The Physiology of a Problematic Wound

ACLES Annual Conference

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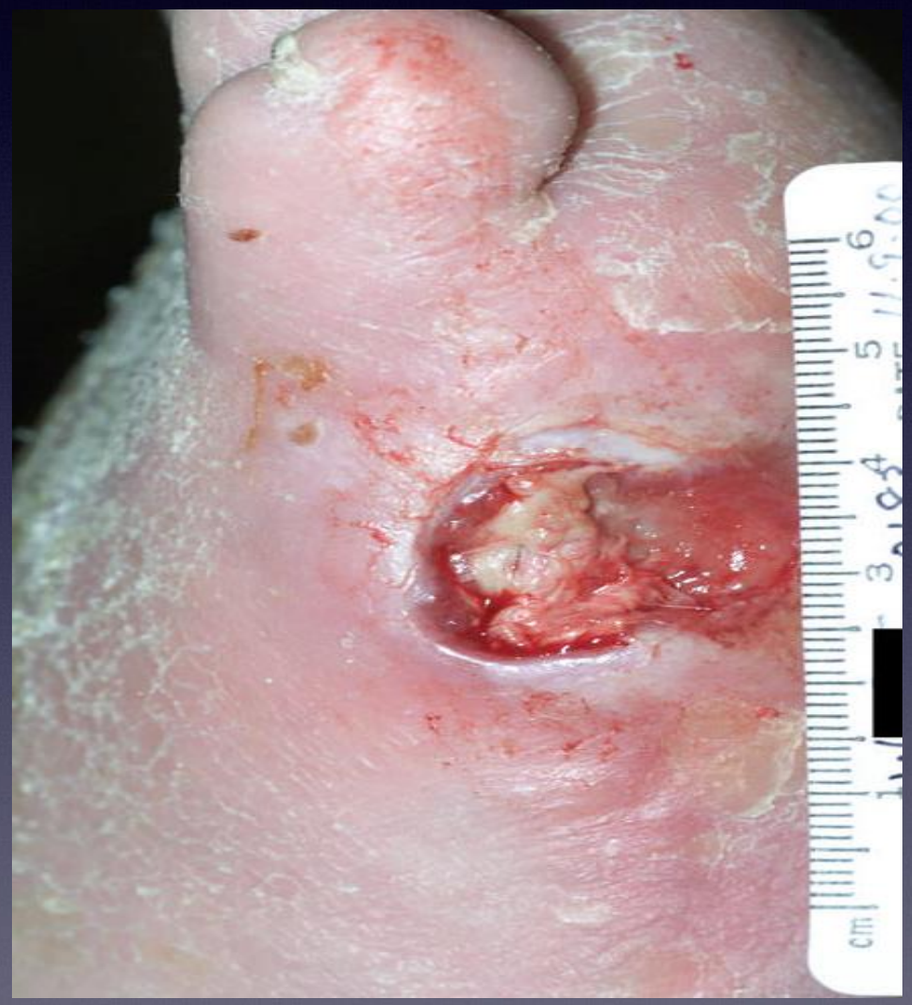
Richard T. Bauer III DPM, AACFAS
Summit Foot and Ankle
1072 Troy-Schenectady Road, Suite 303
Latham, NY 12110
Medical Director, Seton Wound Care Center
rbauer.dpm@gmail.com

St Peter's Health Partners

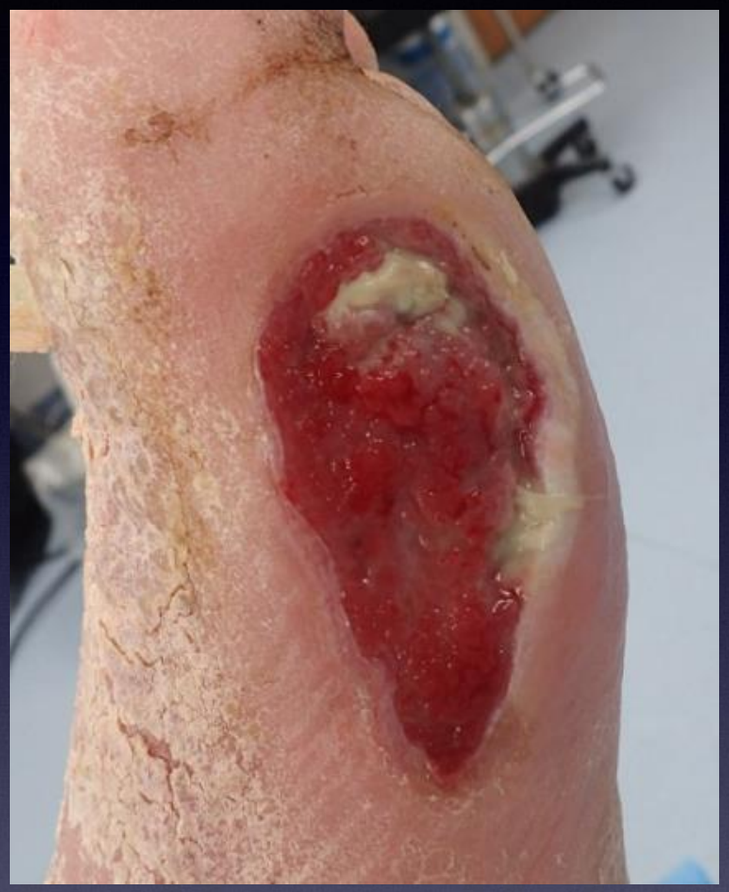
Objectives

- Refresher on Physiologic Wound Healing
- Review pathophysiology at the systemic and cellular level
- When is standard wound care not enough?
- Integration of advanced therapies and understand how they affect, optimize the local wound environment.
- Exogenous materials offered by Amniotic Allografts.

End Point
Don’t let this…….Become This!



Common Problems

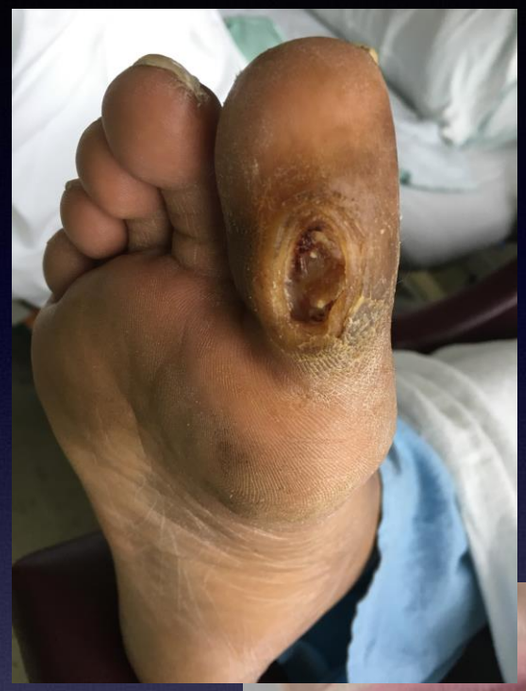


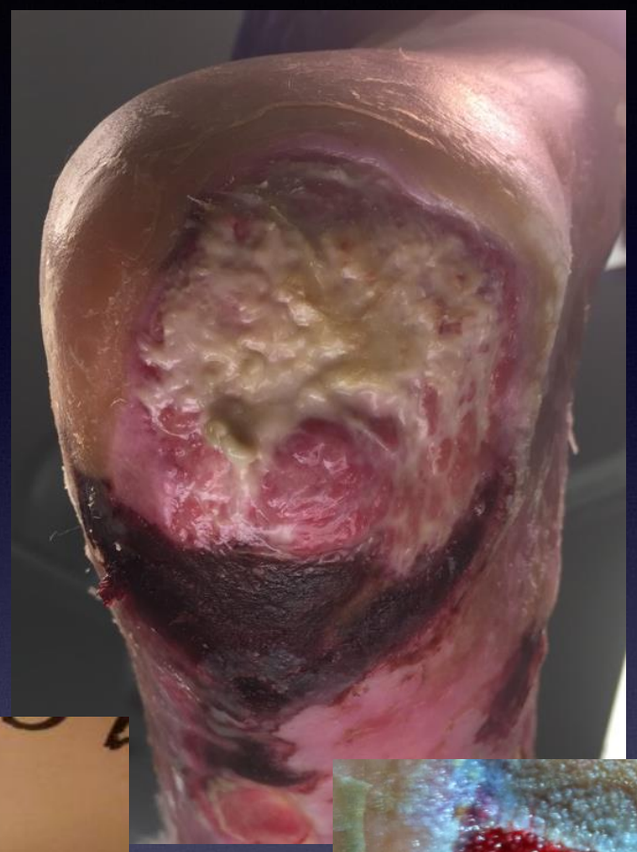
- Diabetic Foot Ulcers
- Venous Leg Ulcers
- Pressure Ulcers
- Traumatic Wounds with Co-morbs
- Arterial Wounds

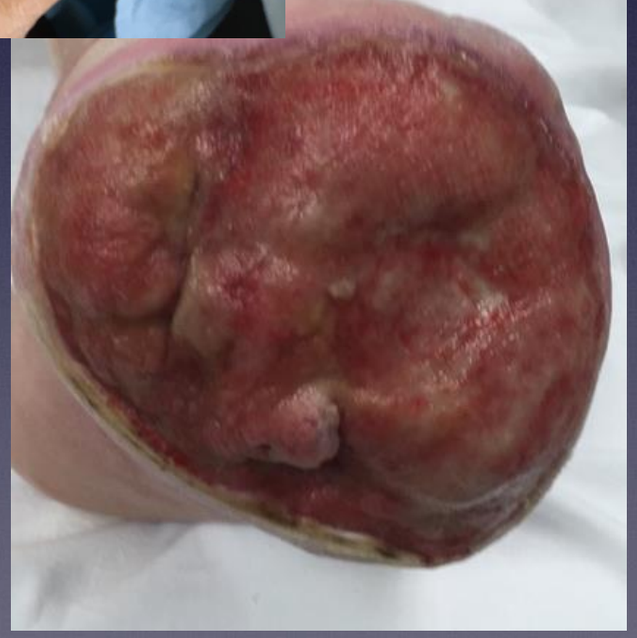
Health and Fiscal Implications

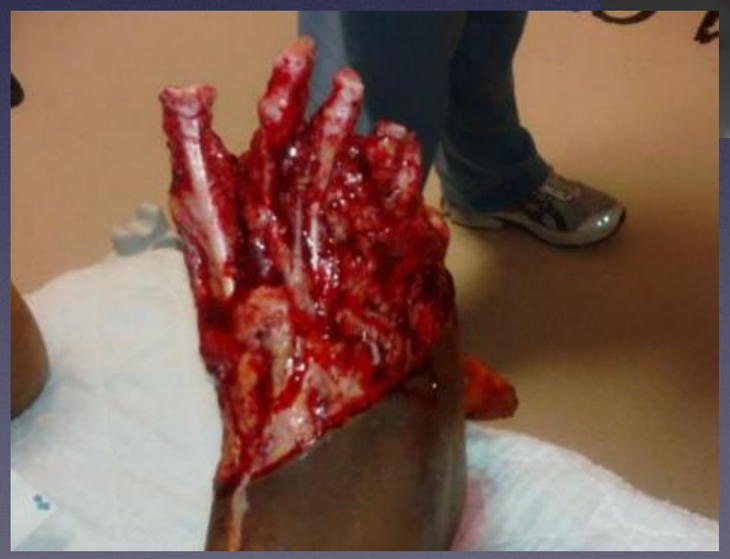
- 70% Chronic Wounds are complicated by Diabetes, Venous Hypertension and Pressure
- Estimated to cost $60 billion annually
- Wound presence and duration is an independent risk factor for infection, hospitalization and amputation; all which drive up cost of care.
- Nearly all chronic wounds have some degree of Cardiovascular disease, Cerebral Vascular disease and Peripheral Vascular disease leading to increased morbidity and mortality.
- Quality of Life?

