

Evidence-based Practice in Wound Care

Case Western Reserve University School of Medicine

Chronic Wounds
are
ALWAYS
Manifestations of Other Systemic
Problems

Bonnie Nicklas, DPM

Assistant Professor, Department of Surgery CWRU School of Medicine
Staff Podiatrist, Louis Stokes Cleveland Veterans Affairs Medical Center

Chronic Wounds are always 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

■ 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

■ 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

■ 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



The Science of Wound Healing

Three distinct phases:

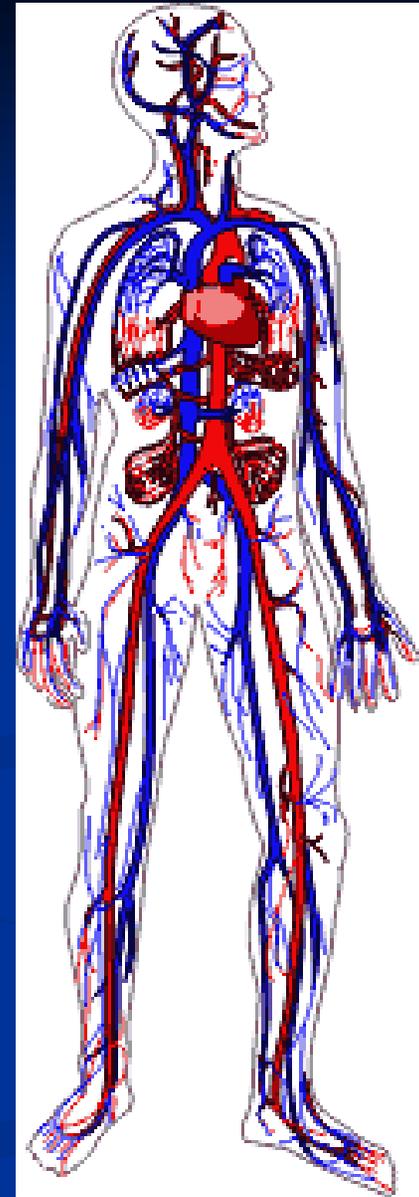
- Inflammation
- Proliferation
- Maturation

Schilling, J. Wound healing *Surg.Clin. North Am.* 56: 859, 1976

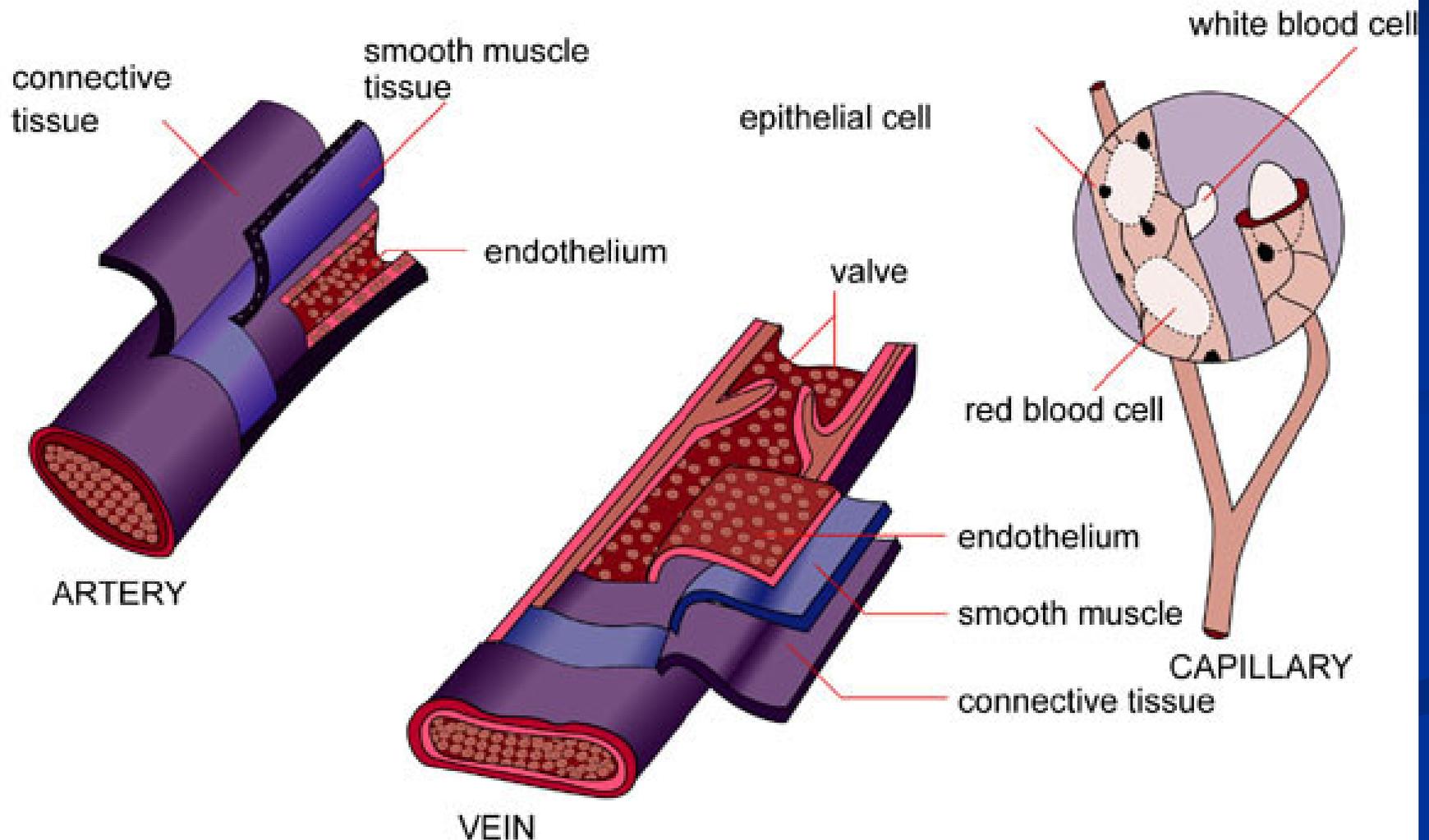
3 (4?) Phases

- Hemostasis: Initiating step
Foundation for Healing

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



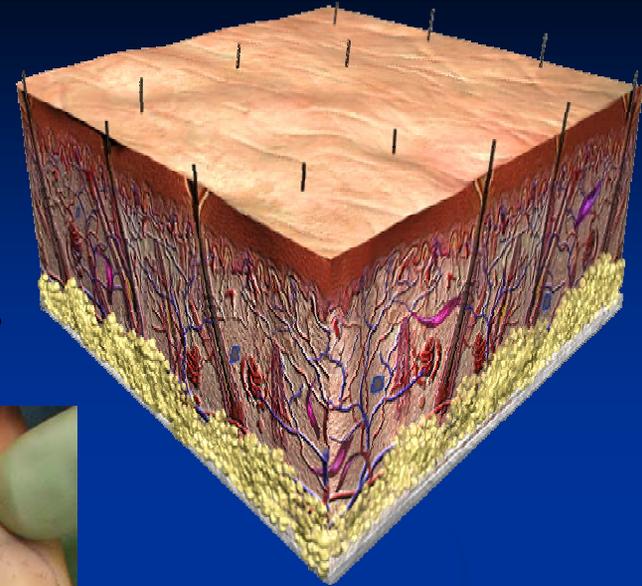
Hemostasis: Vasoconstriction



Hemostasis: Day 0

- Blood vessel vasoconstricts
- Coagulation cascade: endothel, platelets
- Clot forms: collagen

platelets
thrombin
fibronectin
cytokines
GF



Kurkinen, M. et al. Sequential appearance of fibronectin and collagen in experimental granulation tissue. *Lab. Invest.* 43: 47, 1980

