exuderm	Medline
Hydrocol	Bertek
Procol	DeRoyal
RepliCare	Smith + Nephew
Restore Plus	Hollister
Sorbex	Bard Medical
Tegasorb	3M
ULTEC	Kendall
Foams	
Allevyn	Smith + Nephew
Biatain	Coloplast
CarraSmart Foam	Carrington Laboratories
CURAFOAM	Kendall
Cutinova Foam	Beiersdorf-Jobst
Flexzan	Bertek
LYOFOAM	ConvaTec
mepilex	Mölnlycke
Mitraflex	Mölnlycke
POLYDERM	DeRoyal
Polymem [a]	Ferris
Sof-Foam	Johnson & Johnson
Tielle [a]	Johnson & Johnson
VigiFOAM	Bard Medical
Absorptive Wound Fillers	
Alginates:	
AlgiDERM	Bard Medical
AlgiSite	Smith + Nephew
CarraGinate	Carrington Laboratories
Comfeel SeaSorb	Coloplast
CURASORB	Kendall
KALGINATE	DeRoyal
KALTOSTAT	ConvaTec
melgisorb	Mölnlycke
Restore CalciCare	Hollister
Sorbsan	Bertek
Tegagen	3M
Others (mainly starch copolymers):	
AQUACEL	ConvaTec
Bard Absorption Dressing	Bard Medical

Product	Company
Absorptive Wound Fillers - Others (continued)	
Comfeel Powder or Paste	Coloplast
FlexiGel STRANDS	Smith + Nephew
Comfeel Triad	Coloplast
Nonabsorbent fillers:	
MULTIDEX Gel or Powder	DeRoyal
Biafine	Medix Pharmaceuticals Americas
Hydrogels	
Amorphous:	
Biolex Wound Gel	Bard Medical
Carrasyn	Carrington Laboratories
Purilon Gel	Coloplast
CURAFIL	Kendall
Curasol	Healthpoint
DuoDERM Hydroactive Sterile Gel	ConvaTec
IntraSite	Smith + Nephew
normlgel	Mölnlycke
NuGel Collagen Wound Gel	Johnson & Johnson
Restore Hydrogel	Hollister
SoloSite	Smith + Nephew
Tegagel	3M
Sheet:	
AQUAFLO	Kendall
AQUASORB	DeRoyal
CarraDres	Carrington Laboratories
ClearSite	CONMED
CURAGEL	Kendall
Elasto-Gel	Southwest Technologies
Flexderm	Bertek
NuGel Wound Dressing	Johnson & Johnson
Vigilon	Bard Medical
Collagens	
100% collagen:	
hyCURE	Hymed Group
Medifil (particles, pads, gel)	BioCore Medical Technologies
SkinTemp	BioCore Medical Technologies
Combination Products:	
FIBRACOL	Johnson & Johnson
Woun'Dres Collagen Hydrogel	Coloplast
Antimicrobials	
Acticoat	Smith + Nephew
Arglaes	Medline
Iodosorb Gel and Iodoflex Pad	Healthpoint
KERLIX A.M.D.	Kendall
Silveron	Silveron Consumer Products
Contact Layers	
Adaptic Non-Adhering Dressing	Johnson & Johnson
Dermanet	DeRoyal
mepitel	Mölnlycke
N-terface	Winfield Labs
Tegapore	3M

This list is not all-inclusive of every dressing on the market. No inferences should be made regarding the inclusion or exclusion of products on this list.

[a] Composite dressings

Hydrogels

- Indicated for dry to minimally exudating wounds
- Granulating or Necrotic wounds----Except A Dry Ischemic ulcer
- Wounds of any etiology including infected wounds if changed daily

Antimicrobials

- Indicated for Infected wounds
- Contain either slow released Iodine or Silver Base which release Silver Ions (toxic to bacteria----nontoxic to human cells
- These dressings DECREASE Bacterial Bioburden

Off-Loading Devices

Off Loading Devices

Relief of Plantar Pressure Force Load (N/cm2)

Bledsoe Conformer C.A.M. Walker (Controlled Ankle Motion)