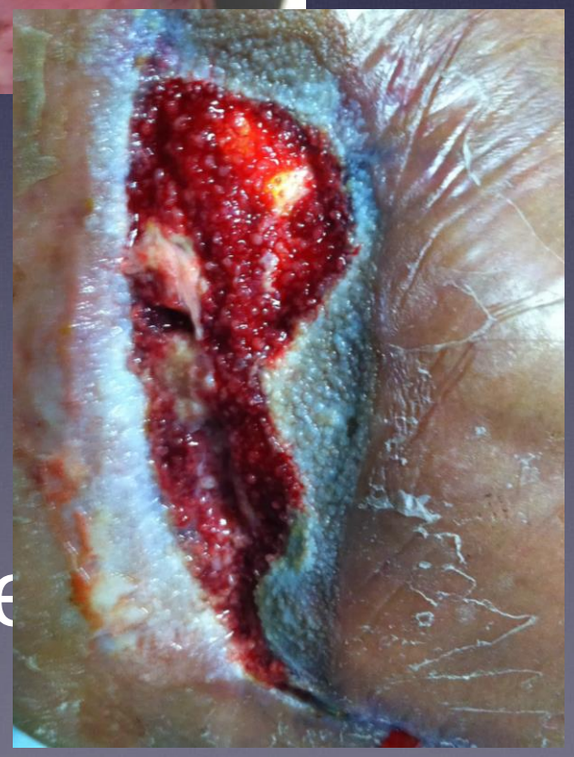
Problematic Wounds











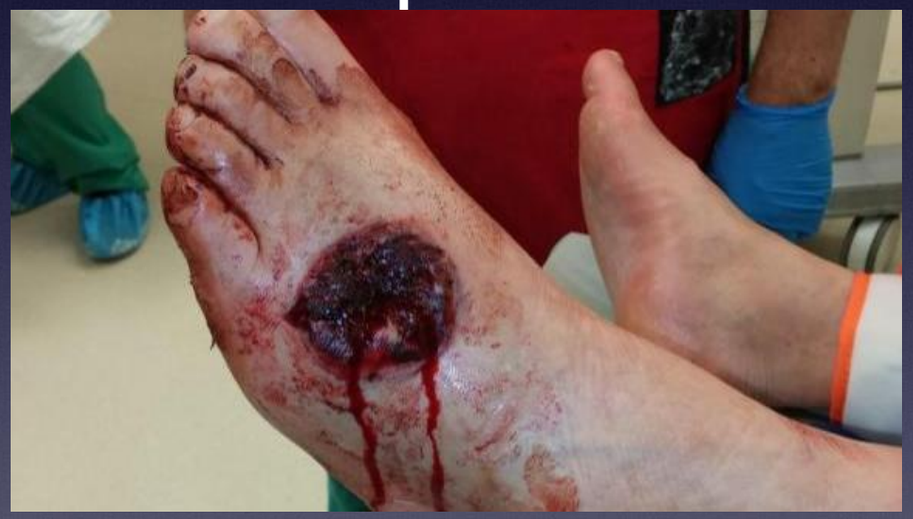
Come In All Different Shapes and Size

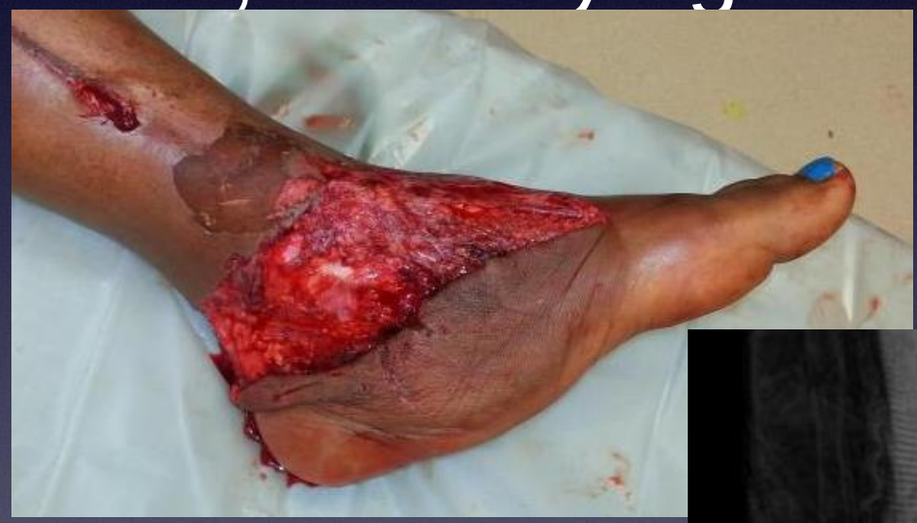
Problematic Wounds

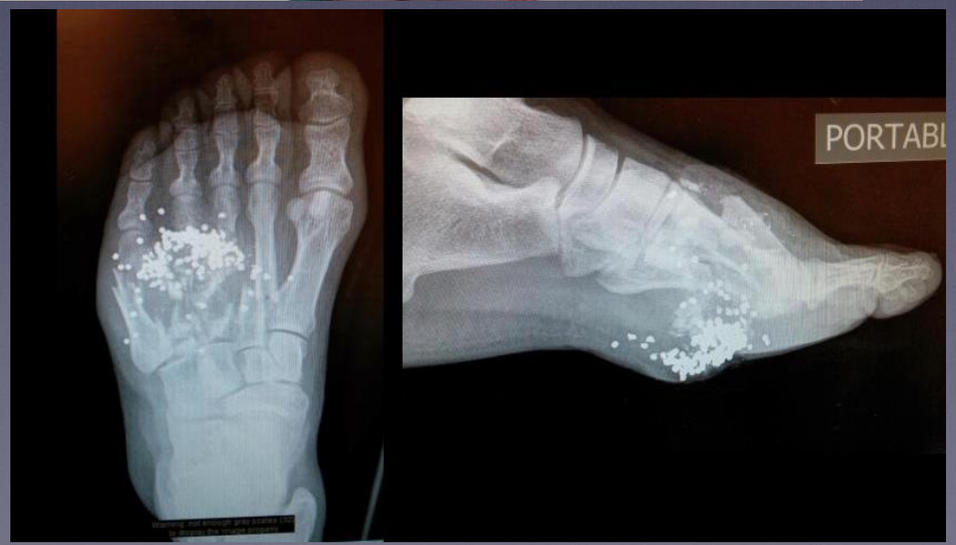
- Not Amenable to Primary Closure
- Healing by secondary intention, minimal progression with conservative treatment.

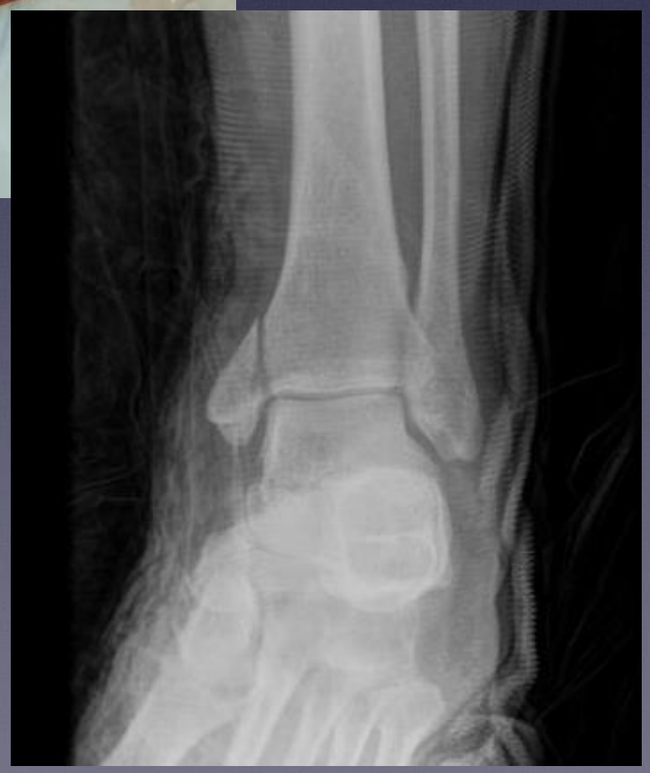
Contributing Factors

- Traumatic Wounds
  - Tissue loss, Crush injury, Contamination Unstable Open Fractures, Underlying Co-