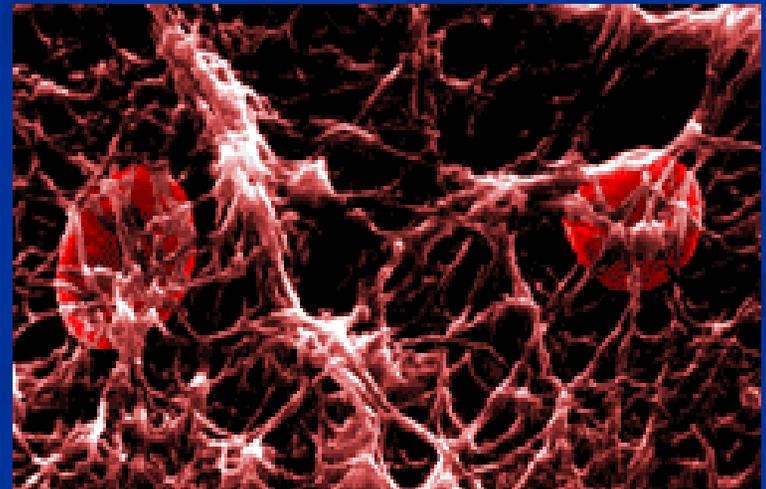
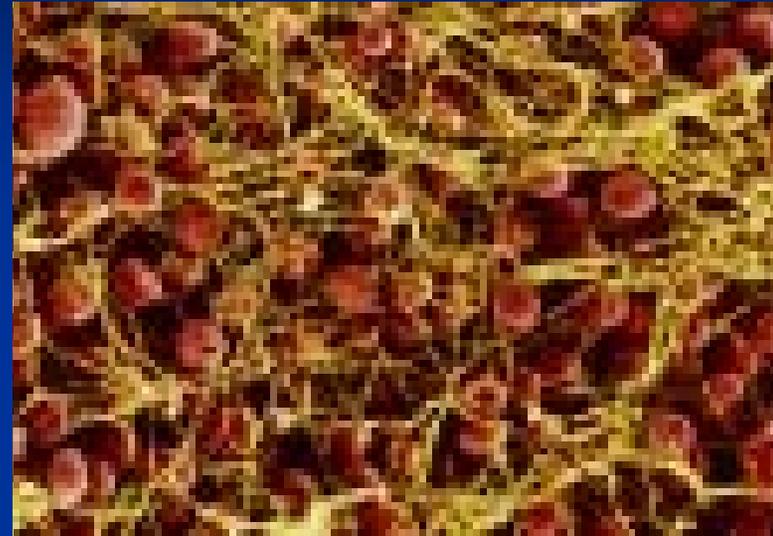
Hemostasis: Clot Forms

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



Initiate inflammatory response

Kurkinen, M. et al. Lab. Invest 43: 47, 1980



Stage 1: Inflammation: ~Day 0-6

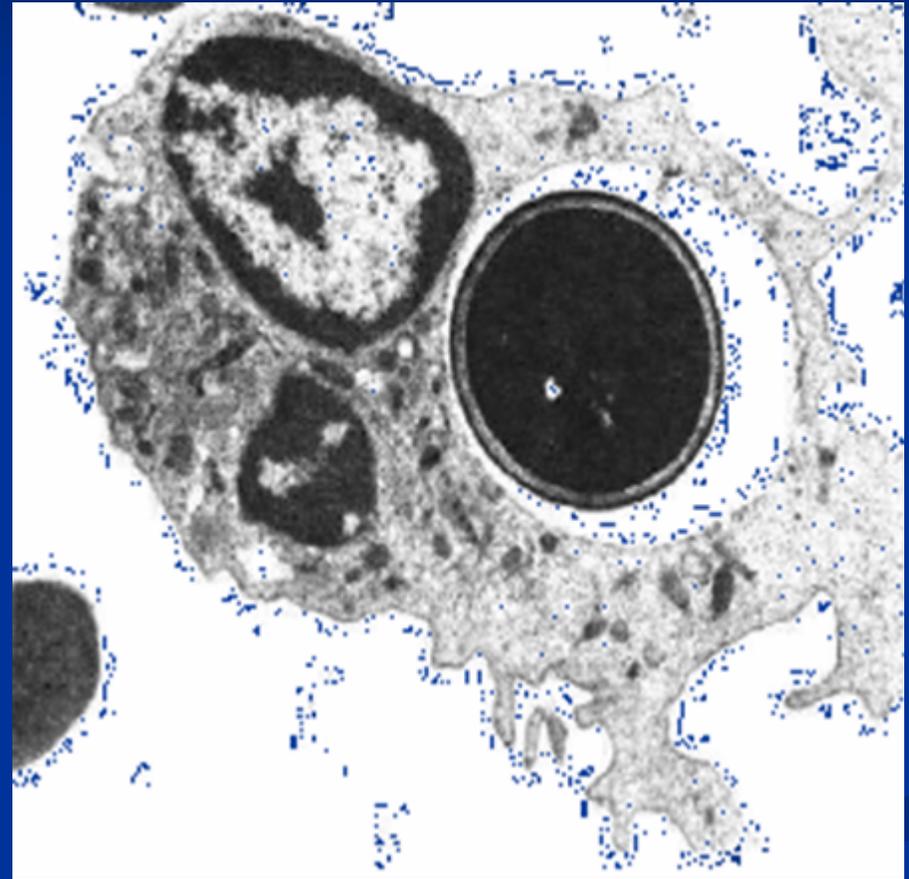
- **Chemotaxis & Activation**
 1. Neutrophil response
 2. Inflamm mediators accumulate
 3. Prostaglandins are elaborated
 4. Blood vessels vasodilate
 5. Platelets release IL-1, TNF- α , TGF- B , PF-4. PMNs elaborate proteases and MMPs to form rad to kill bacti and clear matrix



Pohlman, T., et al. An endothelial cell surface factor (s) induced in vitro by lipopolysaccharide, interleukin 1 and tumor necrosis factor-alpha increases neutrophil adherence by a CDw18-dependent mechanism. J. Immunol. 136-4548, 1986