- Innersole molded to the foot shape
- Distributes weight more efficiently than a total contact cast
- Aluminum arms re-formable to fit any leg size or shape
- Computer designed rocker bottom simulates normal gait

Bledsoe Conformer C.A.M. Walker (Controlled Ankle Motion)

- Auto-mold insert provides instant Continued customized pressure relief


Charcot Restraint Orthotic Walker {CROW}

Total Contact Cast

- “The Standard” for plantar ulcer offloads
- Custom molded to patient model
- Increased patient compliancy for non-ambulation

Total Contact Casting Made Easy: The GOLD Standard in Off-Loading

TCC-EZ®

TOTAL CONTACT CAST SYSTEM


45

Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy cont'd

- O_2 is transported by the blood in two different ways
- Chemically bound to hemoglobin
- Physically dissolved in plasma {Henry's Law}

HBO cont'd

Henry's Law

The quantity of a gas that will dissolve in a liquid is proportional to the partial pressure of the gas and its solubility coefficient, when the temperature remains constant.

{Concentration of dissolved gas = pressure x solubility coefficient}

Henry's Law in Action

- When a subject is breathing 100% O_2 at 3 atm this will result in rise of physically dissolved O_2 in plasma from 0.32 vol% (air at 1 atm) to, theoretically, 6.8 vol% O_2
- Consequently, the total circulating oxygen content of blood would increase from 20.1 to 26.9 vol%

Hyperbaric Oxygen Therapy Effects

- Elevates tissue oxygen levels even in patients with significant PVD.
- Antibacterial capabilities
- Wound healing potential is increased
- Antibacterial effects

  -increases white blood cell function in forming high energy oxygen radicals.

HBO Cont'd

Wound Healing Effects

- In both normal and ischemic wounds epithelial tissue spread is increased when Oxygen tention is elevated.
- Angiogenesis has also been accelerated under HBO Conditions.
- New capillaries spread into the new collagen matrix of the healing wound, increasing surrounding tissue oxygen tention and stimulating new collagen production.
- As arterial Oxygen tention increases from 40 to 200 mm Hg Hydroxyproline doubles thus increasing Collagen Synthesis.

HBO / Wound Healing Cont'd

- Transcutaneous oxygen pressure values of less than 20 mm Hg demonstrate extremely poor wound healing.
- $TcPO_2$ levels greater than 20 mm Hg demonstrate a much higher healing potential
- $TcPO_2$ levels of 40 mm Hg or more offer the best healing potential.

HBO/Antibacterial Effects Cont.

- Oxygen augments bacterial action of various antibiotics especially Aminoglycosides and Sulfonamides.
- HBO therapy has direct lethal effects on anaerobic and microaerophilic organisms

HBO Mechanisms

Immunologic

- ✓Increases killing by PMNs
- ✓Lethal to some anaerobes
- ✓Inhibits toxin formation by some anaerobes
- ✓Oxygen free radicals
- ✓Enhances bactericidal activity of antibiotics

Microcirculatory

- ✓Increases flexibility of RBCs
- ✓Promotes growth of capillaries (neovascularization)

Transcutaneous Oxygen Pressure {$TcpO_2$}

- Has been shown to be a valuable tool in predictive healing vs. non healing in diabetic ulceration.
- Pecoraro et. al. Found that patients with a $Tcpo_2$ level less than 20mm hg as compared to $Tcpo_2$ levels of greater than 40mm hg had a 39 fold increase in failure of wounds to heal.