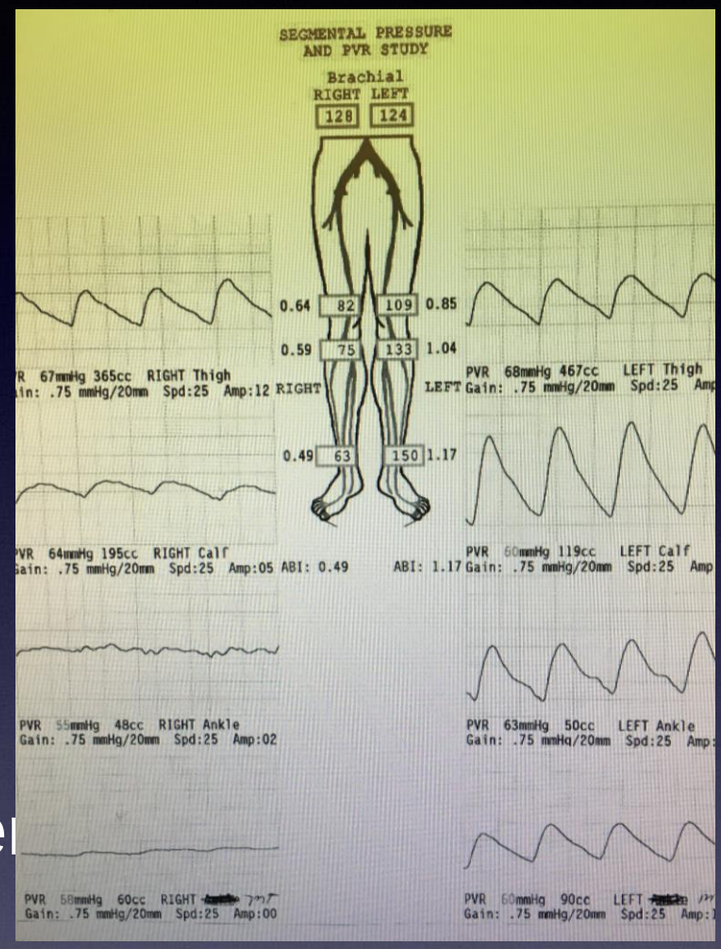






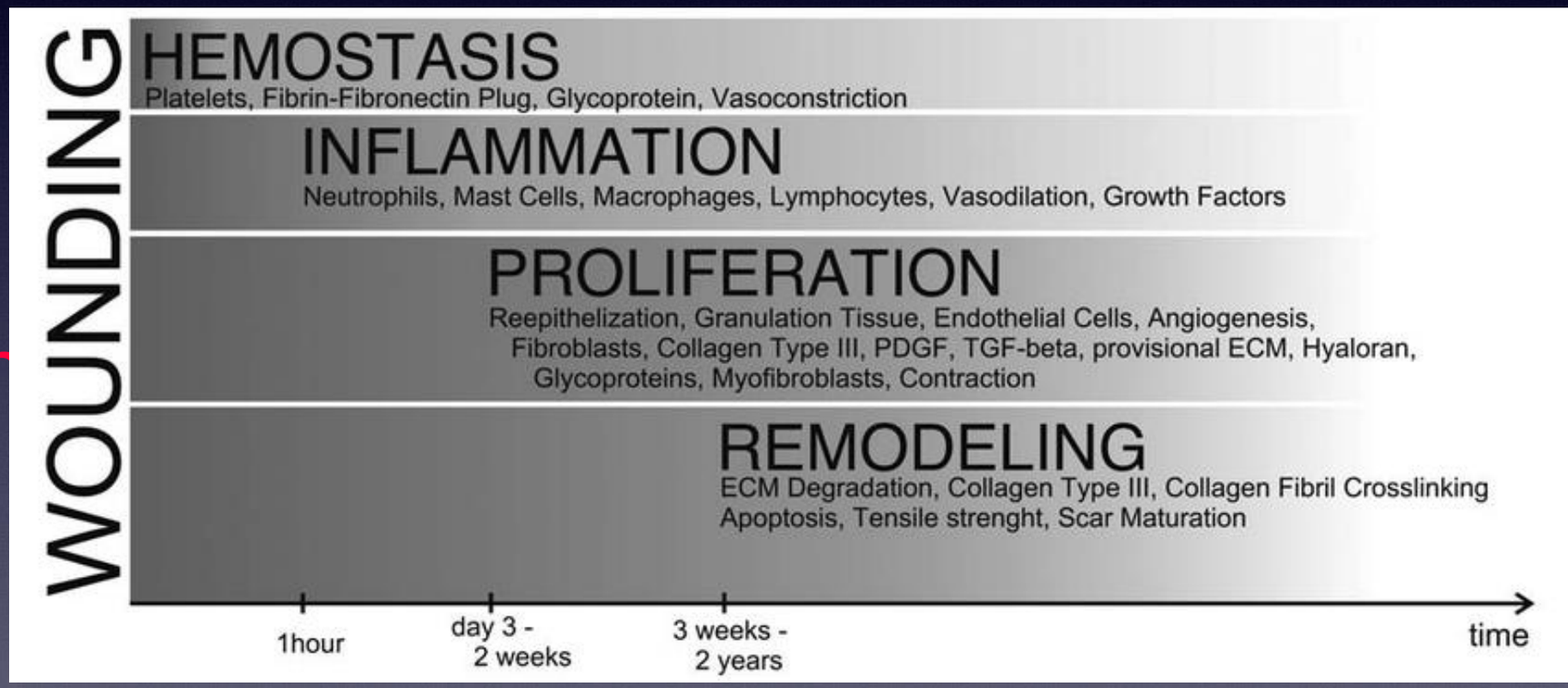
Contributing Factors

- Uncontrolled Diabetes
- Peripheral Neuropathy
- Peripheral Vascular Disease
  - Occlusive Disease, microangiopathic
- Venous Hypertension, Venous Stasis, Lymphade
- Connective Tissue Disorders and inflammatory arthropathies
  - Rheumatoid Arthritis, SLE, Scleroderma,
- Necrotic Tissue or Presence of infection.



Physiologic Wound Healing

- Tissue Injury
- Hemostasis
- Inflammation
- Proliferation
- Remodeling



1. Keloids: Current concepts of pathogenesis https://www.researchgate.net/publication/26702097_Keloids_Current_concepts_of_pathogenesis_Review

Physiologic Wound Healing

- Hemostasis - Initiates 3 Overlapping phases
  - Characterized by Platelet aggregation and degranulation
  - Serotonin released by platelets increases endovascular permeability.
  - Development of fibrin clot.
  - PDGF, TGF-B, FGF, IGF, VEGF, EGF, KGF, CTGF, TNF, IL-1, IL-8,
    - Activate Fibroblasts and stimulate local healing response

Physiologic Wound Healing

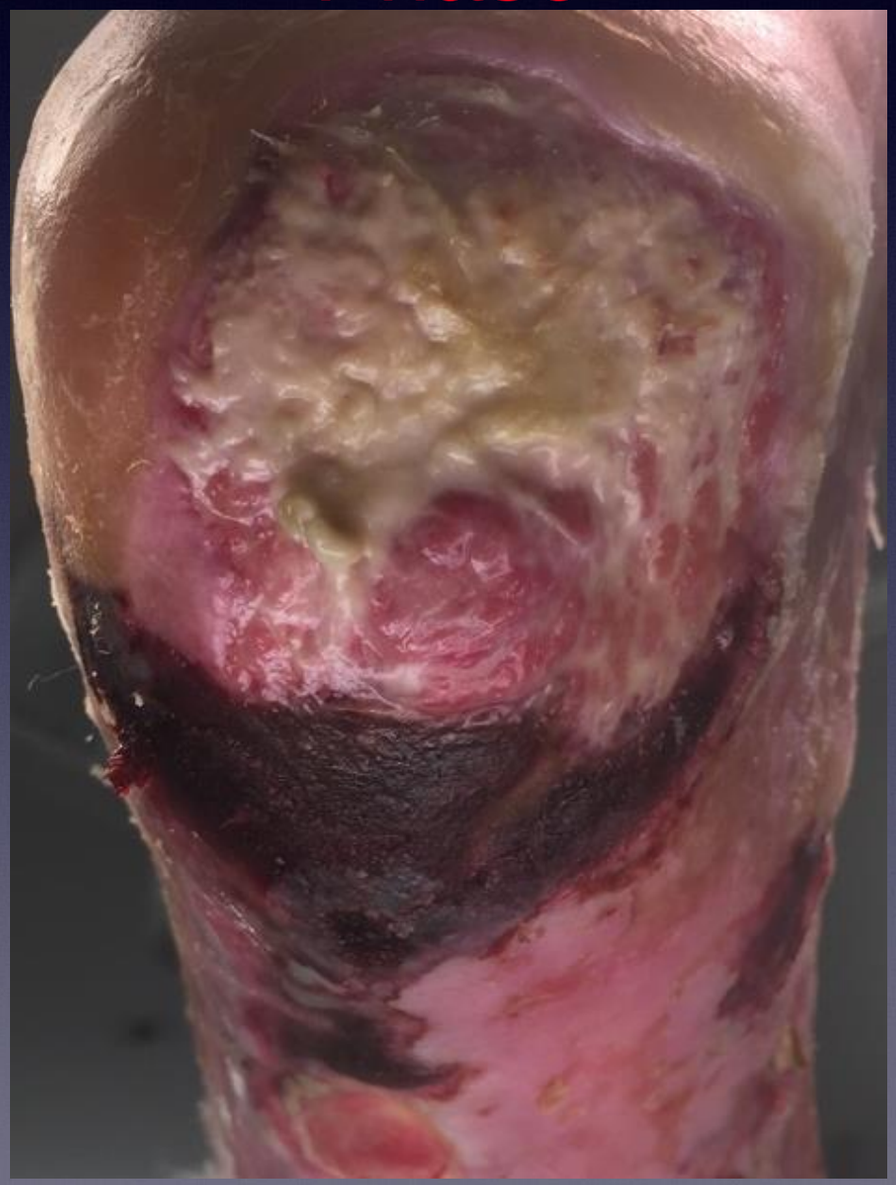
- Inflammatory Phase (Hours to Days)
  - Increase in edema, erythema, warmth and tenderness
  - Release of cytokines and chemokine by platelets
  - Cell Signaling Recruits Leukocytes
  - Leukocyte extravasation - Neutrophil invasion
    - Removing necrotic debride, microbe and deconstruct the fibrin clot.
  - Neutrophils: release pro- and anti- inflammatory factors
    - ROS, GCSF, MCSF
    - VEGF, HGF (angiogenic Growth factors)