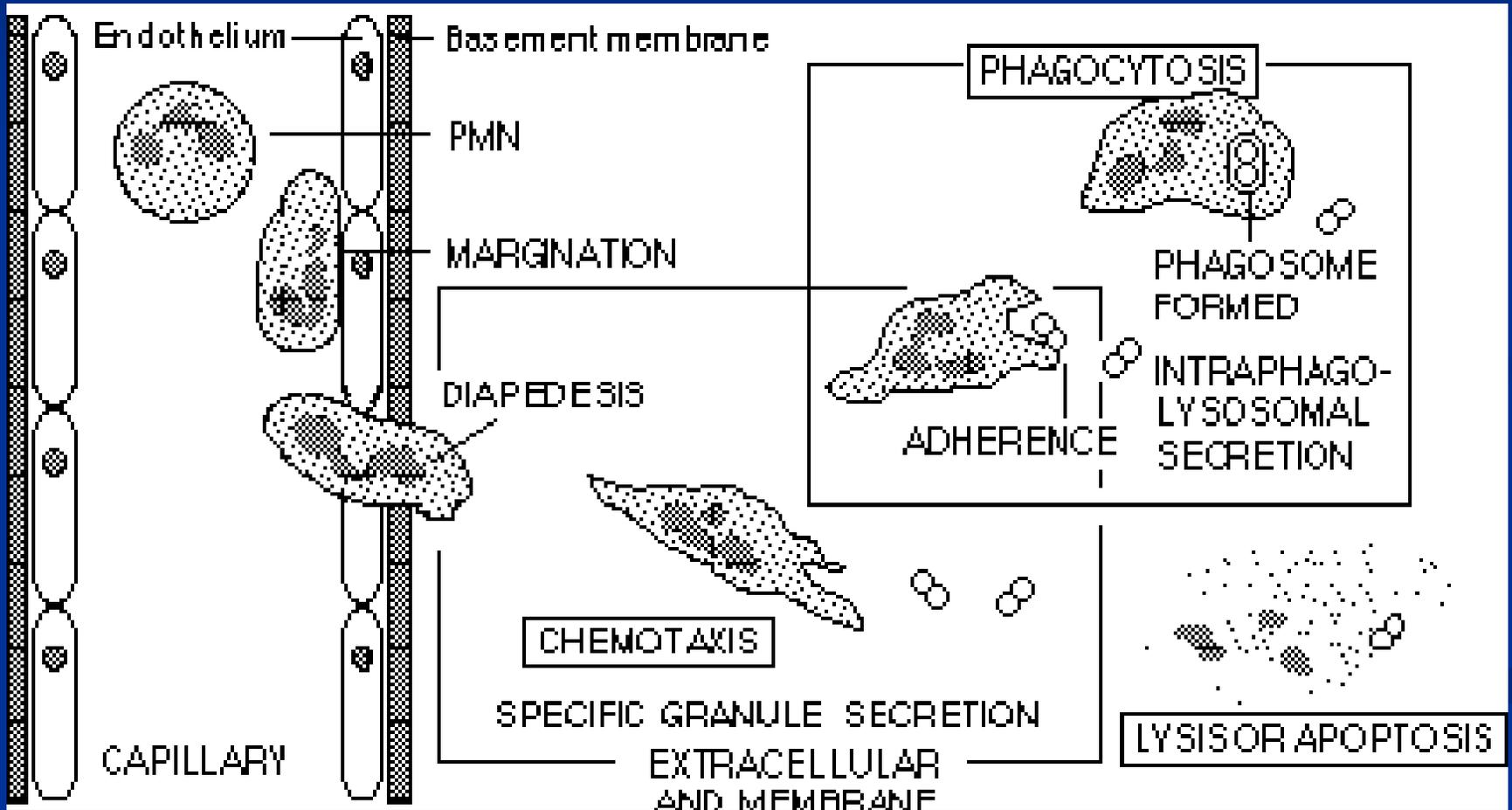
Phagocytosis: Neutrophils

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



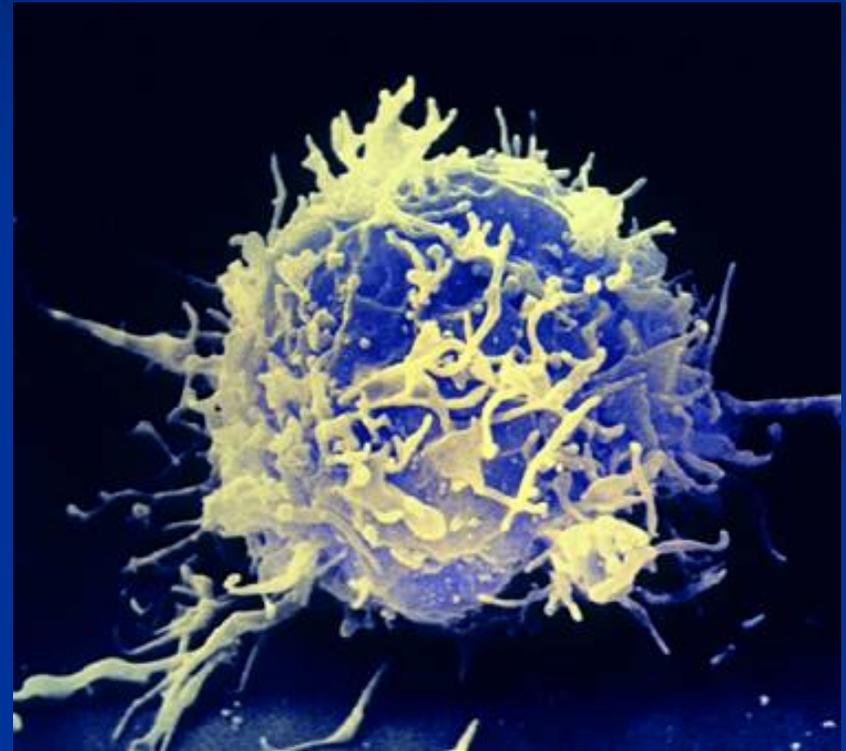
Phagocyte (neutrophil) functions

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



T lymphocyte

Inflammation: Monocytes to Macs

48-96 hours post injury

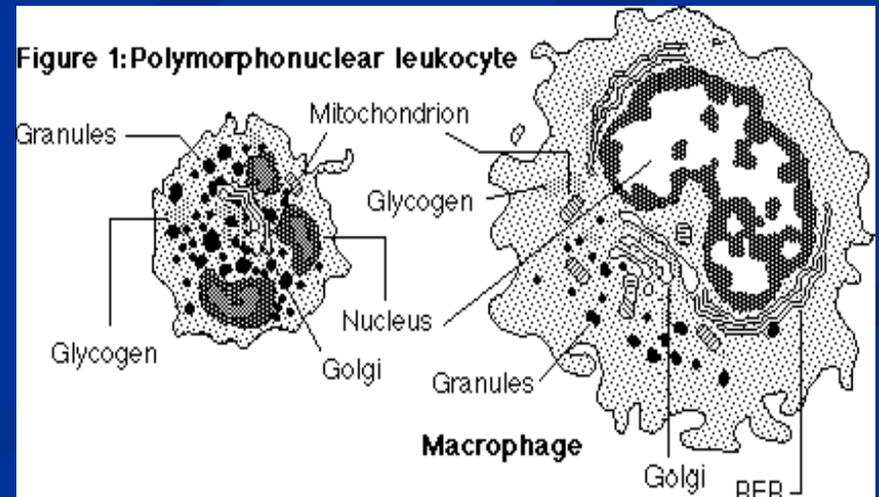
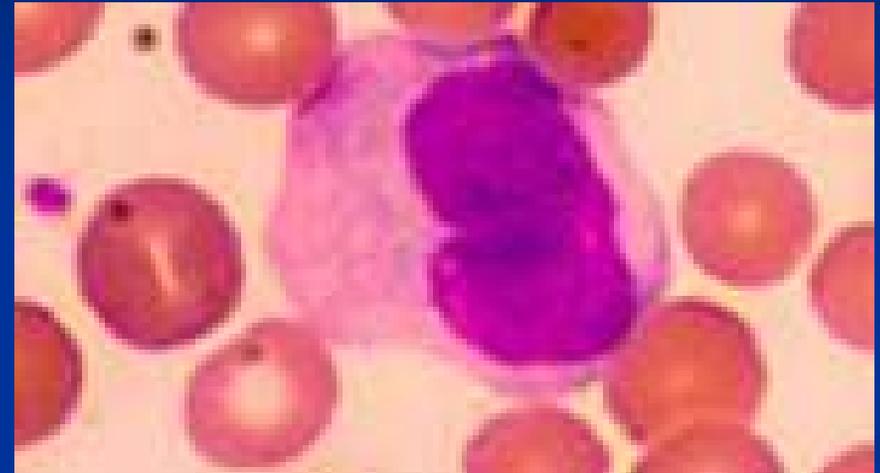
Activated Macrophages
transition wound to
proliferative phase



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.

