Chronic Wounds
are
ALWAYS
Manifestations of Other Systemic Problems

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Manifestations of Other Systemic Problems

- Objectives
  1) List and describe the normal phases of wound healing with clinical correlation
  2) Identify and understand the impact of inherent cellular and biochemical factors involved in normal wound healing
  3) Identify systemic conditions responsible for delay or failure to heal in chronic wounds
Chronic Wounds are always Manifestations of Other Systemic Problems

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The Science of Wound Healing

Three distinct phases:

- Inflammation
- Proliferation
- Maturation

3 (4?) Phases

- Hemostasis: Initiating step
  Foundation for Healing

1. Inflammation: Vasodilitation
   Inc Vasc Perm
2. Proliferation: Substrate Phase
3. Maturation (Remodelling)

Hemostasis: Vasoconstriction
Hemostasis: Day 0

- Blood vessel vasoconstricts
- Coagulation cascade: endothel, platelets
- Clot forms: collagen
  - platelets
  - thrombin
  - fibronectin
  - cytokines
  - GF

Hemostasis: Clot Forms

- **Platelets activate coag cascade.**
  Fibrin clot becomes scaffold for invading cells, eg PMNs, monos, fibroblasts, endo cells.

- **Concentrates cytokines and GF**

  Initiate inflammatory response

Stage 1: Inflammation: ~Day 0-6

- Chemotaxis & Activation
  1. Neutrophil response
  2. Inflamm mediators accumulate
  3. Prostaglandins are elaborated
  4. Blood vessels vasodilate
  5. Platelets release IL-1, TNF-α, TGF-β, PF-4. PMNs elaborate proteases and MMPs to form rad to kill bacti and clear matrix

Phagocytosis: Neutrophils

- PMNs respond to bacterial chemotaxins.
- PMNs Engulf microbes phagocytosis results.
- Lysosomes destroy & neutrophil will die.

www.jdaross.cwc.net/nonspecific_cellular_defence.htm
PMNs squeeze through the capillary walls and kill the invaders (e.g., bacteria) by phagocytosis.
T lymphocyte

- Specialized white blood cells
  1. Identify invading organisms
  2. Destroy invading organisms
  3. Others regulate immune system

NIBSC/Science Source/Photo Researchers, Inc.
Inflammation: Monocytes to Macs

48-96 hours post injury

Activated Macrophages transition wound to proliferative phase

↓

Synthesize

VEGF, FGF, TNF-α, (angiogenesis)

and

TGF, EGF, PDGF (fibroplasia)
Macrophages

- **Macrophages**: large phagocytes
  - Wander through the body
  - Consuming foreign particles
    - eg: dust, yeast, bacteria.
    - Even asbestos particles.

Mac Engulfing Bacterium

Dennis Kunkel/CNRI/Phototake NYC
Macrophages and Staph Aureus

- **Macrophages release**
  Chemoattractants
  (PDGF, TNF-α, IL-6, G-CSF, GM-CSF)

  to recruit more macs and fibroblasts.

- **iNOS is activated** by inc conc of IL-1 and TNF-α, resulting in NO being synthesized. NO kills pathogens, eg. s. aureus.
Macrophage and Candida

Mac uses internal cytoskeleton to envelop C. albicans cells
Kills yeast cells by "Oxidative Burst"
Stage 2: Proliferation ~Day 7-21

- Activated macrophages transitions to prolif phase
  Mediates angiogenesis by synthesizing VEGF, FGF, TNF-α,
  Mediates fibroplasia by synth: TGF-β, EGF, PDGF, IL-1, TNF-α

- PMNs enter wound: clean up
- Fibroblasts: syn coll & prolif
- Endothelials: capillary buds


www.amplab.de/3D-Images/angiogenesis
Endothelial cells/angiogenesis

- **Endothelial cells are unique:**
  form new capillaries: (angiogenesis).

- **Angiogenesis is regulated** by coop.
  between endothelial & other cells
  1) monos
  2) macros
  3) fibros
  4) pericytes
  5) cytokines (VEGF, integrins).