Physiologic Wound Healing

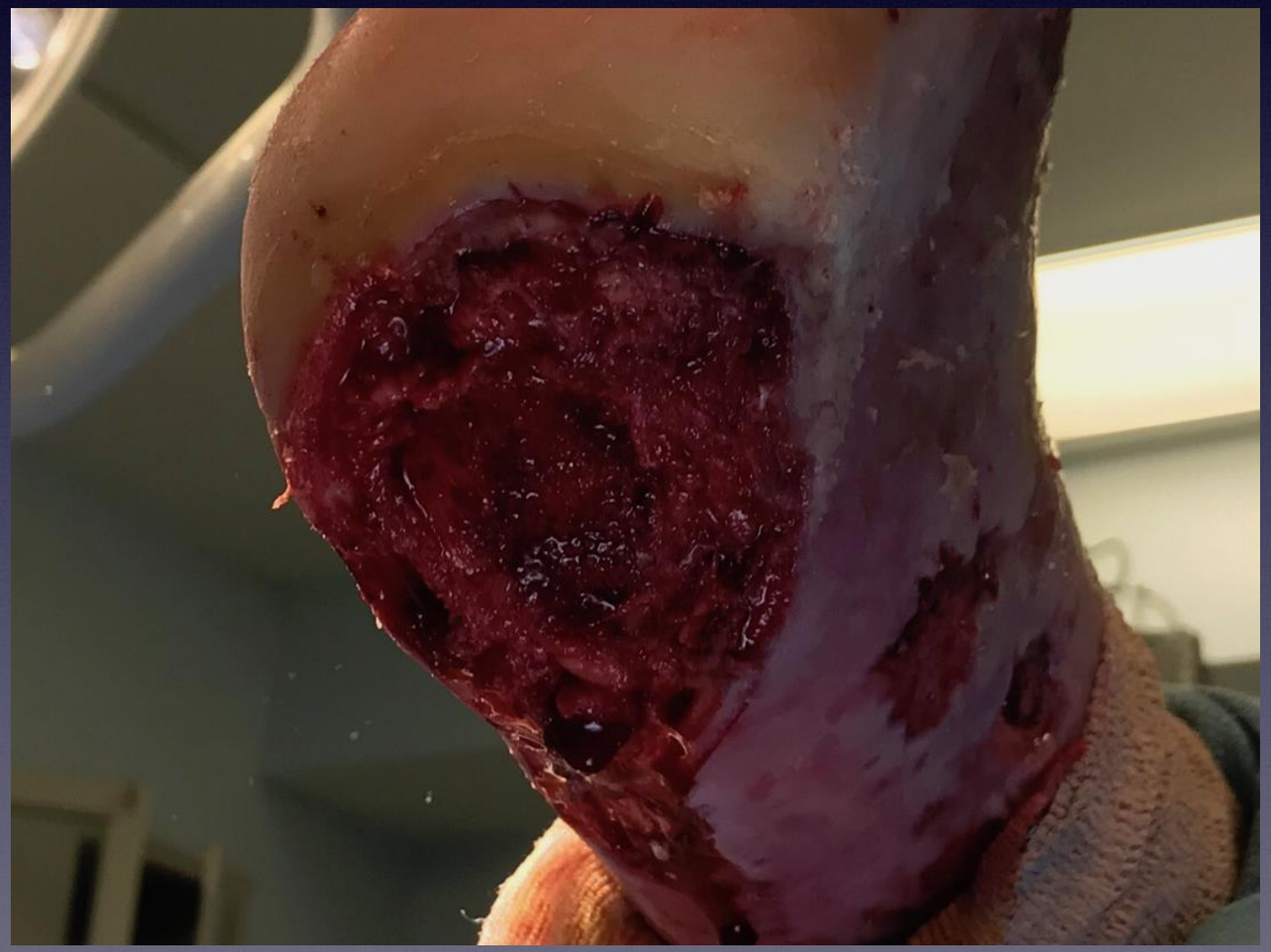
- Inflammatory Stage
  - Macrophages
    - M1 - upregulate MMP's as well engulf pathogens
    - M2 - down regulate MMP's
    - M2>M1 indicate normal wound progression
  - Lymphocytes
    - Balance of Helper T-Cells and Cytotoxic T-Cells
    - Regulate Fibrous Tissue Growth.

Physiologic Wound Healing

Prolonged Inflammatory Phase



Revert Back to Hemostasis



Physiologic Wound Healing

- Proliferative Phase (Days-Weeks)
  - Resident Cells: fibroblasts, keratinocytes, Mesenchymal stem cells
  - Production of Extra cellular matrix
    - Type III Collagen, Hyaluronan, fibronectin
    - Disorganized however necessary for cell signaling
- MMPS's degrading tissue as new is synthesized.
- Active Replication, vertical mitosis
- Granulation, kerotinocyte migration and wound contracture myofibroblasts formation of desmosomal junctions.

Physiologic Wound Healing

- Remodeling Phase (weeks - months)
  - Fibroblasts slow production of ECM
  - Type II Collagen remodeled into Type I
  - Prevention of Scare tissue
  - Mechanically stronger

Needs and Wants

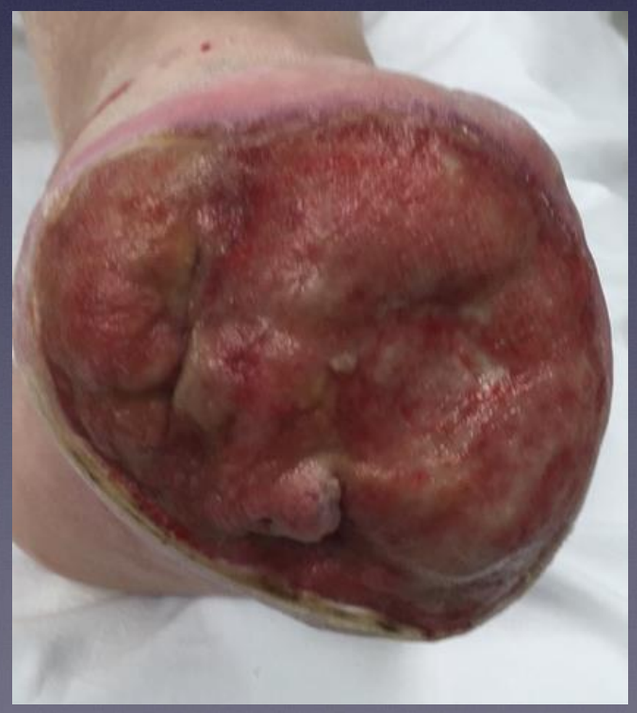
Chronic Wound		**Wound Closure**
Hypoxia and inflammation		**Angiogenesis and decreased inflammation**
Growth Factor and ECM Deficient		**Granulation**
Cell Senescence, Low concentration of MSC		**Chemotaxis and Tissue Repair**

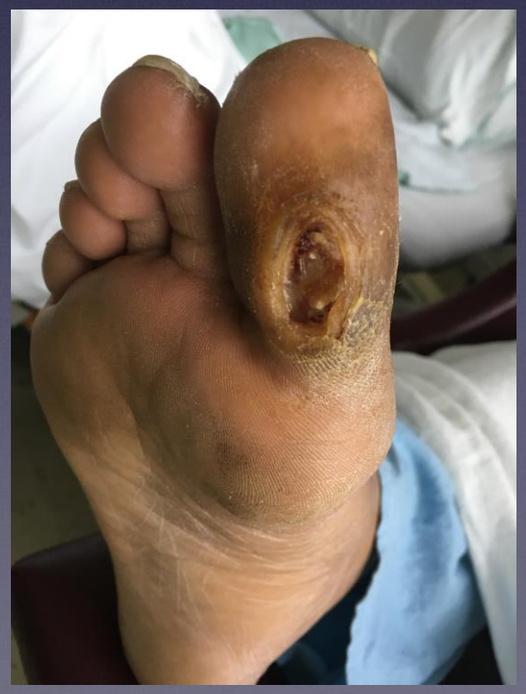
Principles of Standard Wound Care

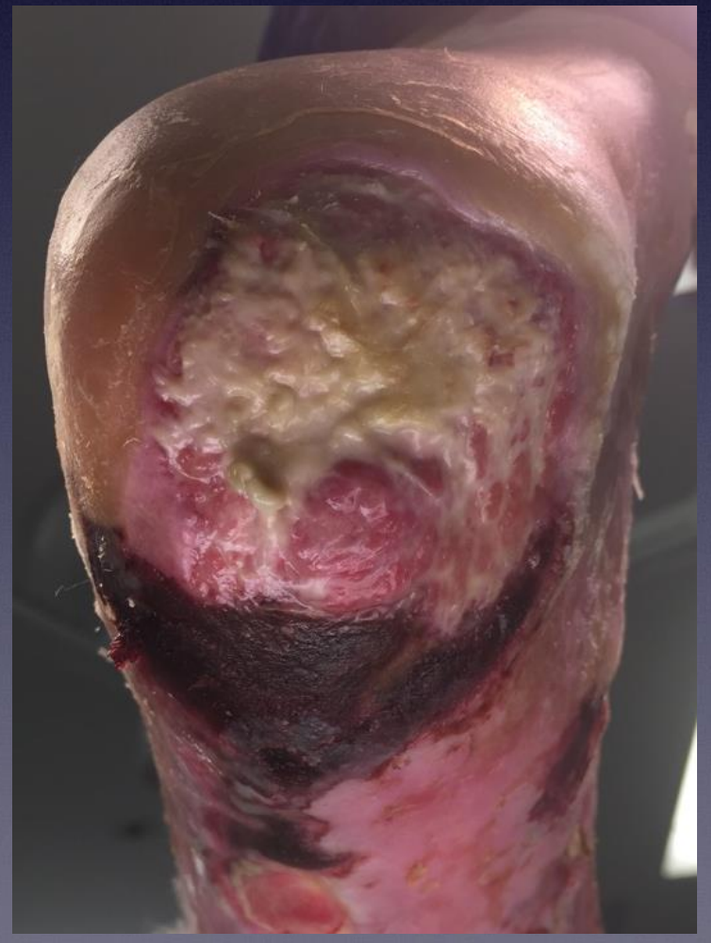
- Adequately perfused
- Metabolic syndrome addressed
- Appropriately offloaded
- Infection Addressed, soft tissue and or bone
- Thorough wound preparation, debridement and removal of all necrotic and non-viable tissue

Exogenous Support

- Mechanical Debridement
- Sharp Excision Debridement
- Enzymatic Debridement







Balancing the Environment

- IF IT IS WET - - DRY IT
- IF IT IS DRY - - WET IT
- Edema, Lymphedema Control
- Compression
- Diuresis

Examine our Needs

- Essential Components for Wound Healing
  - Intrinsic Growth Factors to Promote Tissue Regeneration
  - Extracellular Matrix
  - Active Proliferating Cells, Mesenchymal Stem Cells

Advanced Therapies

- Collagen Substrate Dressing w/; w/o silver
- Bovine Matrices
- Porcine Urinary Bladder
- Cultured Epidermal grafts
- Platelet Rich Plasma
- Recombinant Platelet Derived Growth Factor
- ECM with cultured fibroblasts and/or keratinocytes
- Amniotic Allografts
- NPWT
- HBOT

Brief History

- OB/GYN, Surgery, Neuro surgical and Dental Applications date back to early 20th century.
- 1913 - The Grafting of preserved amniotic membrane to burned and ulcerated surfaces, substituting skin grafts. *Maximiliam Stern, MD*
- 1940 - Plastic Repair of Conjunctival Defects with fetal membranes. *D Roth A MD*