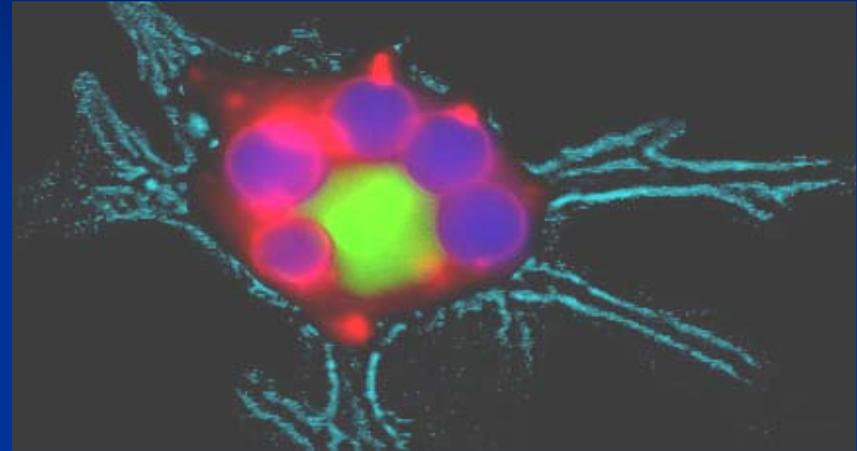


Mac Engulfing Bacterium

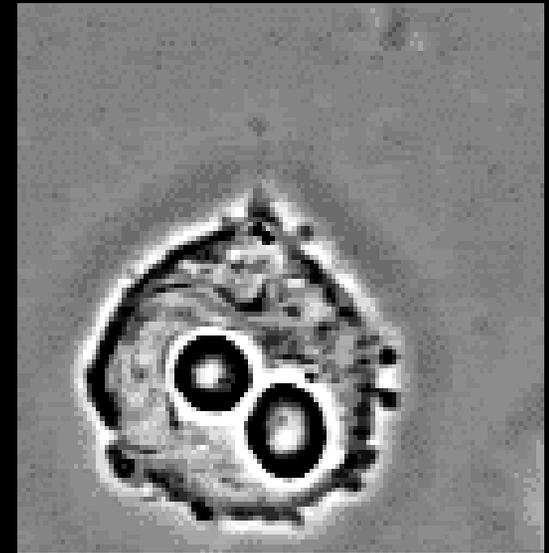
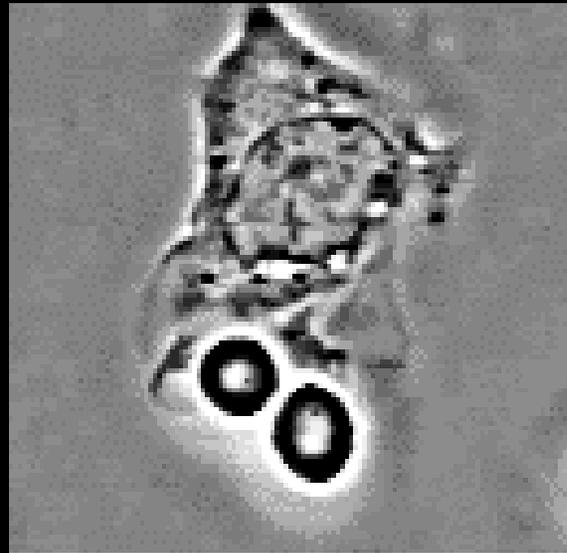
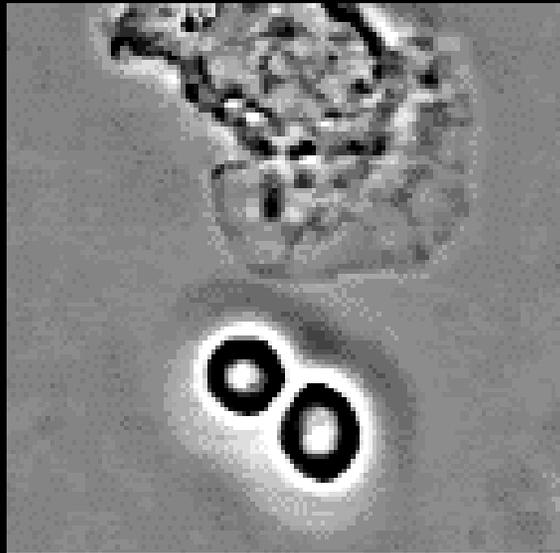
Dennis Kunkel/CNRI/Phototake NYC

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



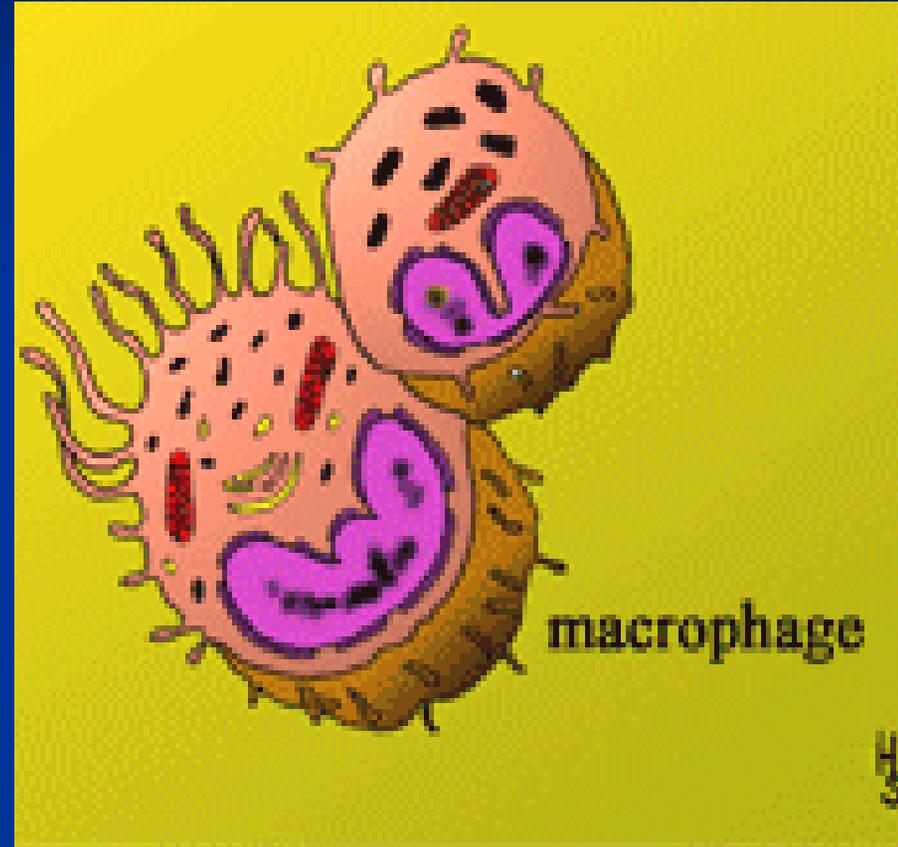
©James A. Sullivan

www.cellsalive.com

Mac uses internal cytoskeleton to envelop *C. albicans* cells
Kills yeast cells by “Oxidative Burst”