Proliferation: Fibroblasts

- Fibroblasts release IFN-\(\gamma\), causing monos to transform to MACs.

- Fibroblasts synthesize proteoglycans & fibronectin

Provisional matrix
(Collagen type III first, then I)
Fibroblasts and collagen

- **Fibroblasts** synthesize collagen and transform into myofibroblasts (wound cont)

- **Collagen** forms and provides structure and strength for a new outer layer of skin.

- **Fibroblasts** proliferate
**Stage 3: Maturation (Remodelling)**

- Alignment changes from random to organized
- Matrix deposition problems (disease, diet) result: wound strength is compromised.

Fibroblast in a network of collagen fibers

[Image: dba.med.sc.edu/PPT/Connective/tissue/images]
Alignment changes from random to organized

[Image of a section of tissue with labels for Collagen Fibers and Elastin]

http://www.netwellness.org/default.cfm
Blood: Essential for Wound Healing

- Blood supply: Vessels, Cells, Plasma
  Blood: only fluid tissue in the body.
- Transportation: del O₂ and nutrients
  return waste and CO₂
- Distribution of: nearly everything
- Protection with: clot formation
  prevention of infection
Oxygen and wound healing

- Wounds do not heal in tissue that does not bleed.

- **Blood**: Main body temp, pH, carries O$_2$

- **O$_2$**: helps produce granulation tissue ensures resistance against infection effects fibroblasts & collagen prod

World J Surg. 2004 Oct;28(10):1068-9; 9; Dennis Kunkle, Univ of Hawaii

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Oxygen and wound healing

- Low oxygen concentration can arrest the process of wound healing.

Oxygen and wound healing

- Sickle cell anemia: failure to deliver O2
Nutrition and Wound Healing

- Poor nutrition can arrest the wound healing process.

- Main component of the nutrition is O₂.

- Deficiencies of:
  1. Vitamin A
  2. Vitamin C
  3. Zinc

  Impair normal wound healing mechanisms.


Vitamin A

■ Benefits wound healing by:

1. Enhancing early inflam. phase
2. Increasing macs at wound site.
3. May improve stimulation of the immune response

Vitamin C

Benefits wound healing by:

1. Enhancing neutrophil prod.
2. Increasing angiogenesis
3. Acts as an antioxidant
4. Helps in collagen prod

Zinc

- Benefits wound healing by:
  1. Assisting with cell division and protein synthesis
  2. Assisting body’s ability to synthesize protein and collagen

Protein Malnutrition

- **Protein:** needed for tissue regeneration and repair.

- **Protein mal:** impairs normal wound-healing mechanisms.

- **Can delay wound healing by exacerbating the inflammatory phase of the wound.**

Malnutrition and Lymphocytes

- Lymphocyte counts are indicators of malnourishment.

- A count of less than 800 indicates severe malnourishment.

Case: Failure to heal --- Gangrene
Failure to heal---Why??

- Diabetes: BS, Neuro, Vasc
- Diabetes: Immunopathy
- Tobacco Use: O$_2$ Delivery
- Hx of Cancer
- Over 70 years of age
- Nutrition: Generally poor
  - Etoh use
  - No DM diet
PE: Vascular Compromise

Red blood cells contain several hundred hemoglobin molecules which transport oxygen.

Hemoglobin molecule

Oxygen binds to heme on the hemoglobin molecule.
Non Invasive Vascular Studies

**Doppler**

- Right Femoral: 196 - Brachial - 190
- Right Sup. Femoral: Gain: 68%
- Right Popliteal: Gain: 68%
- Right Post. Tibial: Gain: 68%
- Right Dors. Pedis: Gain: 68%
- Right Digit: Gain: 68%

- Left Femoral: Gain: 68%
- Left Sup. Femoral: Gain: 68%
- Left Popliteal: Gain: 68%
- Left Post. Tibial: Gain: 68%
- Left Dors. Pedis: Gain: 68%
- Left Digit: Gain: 68%