July 5, 2006


August 7, 2006 {4 weeks}
1
2
3
4
Apligraf
888-


August 30, 2006 {8 weeks}

November 29, 2006 {21 weeks}


August 2, 2006 {Medial View}


August 2, 2006 {Lateral View}

October 2, 2006 {Medial View} {8 weeks}

October 2, 2006 {Lateral View} {8 weeks}

November 27, 2006 {Medial View} {17 weeks}

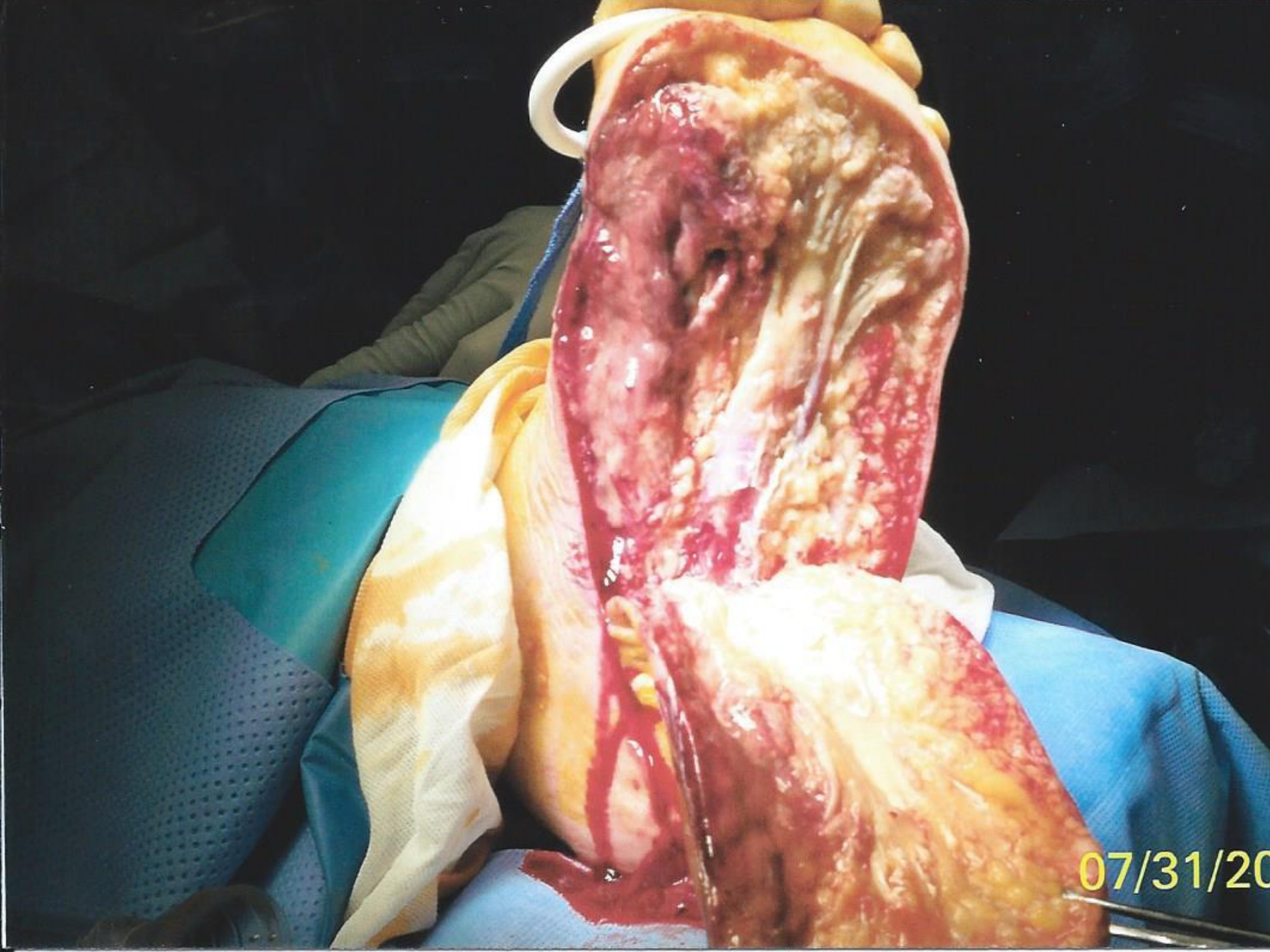
November 27, 2006 {Lateral View} {17 weeks}

Case Study

- **58 YO Caucasian Male admitted to the ICU for DKA and Sepsis**
- **PMH: HTN, DM (Uncontrolled), Hyperlipidemia**
- **WBC: 24,000**
- **Temp: 101.1**