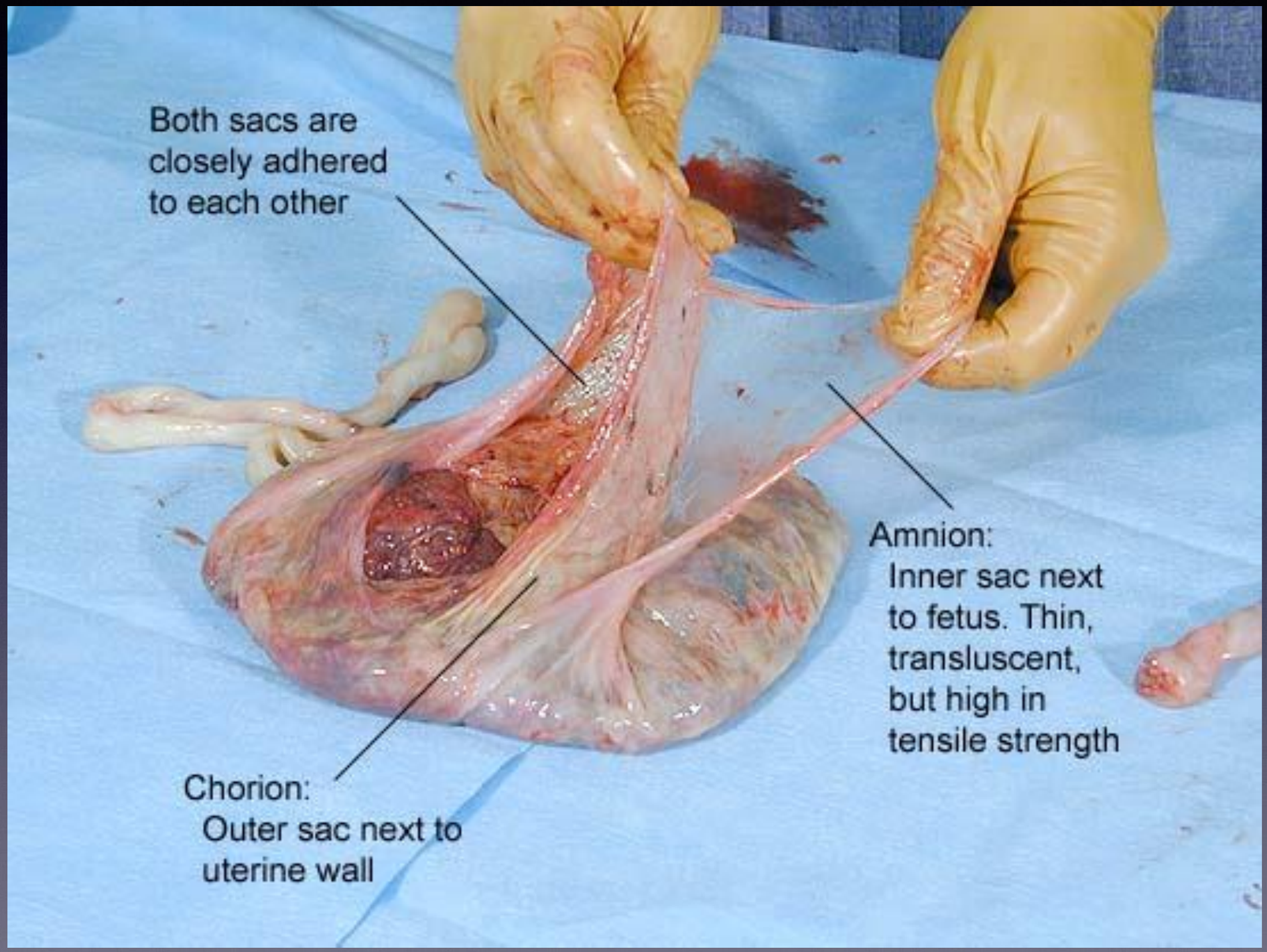
Brief History

- Common uses through the mid 19th century
  - Ophthalmology
  - Plastic Surgery - Burn Wound Care
- Lapse in published research from 1960’ to late 1980’s
  - Preparation and preservation of tissue re-evaluated.

Why Amniotic Membrane?

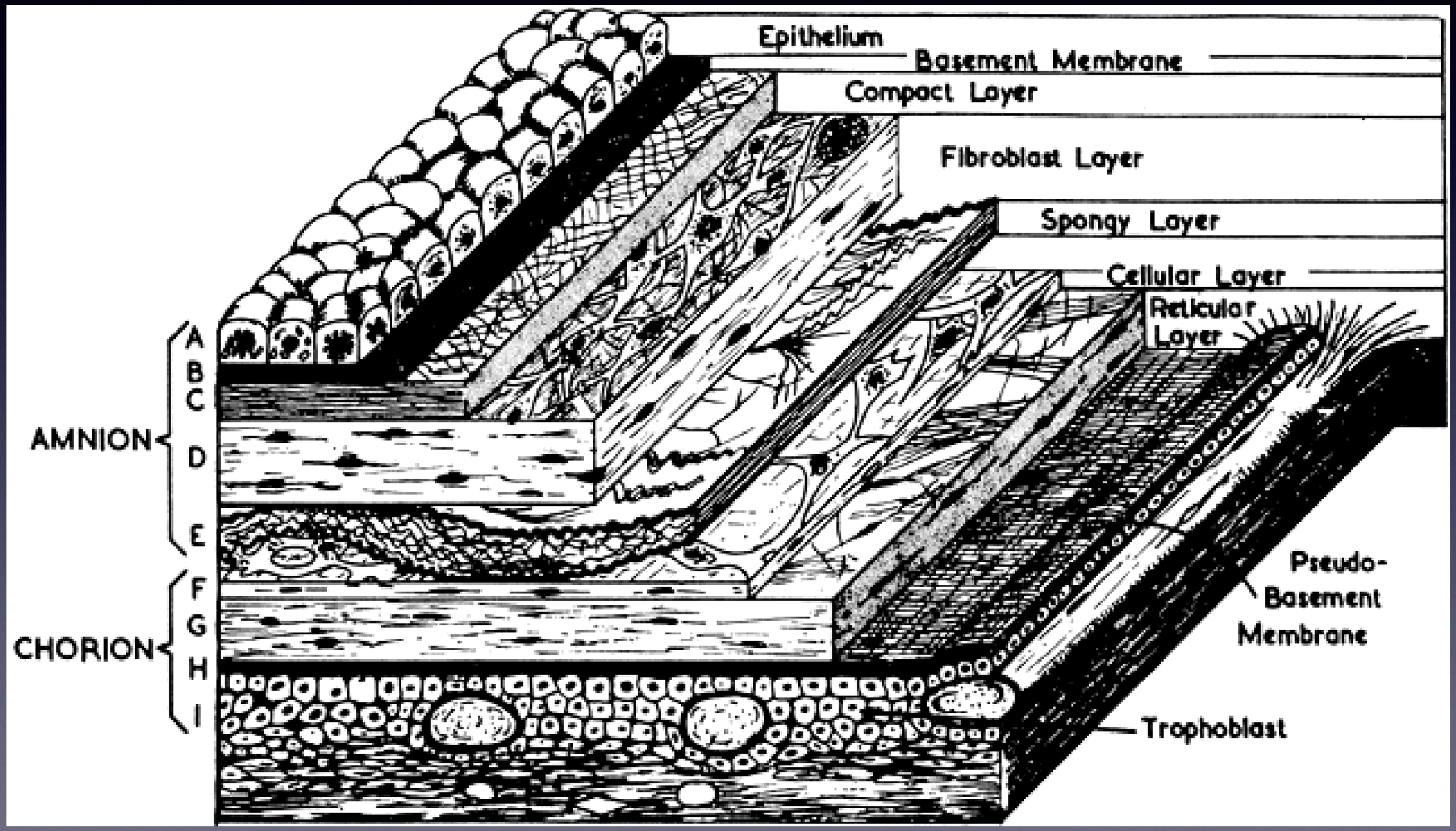
- “There is no harm done should there be no take.” -M Stern
  - No need for razor, dermatome or anesthetic
- Inherent properties including
  - Shiny membrane
  - Mucofibrous base with cuboid epithelium inner layer
  - Islands of stratified epithelium resembling human skin.

Amniotic Membrane

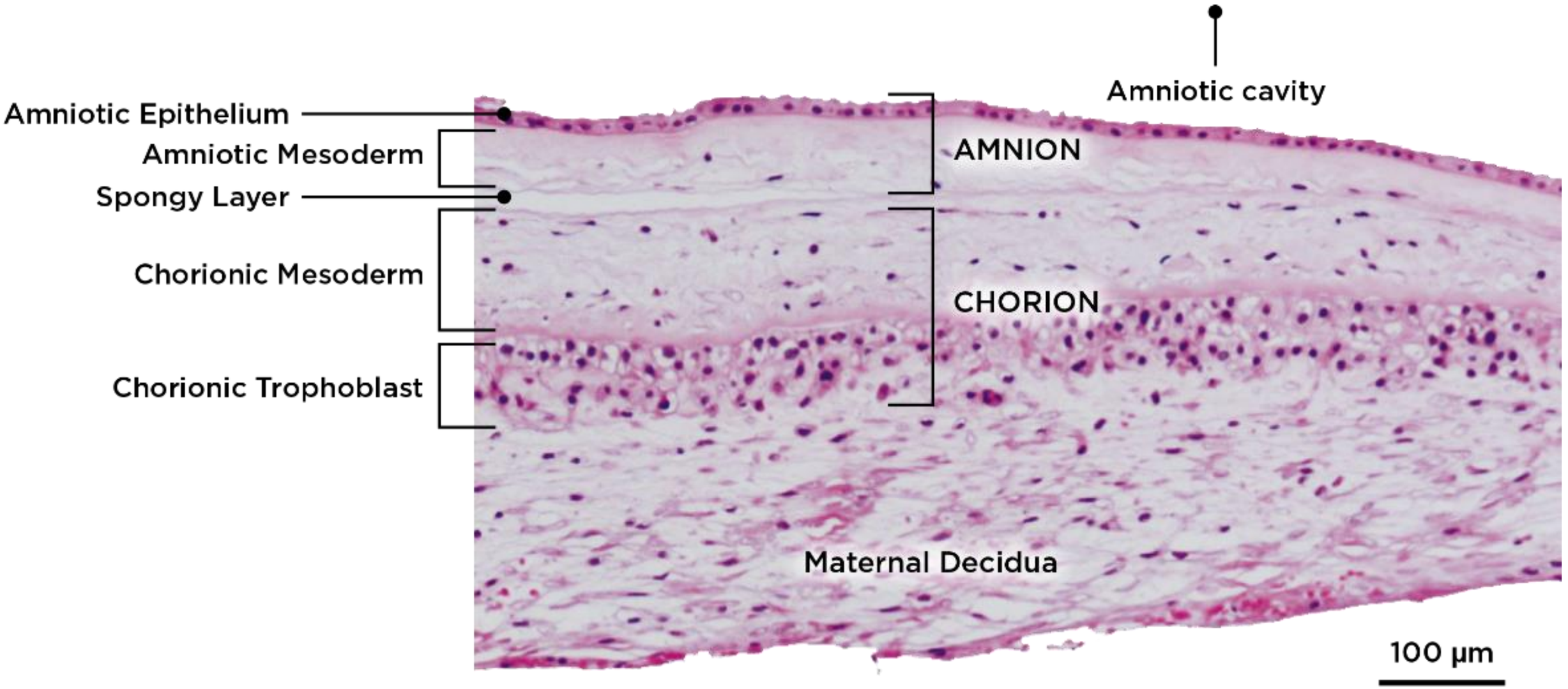


http://library.med.utah.edu/nmw/mod2/Tutorial2/separation.html

Human Amniotic Membrane



Human Amniotic Membrane



3 Major Components of Amniotic Membrane

- Collagen Extra Cellular Matrix
  - Collagens, Type IV, V and VII
  - Elastin
- Structural proteins
  - Fibronectin, proteoglycans, glycosaminoglycans, laminas
  - Important for extracellular transport