**PVR**

- Right High Thigh: 40 MM Gain: 20%
- Right Low Thigh: 17 MM Gain: 20%
- Right Calf: 255 - 77 - 112
- Right Ankle: 117 - 131
- Right Metatarsal: 85 PT DP - 110

- Left High Thigh: 43 MM Gain: 20%
- Left Low Thigh: 40 MM Gain: 20%
- Left Calf: 188 - 77 - 112
- Left Ankle: 117 - 131
- Left Metatarsal: 85 PT DP - 110
Doppler

Gain: 68%

R) Post. Tibial

Gain: 68%

R) Dors. Pedis

Gain: 68%

R) Digit

Gain: 68%

L) Post. Tibial

Gain: 68%

L) Dors. Pedis

Gain: 68%

L) Digit

Gain: 68%

0.43 - Ankle/Brachial - 0.56 Index
PVR
Angiograms
Successful healing---How??

- Dm: Hyperglycemia
  Neuropathy
  Vasculopathy
  Immunopathy
- Tob Use: O₂ Delivery
- Hx of Cancer
- Over 70 years of age
- Nut: Poor: Etot use
  No DM diet
Successful healing---How??

- **Dm: Hyperglycemia**
  - Neuropathy
  - Vasculopathy
  - Immunopathy
- **Tob Use: O₂ Delivery**
- **Hx of Cancer**
- **Over 70 years of age**
- **Nut: Poor: Etoh use**
  - : No DM diet

- **DM: BS:Tight glyc cont.**
  - Neuro: Protection
  - Vasc: Bypass Sx
  - Immunopathy: Abx
- **Tob Use: No smoking!!**
- **Medically Optomize**
- **Recognize**
- **Improve Nut: No etoh**
  - : DM diet
Femoral-Above Knee/ Below Knee-Dorsalis Pedis RSVB Graft
**Dx:** Chronic ulcer, severe pvd, myonecrosis, gangrene  
**Tx:** Revascularization, debridement, forefoot amp,dpc
From this... To this...
Wound Healing: Phase 1

Inflammatory Phase

Phase 1: Inflammatory Phase  First few days post inj/sx

Inflammatory cells, macrophages, platelets, pmns
Hemostasis

**KEY Cells:** Endothelial cells, Platelets

**KEY Cellular Components:** Factor XIII, GF, Mediators, cytokines

**KEY Elements:** Vasoconstriction, Clot forms, platelets release GF, cytokines, attract PMNs and fibroblasts

Inflammation

<table>
<thead>
<tr>
<th>KEY Cells:</th>
<th>KEY Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cells</td>
<td>Hypoxia, lactate, acidity</td>
</tr>
<tr>
<td>Macrophages, PMNs</td>
<td>Monos become macrophages</td>
</tr>
<tr>
<td>Platelets</td>
<td>FGF-2</td>
</tr>
<tr>
<td></td>
<td>PDGF-BB</td>
</tr>
<tr>
<td><strong>KEY Cellular Components</strong></td>
<td>VEGF</td>
</tr>
<tr>
<td></td>
<td>MMPs</td>
</tr>
<tr>
<td>Integrins</td>
<td>Phagocytosis</td>
</tr>
</tbody>
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Proliferation/Angiogenesis

**KEY Cells**
- Endothelial cells
- Macrophages

**KEY Cellular Components**
- Integrins

**KEY Elements**
- Hypoxia, lactate, acidity
- FGF-2
- VEGF
- PDGF-BB
- MMPs

**Proliferation/Granulation**

**KEY Cells**
- Endothelial cells
- Macrophages
- Fibroblasts

**KEY Cellular Components**
- Integrins

**KEY Elements**
- Hypoxia, lactate acidity
- FGF-2
- VEGF
- PDGF-BB
- MMPs

How Do Growth Factors Work?

Different cells secrete different growth factors & can express several different receptors.