Stage 2: Proliferation ~Day 7-21

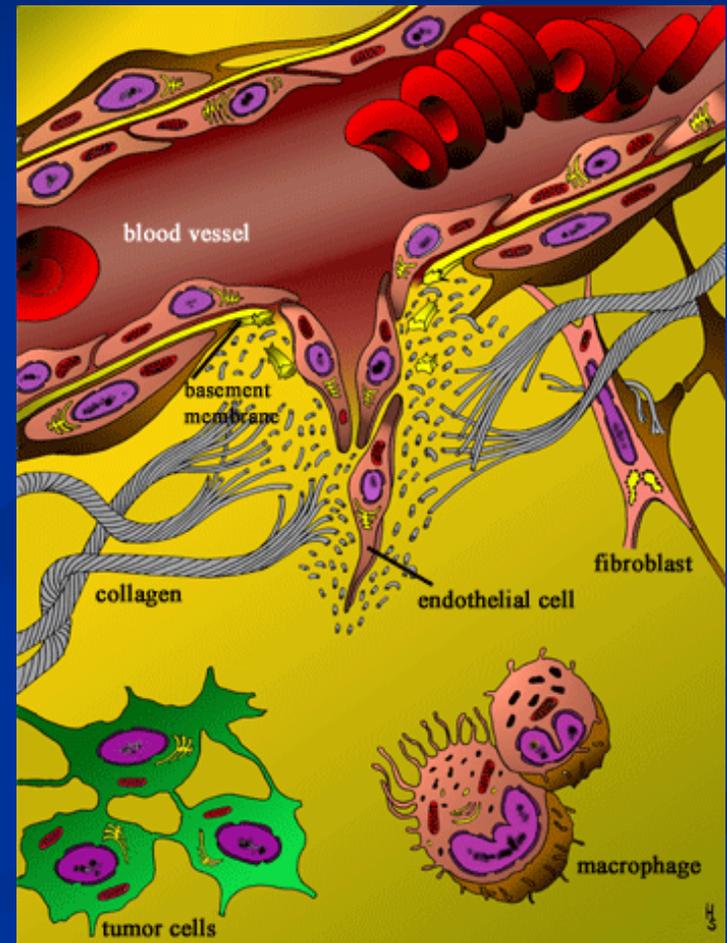
- **Activated macrophages**
-transitions to prolifer phase
Mediates angiogenesis by
synthesizing VEGF, FGF, TNF- α ,
Mediates fibroplasia by
synth: TGF- B , EGF, PDGF, IL-1, TNF- α
- **PMNs enter wound: clean up**
- **Fibroblasts: syn coll & proliferate**
- **Endothelials: capillary buds**



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).

Witte, M., et al Role of nitric oxide in wound repair.
Am J. Surg. 183: 406, 2002



Proliferation: Fibroblasts

- **Fibroblasts release**
IFN- γ , causing monos to transform to MACs.
- **Fibroblasts synthesize**
proteoglycans & fibronectin

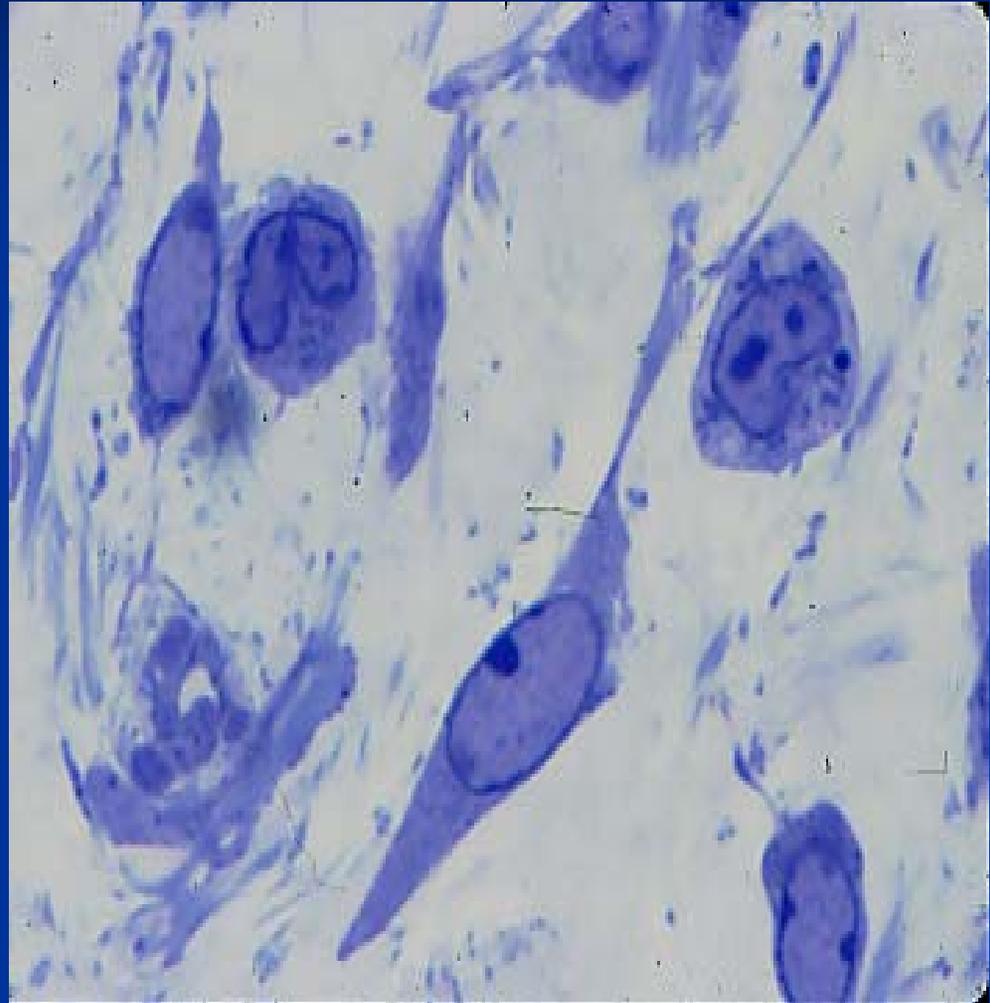


Provisional matrix
(Collagen type III first, then I)