3 Major Components of Amniotic Membrane

- Cellular Components
  - Epithelial Stem Cells
  - Neonatal Fibroblasts
  - Mesenchymal Stem Cells
- Essential in coordinated wound healing

3 Major Components of Amniotic Membrane

- Valuable growth factors and proteins
  - TGF-B3, HGF (antiscarring, antiinflammatory)
  - NGAL, Defensins (antimicrobial)
  - PDGF, VEGF, FGF (angiogenic), EGF
  - TIMPS (Down regulate MMPs)
  - Interleukins IL-4, IL-10 (antiimmunogenic)
  - Very low concentration of Leukocyte Antigens
    - Immunologically inert - not foreign to mom or infant

The Science

Chronic Wound	Human Amniotic Graft	Wound Closure
Hypoxia and inflammation	VEGF, PDGF, TGF, HGF, NGAL Defensins	Angiogenesis and decreased inflammation
Growth Factor and ECM Deficient	Collagen, Elastin, Fibrin, Structural Protein	Granulation
Cell Senescence, Low concentration of MSC	Epithelial Cells, Fibroblasts, MSC	Chemotaxis and Tissue Repair

Preservation and Preparation

- Goals
  - Safe and efficacious preparation achieving sterility eliminating risk of disease transmission
  - Prolonging “shelf life” of Amniotic membrane
  - Preserving viability of the 3 major components

Preservation and Preparation

- Dehydration - dHACM
  - allows for prolonged storage and expedited availability.
    - Acts as a stem cell target
- Cryopreservation - hVWM
  - designed to preserve the native components of human amniotic membrane
  - Preserves viable functioning stem cells

The Evidence

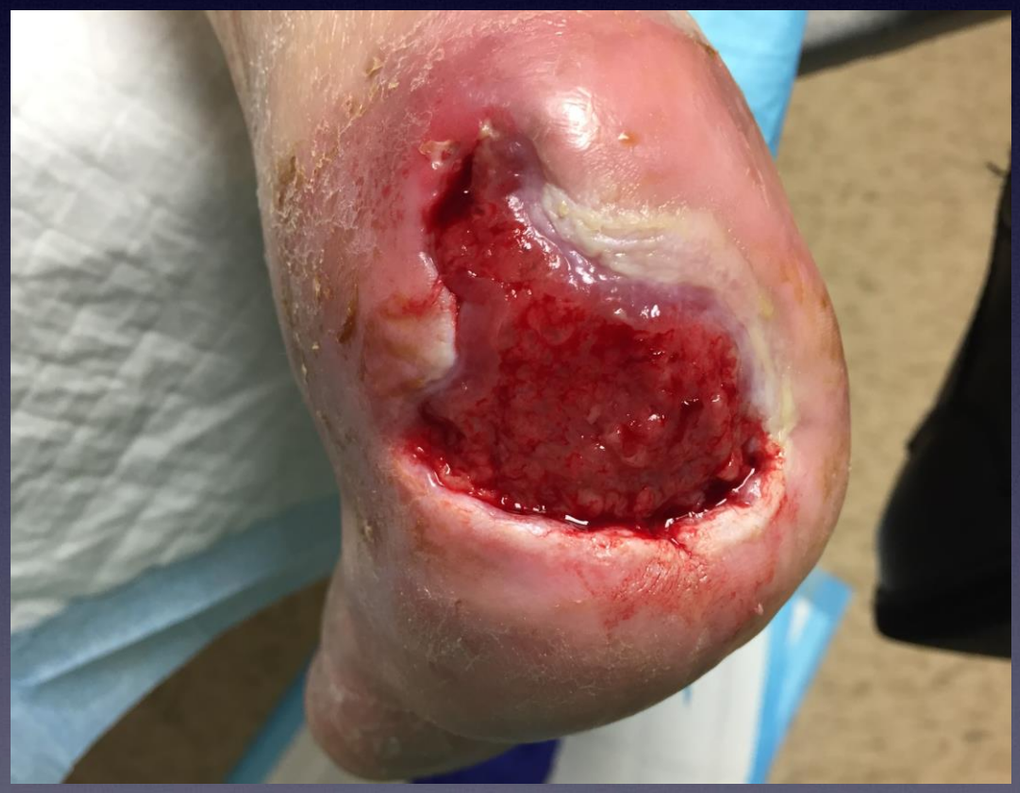
- Lavery, L et al. *Int. Wounds 2014*
- Cryopreservered Amniotic Membrane in the management of chronic DFU's. A Multicenter, double blind RCT
  - Complete Wound Closure 62% vs 21%
  - Time to Closure 42 days vs 7o days
  - Decrease Rate of infection compared to SWC

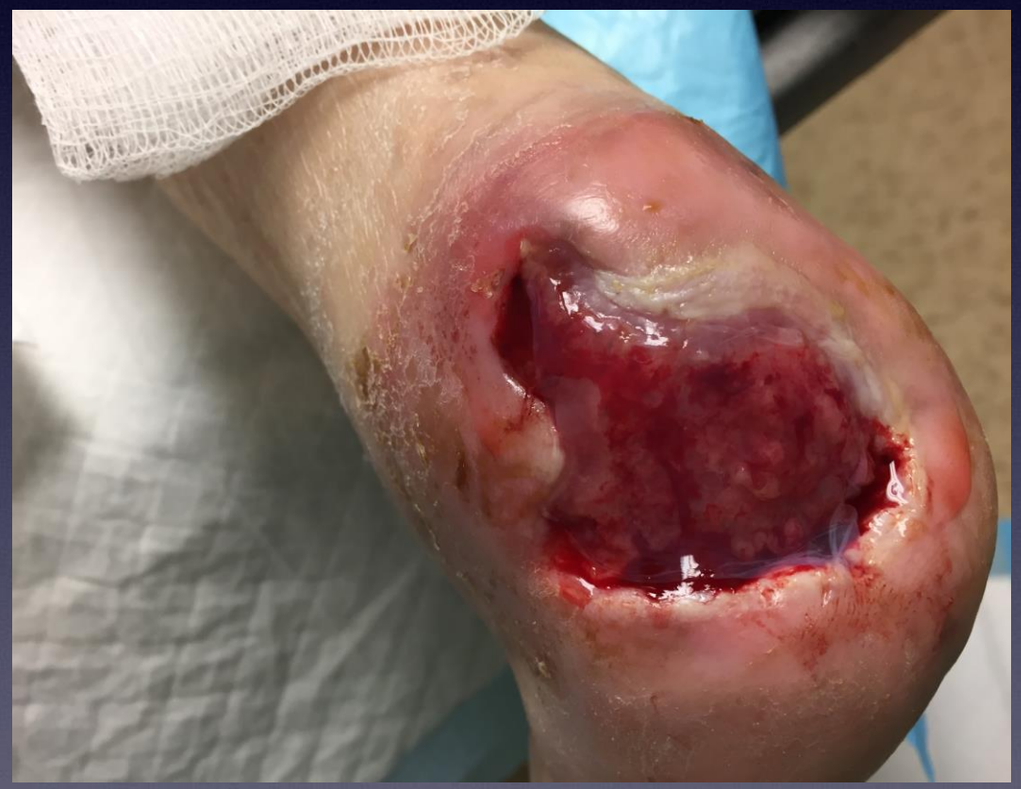
The Evidence

- Zelen, ZM et al. *Int Wounds 2014*
- Dehydrated human amnion/chorion membrane allograft vs SWC for chronic lower extremity diabetic ulerations. Mulicenter RCT
- dHACM groups with 85% and 95% complete closure @ 4 and 6 weeks
- SWC groups with 30% and 35% complete closure @ 4 and 6 weeks

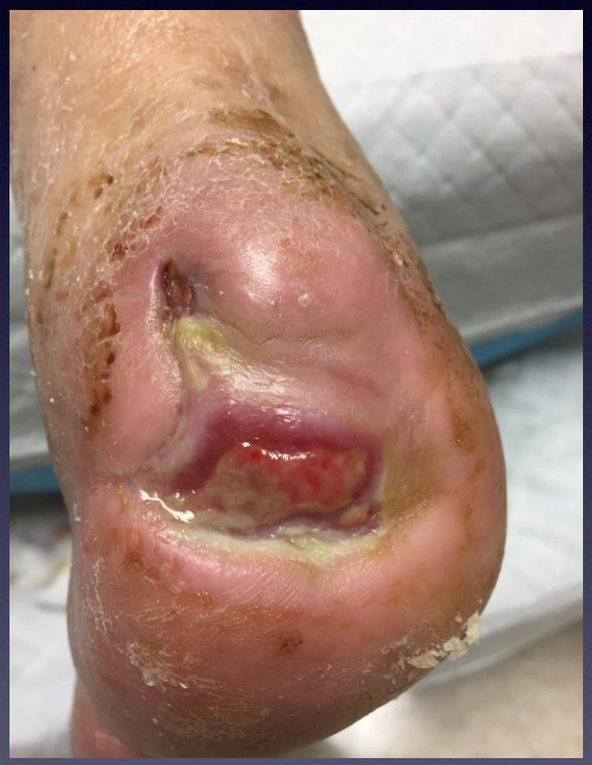
Case #1

- 73 y/o diabetic female s/p charcot reconstruction. Treated with Cryopreserved amniotic membrane