07/31/2013


07/31/20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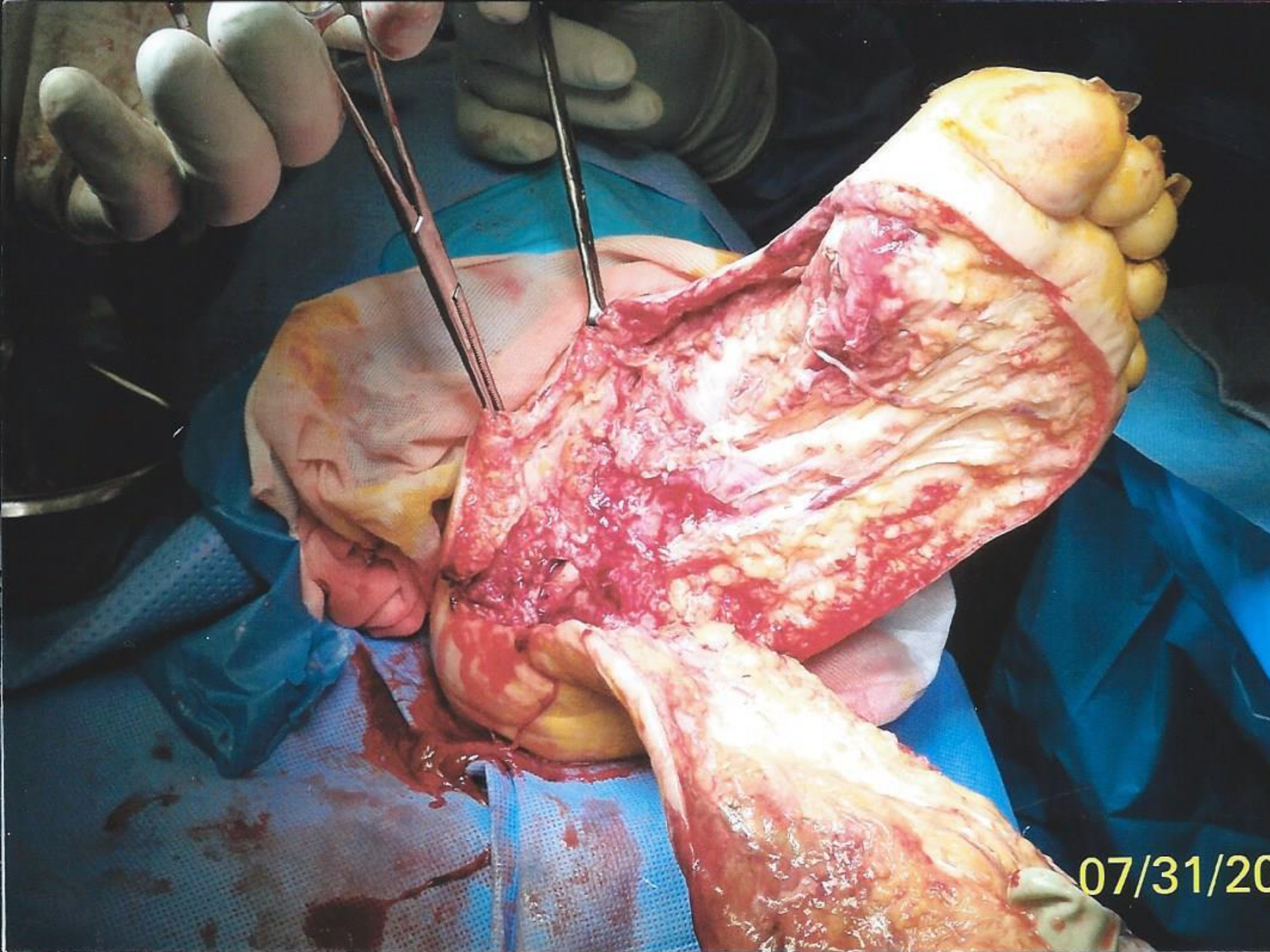
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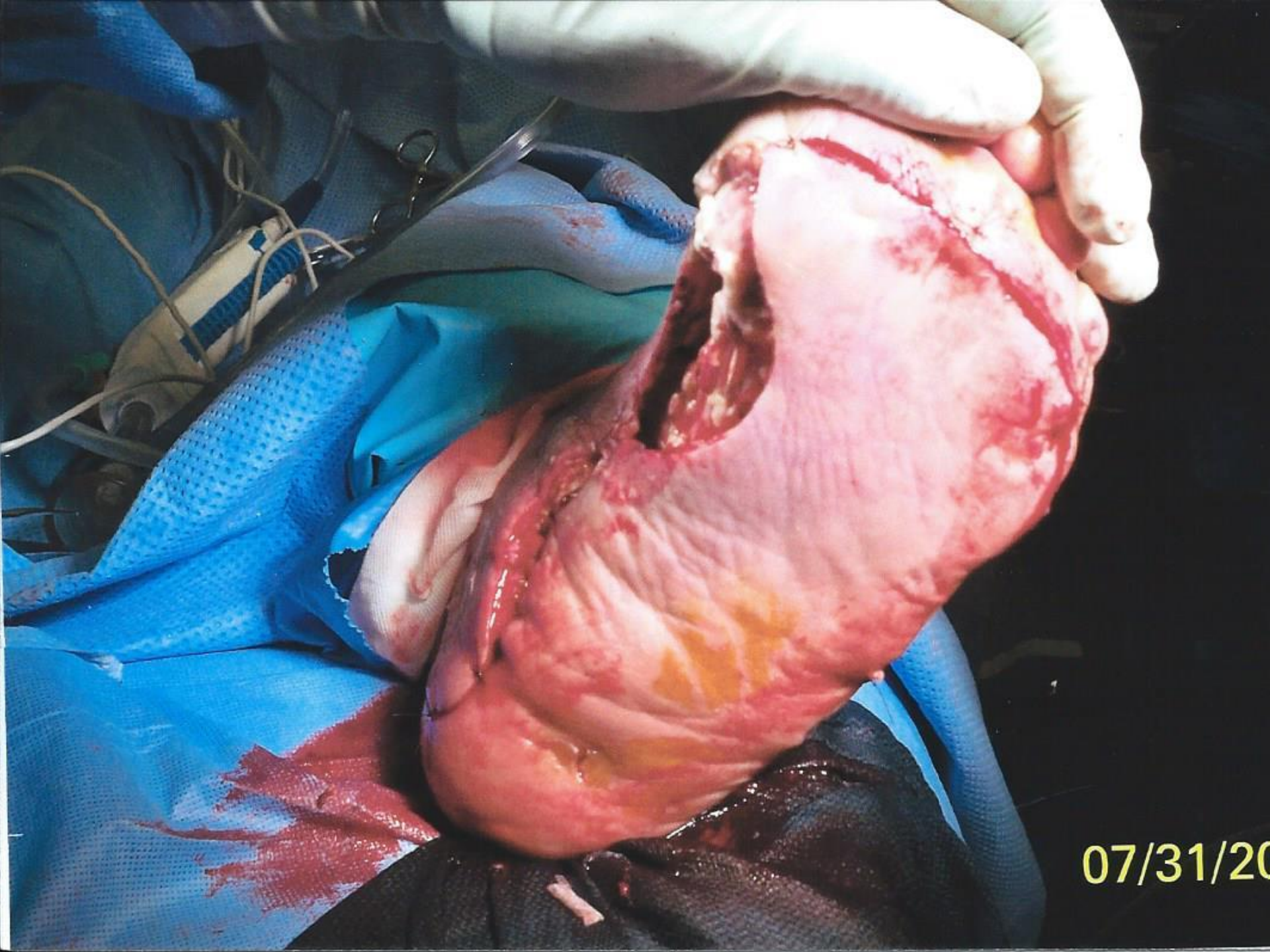