How Do Growth Factors Work?
# Proliferation/Epithelialization

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<tr>
<td>• Epithelial cells</td>
<td>• EGF</td>
</tr>
<tr>
<td></td>
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# Proliferation/Epithelialization

**KEY Cells**
- Epithelial cells
- Keratinocytes
- Fibroblasts

**KEY Elements**
- MMPs
- EGF
- TGF-α
- IL-6

**KEY Cellular components**
- KGF-1 and 2

Platelets, Macros initiate

---

Proliferation/Epithelialization
Phase 3: Remodeling: Scar gains tensile strength, collagen stops

- **Purpose**
  - Re-establish tissue tensile strength

- **Duration**
  - Weeks to months to years

- **Characteristics**
  - Increased collagen crosslinking
  - Increased collagen fiber orientation
  - Apoptosis
  - Decreased cellularity

Remodeling Phase day 21—...
4 years post amp
Summary

Evidence-based Practice in Wound Care

Case Western Reserve University School of Medicine

Chronic Wounds are ALWAYS Manifestations of Other Systemic Problems
Summary: Impaired Wound Healing

Affected by both internal and external factors.

- Insufficient Bld and O2, malnutrition, infection
- Diseases: Immune deficiency: diabetes, HIV
- Tx: meds, radiation, chemotherapy, steroids
- Physiological: Edema, PVD, pH imbalances

Specific Parameters

- **Diab Neuropathy:** Ulcer dev when not offloaded
  - (Focal ischemia, hemorrhage, necro, perforation)

- **Diab Immunopathy:** Disorders of leukocytes
  - (quantity, functions)

- **Diab Vasculopathy:** Failure to deliver blood & O₂
  - (!RBC, PMNs, monos, fibros, endos Platlets, O₂)

- **Vasc disease----clot:** Ca++, Factor XIII deficiency
  - (fail to vasoconstrict Fibrin clot fails, inad scaffold)
Defects of Leukocytes: Function

- Defects of Leukocyte function

**Neutropenia**: (leuk, drug induced angr. cyc neu,)

**Migration/Chemotaxis Impaired**

- **Int cellular dysfxn**: ch-hig synd, lazy leuk synd, job’s syn, dm
- **Inhibition of locomotion**: corticosteroids, dm
- **Deficiencies of chemotaxis**: dm, complement def, chemotactic factor inactivators in serum

Disorders of Leukocytes: Function

- **Disorders of Phagocytosis:**
  - **Opsonin deficiencies** (hypogammaglobulinemia, C3 Comp def, Sickle cell ds)
  - **Impaired engulfment:** drugs eg. Morphine analogs
  - **Impaired degranulation** (impaired discharge of granule contents into phagosome)
    - Chediak Higashi syndrome, drugs: colchicine, corticosteroids, antimalarials

- **Disorders of microbiocidal (killing) mechanisms:**
  - Impaired H2O2 production, chronic granulomatous disease G-6-PO4 dehydrogenase deficiency
  - Drugs: hydrocortisone, sulfonamides, Myeloperoxidase deficiency

Ryan, GB. Et al. *Inflammation, a scope publicaiton*, Upjon Company, Kalamozoo MI P 39
IE: Factors in Delayed Healing

Disturbance or impairment of:

- Vascular system
- Cellular components and/or mediators
- Biochemical components: $O_2$, Nutr, $CO_2$
- Hemostasis, Inflammation, Proliferation, Maturation
- Ability to obtain and maintain homeostasis/balance
History of Wound Healing

2100 BC 1st recorded wound care: 3 gestures
1) Washing wound with etoh & water
2) Application bacteriocidal salve
3) Application of bandages

400 BC I&D
130-200AD Galen: Hemostasis
Dark Ages: Hot Oils, Gunpowder
1563 Ambroise Pare Reformed Wound Care
Middle Ages: Allowed to “rot a bit” through Am civil war
1865 Lister Antisepsis
C Reyer 1846-1890: Earl, Partial Debridement
Depage 1862-1925 Complete Debridement
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History of Wound Healing

What Have We Learned???
History of Wound Healing

What Have We Learned????

2100BC-2006

Hippocrates
“We shall never cease from striving, and the end of all our striving, will be to arrive where we began, and to know the place for the very first time”.

T.S. Elliot
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Thank You