Case #1



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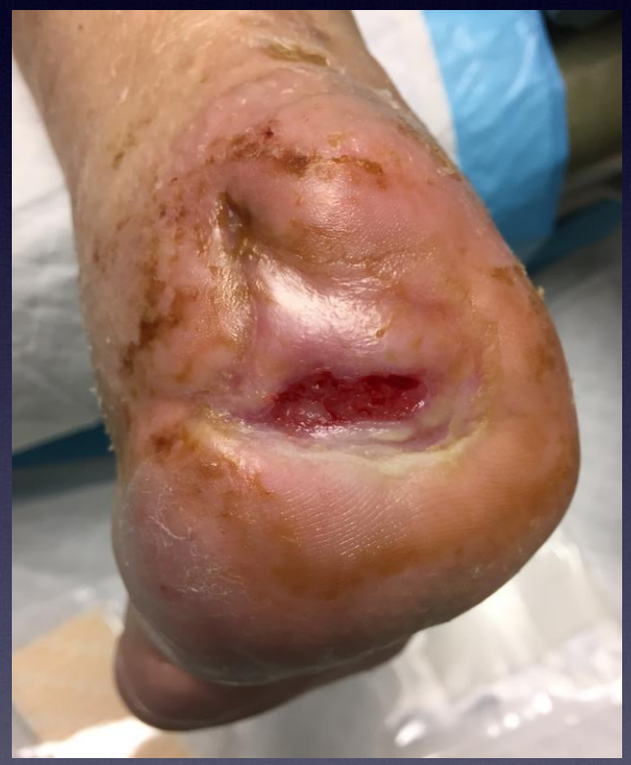

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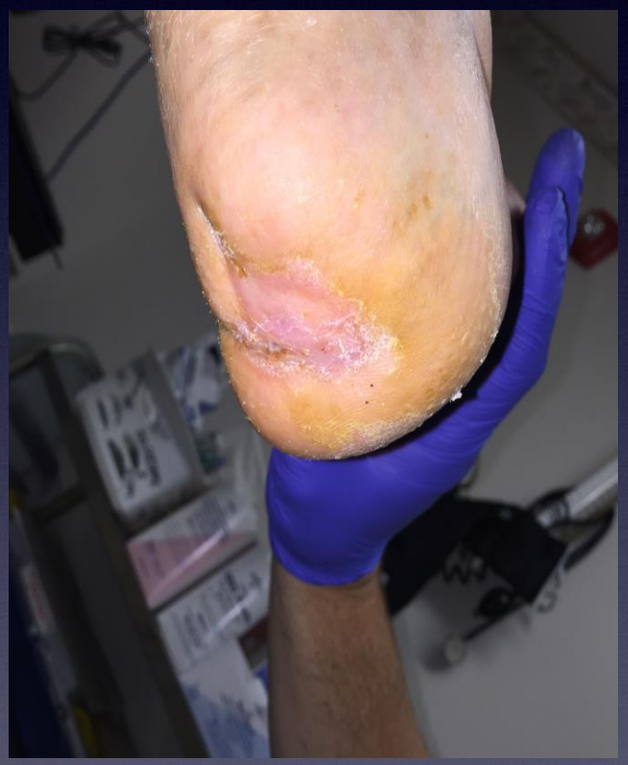
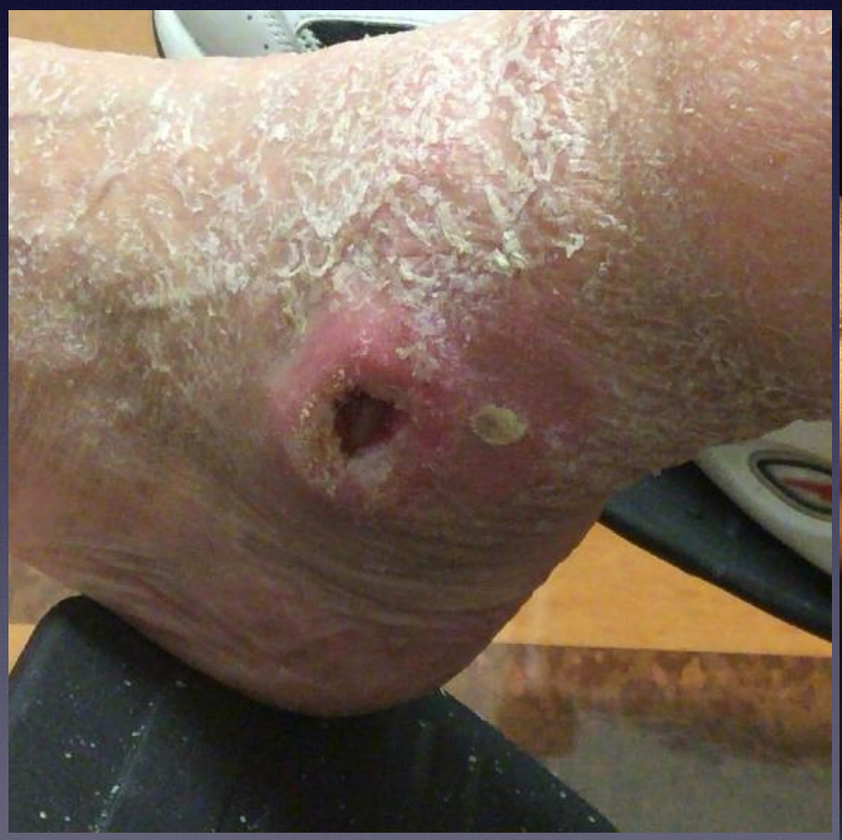
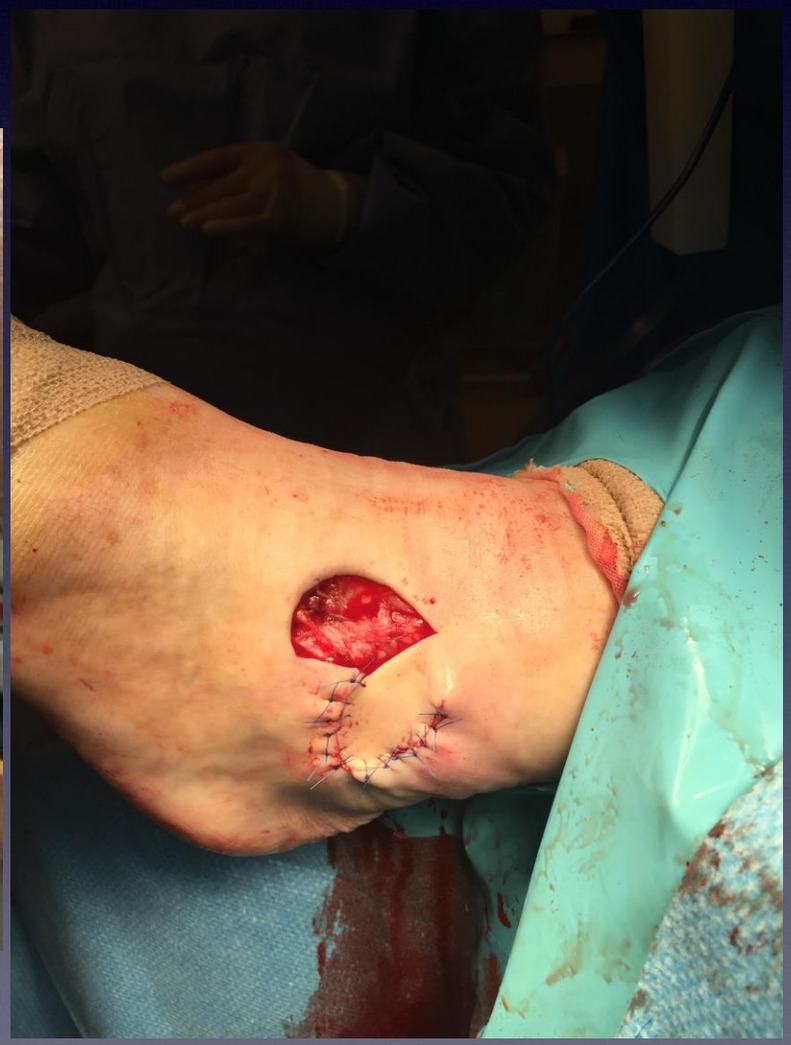