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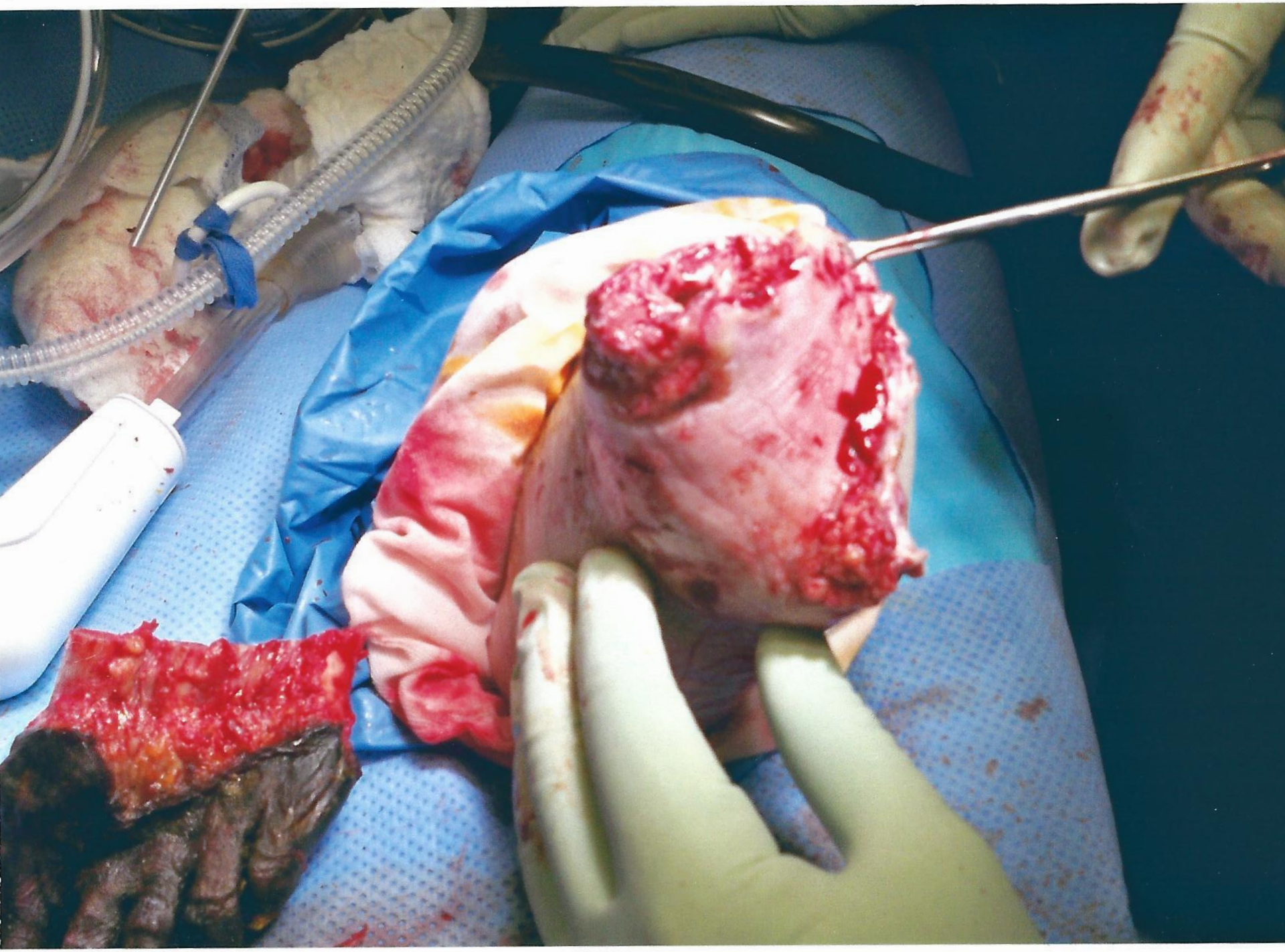
Case Conclusion

- **Pt. has subsequently undergone amputation of Hallux and Partial Ray Resection.**

- **Receiving HBO Therapy in conjunction with Wound Care and is Healing Well**

Case Study

- **61 Y.O. Male**
- **PMH: IDDM, ETOH ABUSE**
- **ACUTE EMBOLISM POSTERIOR TIB ARTERY**
- **RECENT EMBOLECTOMY**
- **WHATS YOUR THOUGHTS SAVE OR BK AMP???**



Thank you