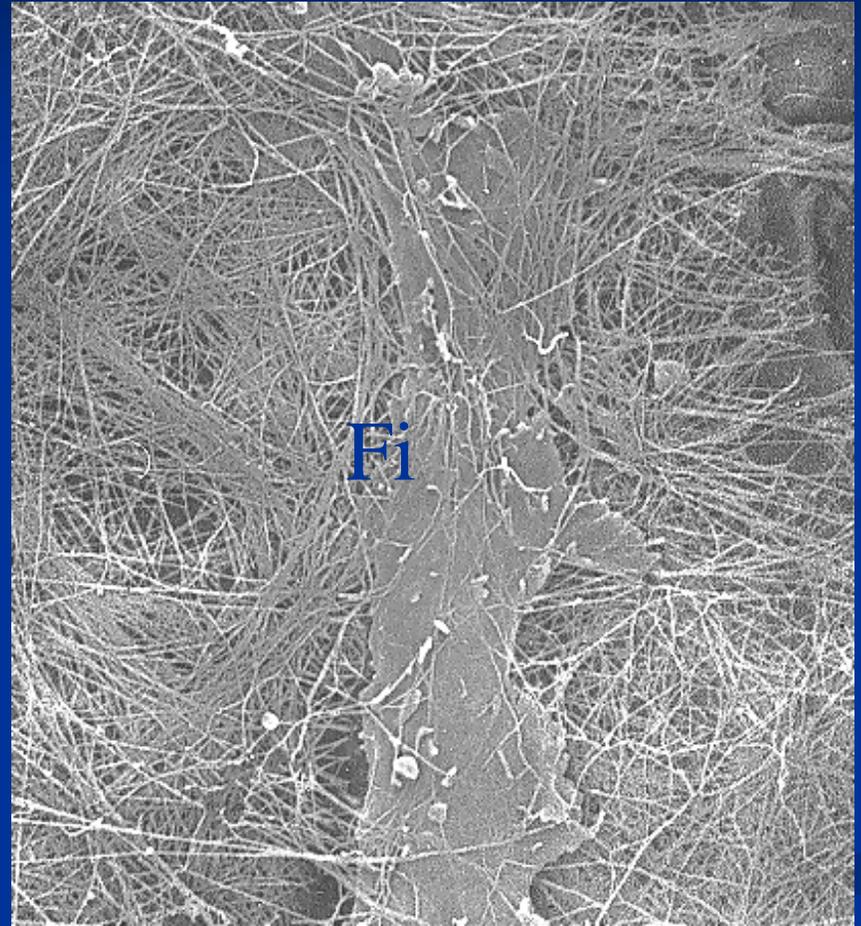
Fibroblasts and collagen

- **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



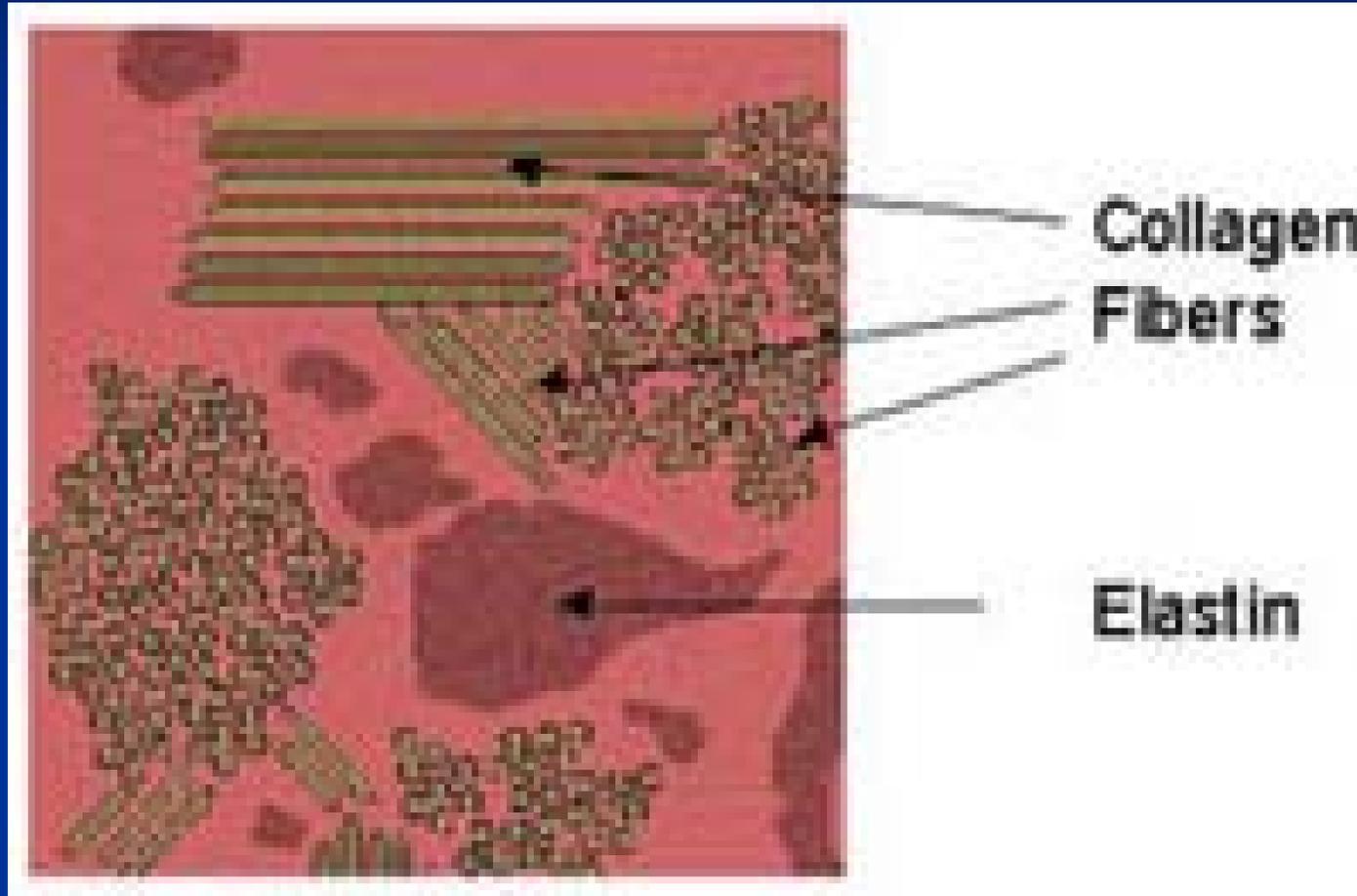
Stage 3: Maturation (Remodelling)

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



Fibroblast in a network of collagen fibers

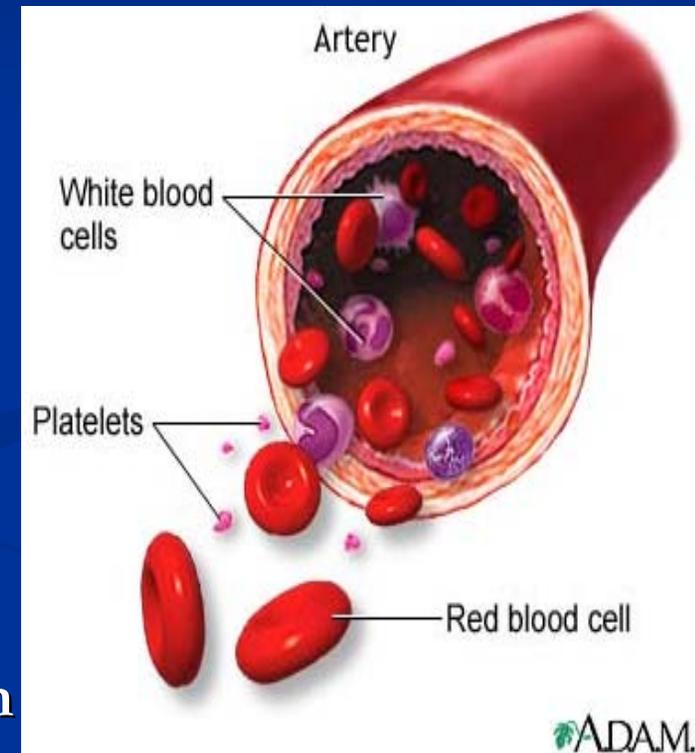
Alignment changes from random to organized