Week 12

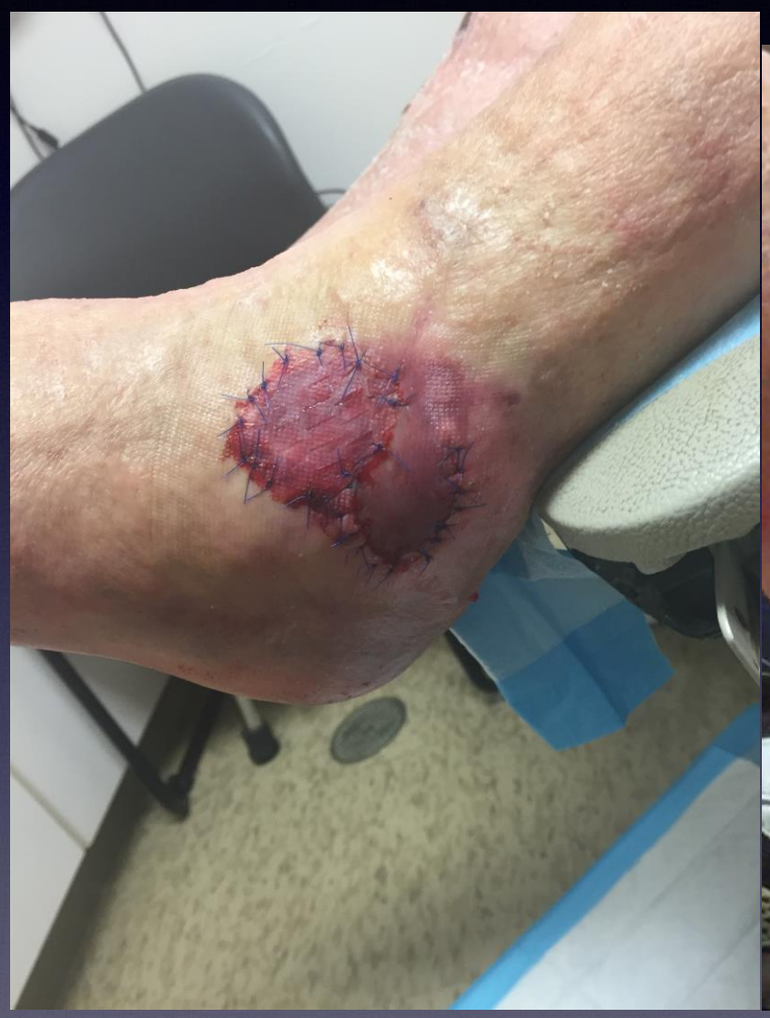
Case #2

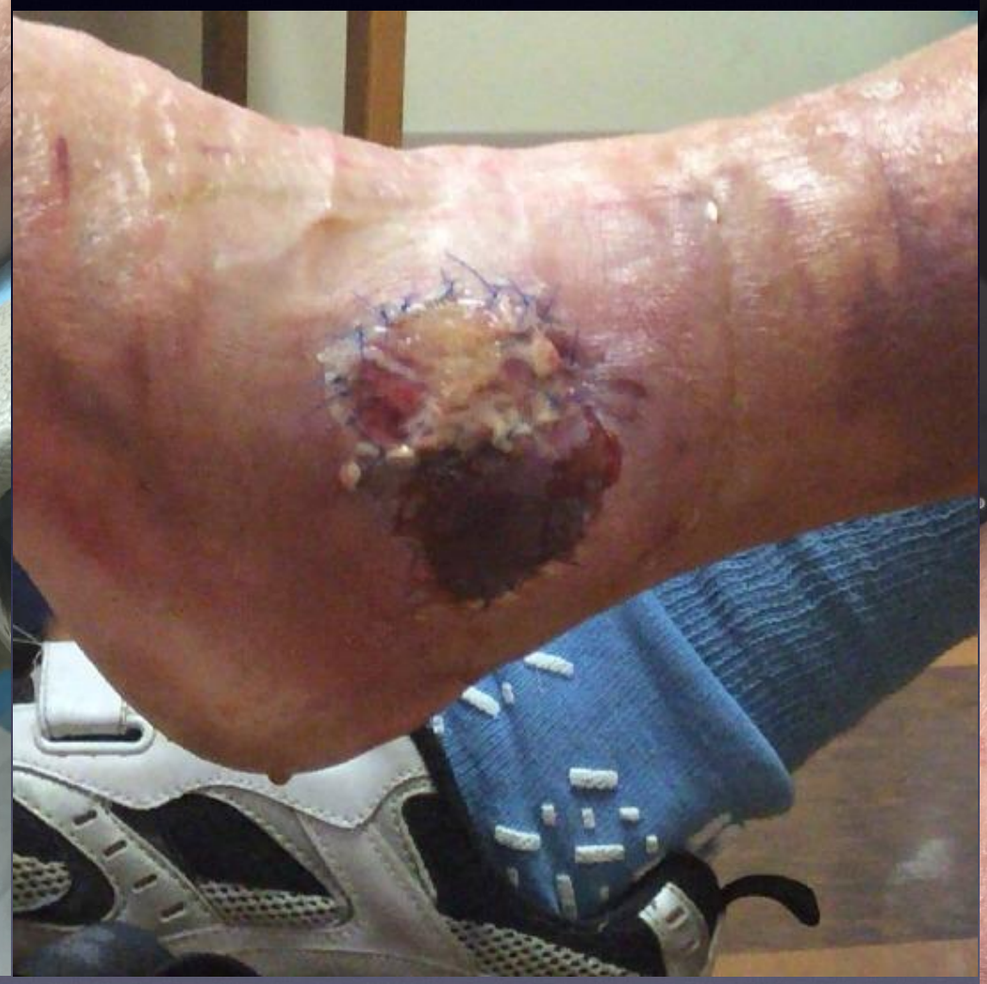
ral vascular disease, s/p stent angio of perineal artery. Non-h

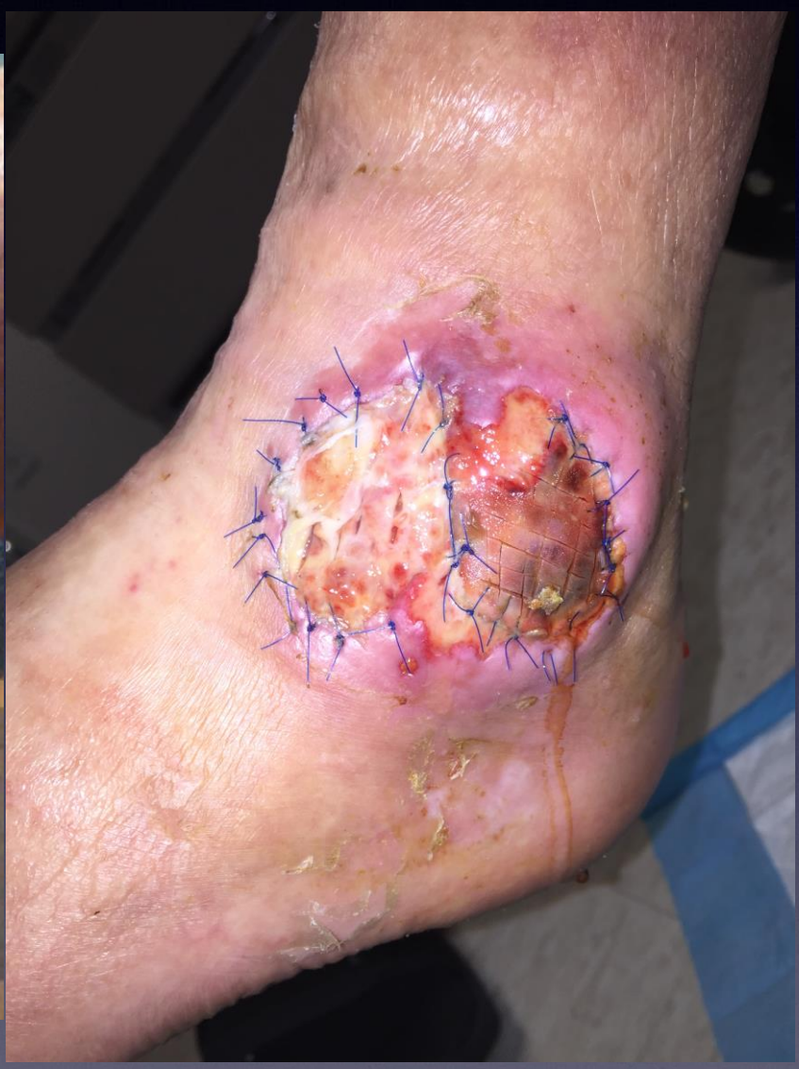




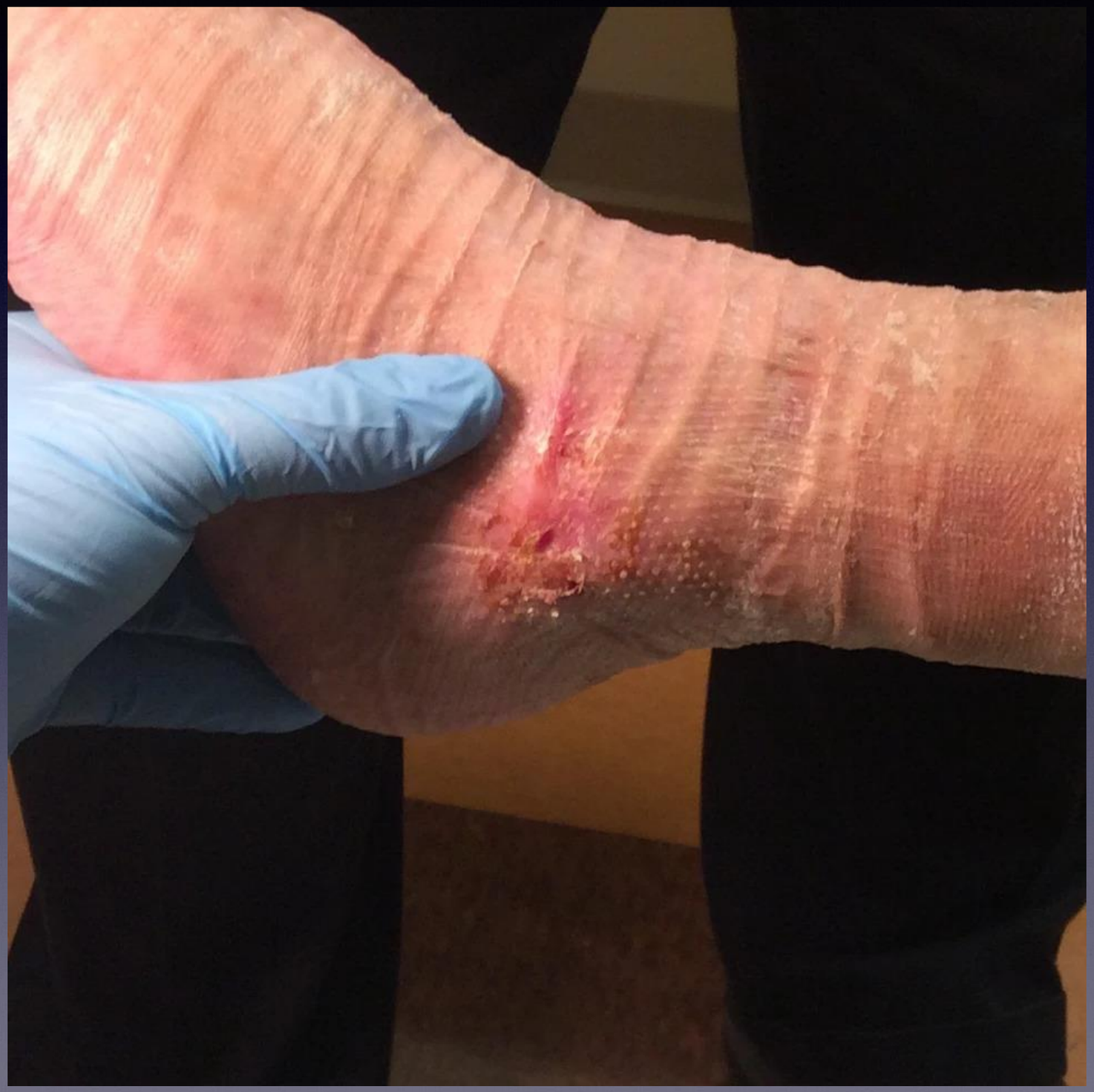
Case #2







Case #2



Summary

- Understanding the Molecular implications of chronic wounds guide treatment and lead to improved outcomes
- Valuable tools present to augment pathologic wound physiology
- Principles of Standard Wound Care Always apply
- Expeditous wound healing improves quality of life

Thank you!

Richard T. Bauer III DPM, AACFAS
Summit Foot and Ankle
1072 Troy-Schenectady Road, Suite 303
Latham, NY 12110
Medical Director, Seton Wound Care Center
rbauer.dpm@gmail.com