<http://www.netwellness.org/default.cfm>

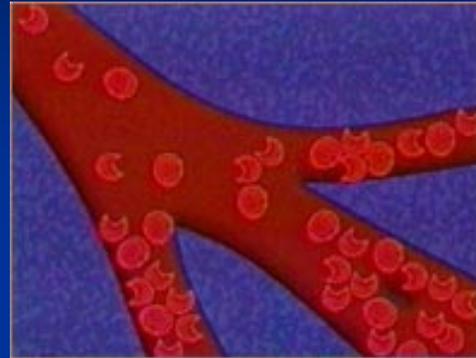
Vascular Disease and Wound Healing: Blood: Essential for Wound Healing

- **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.

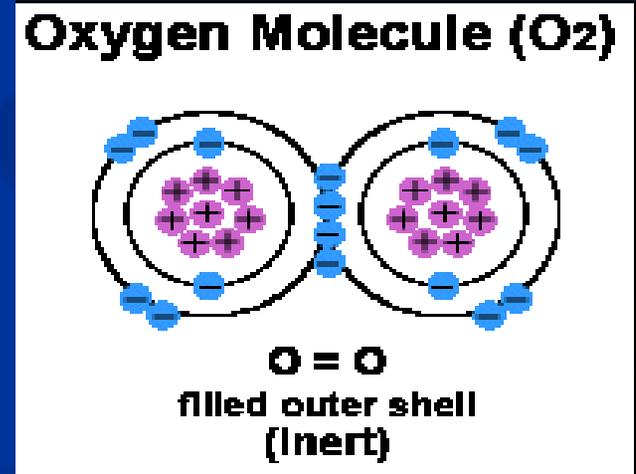
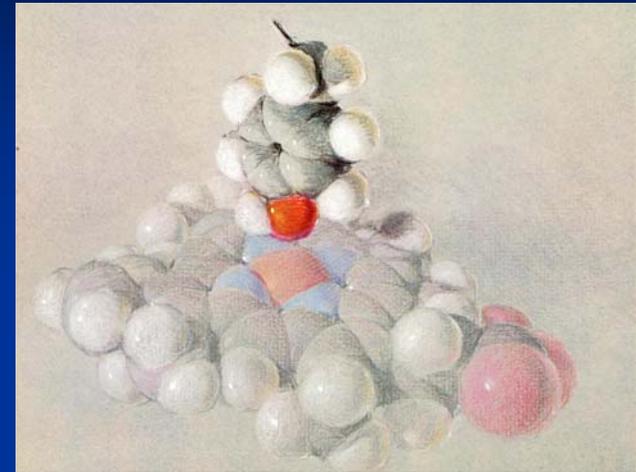
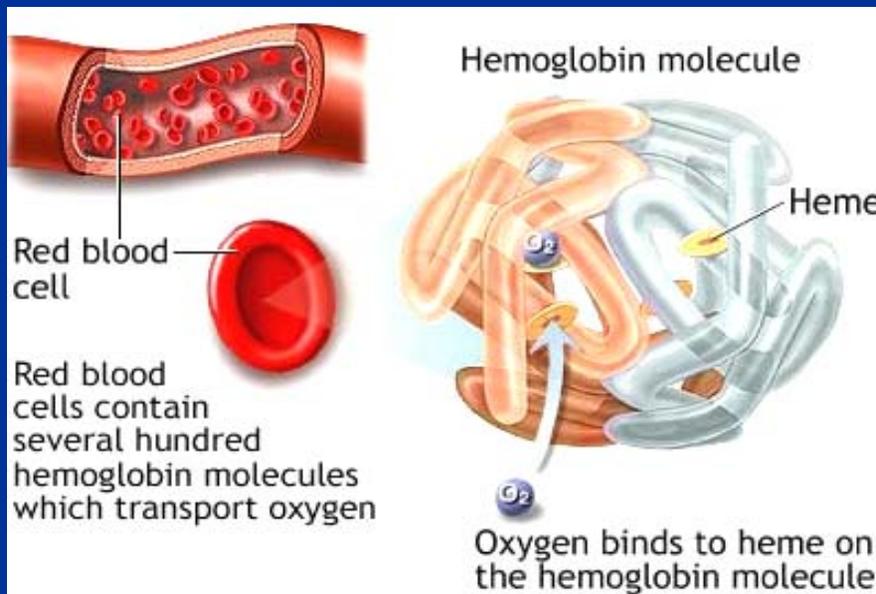


- **Blood:** Main body temp, pH, carries O_2
- O_2 : helps produce granulation tissue
ensures resistance against infection
effects fibroblasts & collagen prod



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

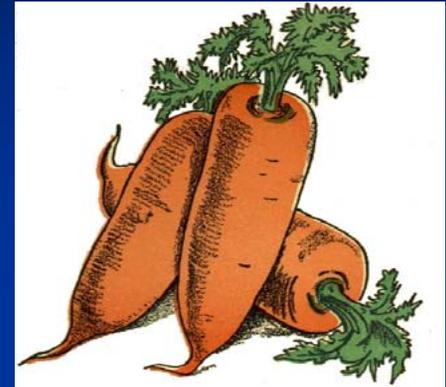
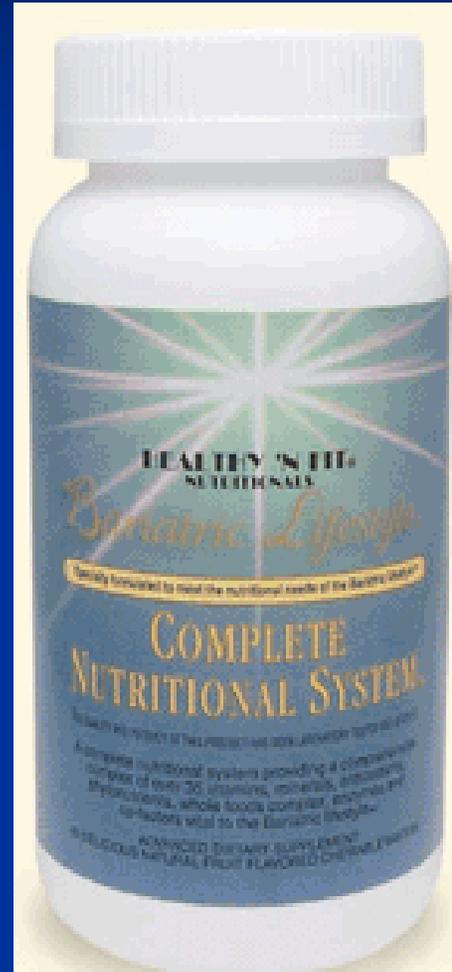
- Poor nutrition can arrest the wound healing process
- Main component of the nutrition is O₂.
- Deficiencies of:
 1. Vitamin A
 2. Vitamin C
 3. ZincImpair normal wound healing mechanisms.

LaVan, FB, Hunt, TK, Oxygen is a controlling factor in wound repair. *Clin Plast Surg.* 1990 Jul;17(3):463-72

MacKay D, Miller AL. Nutritional support for wound healing. *Altern Med Rev.* 2003; 8(4):359-377.

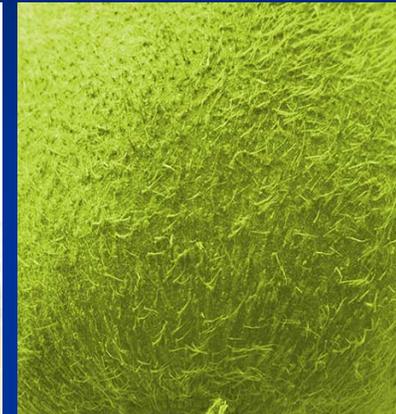
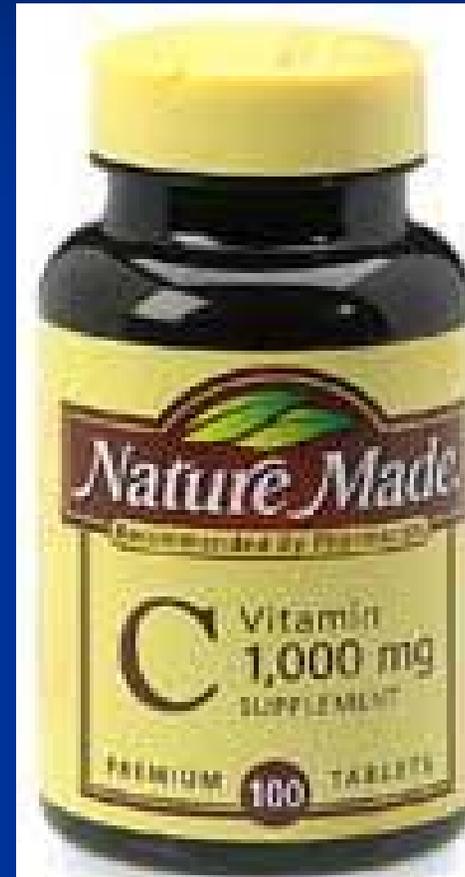
Vitamin A

- **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

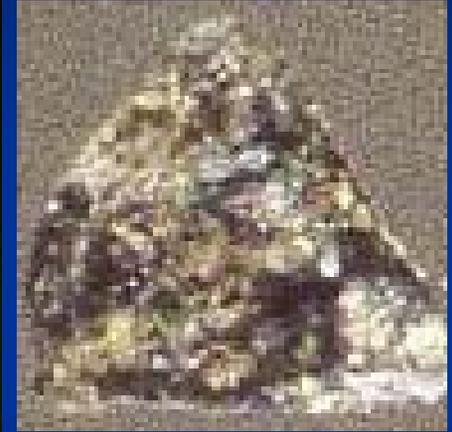
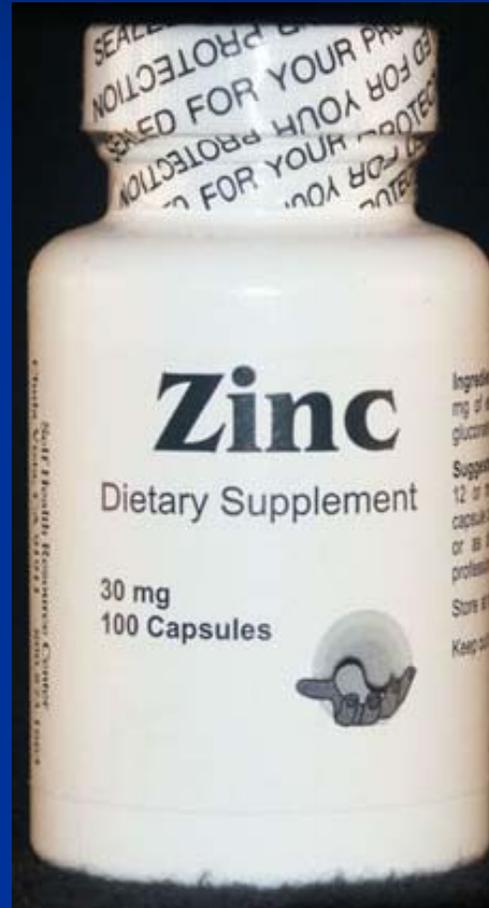
- **Benefits wound healing by:**
 1. Enhancing neutrophil prod.
 2. Increasing angiogenesis
 3. Acts as an antioxidant
 4. Helps in collagen prod



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

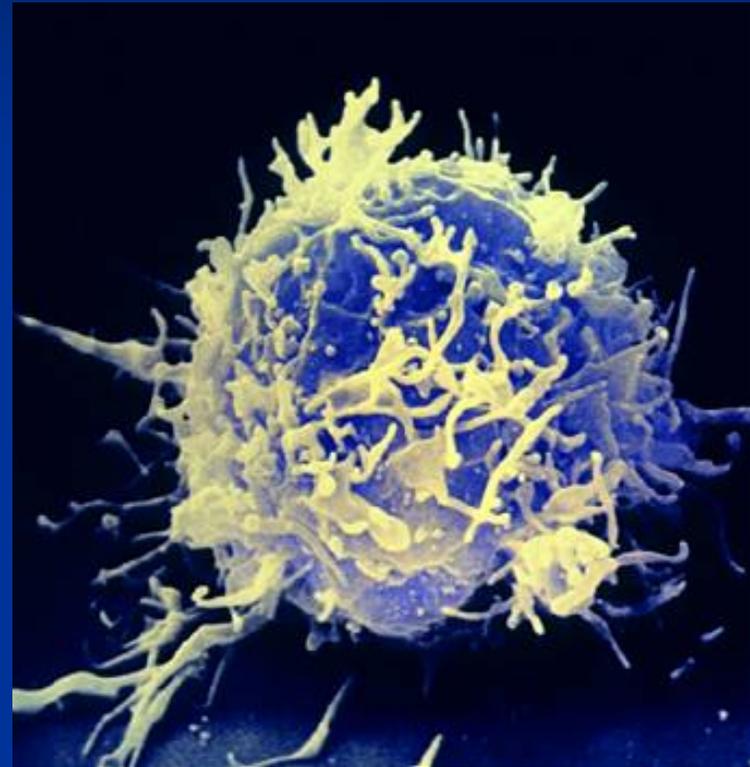
- **Protein:** needed for tissue regeneration and repair.
- **Protein mal:** impairs normal wound-healing mechanisms.
- **Can delay wound healing by exacerbating the inflammatory phase of the wound.**



MacKay D, Miller AL. Nutritional support for wound healing. *Altern Med Rev.* 2003; 8(4):359-377.

Malnutrition and Lymphocytes

- Lymphocyte counts are indicators of malnourishment.
- A count of less than 800 indicates severe malnourishment.



Case: Failure to heal---Gangrene

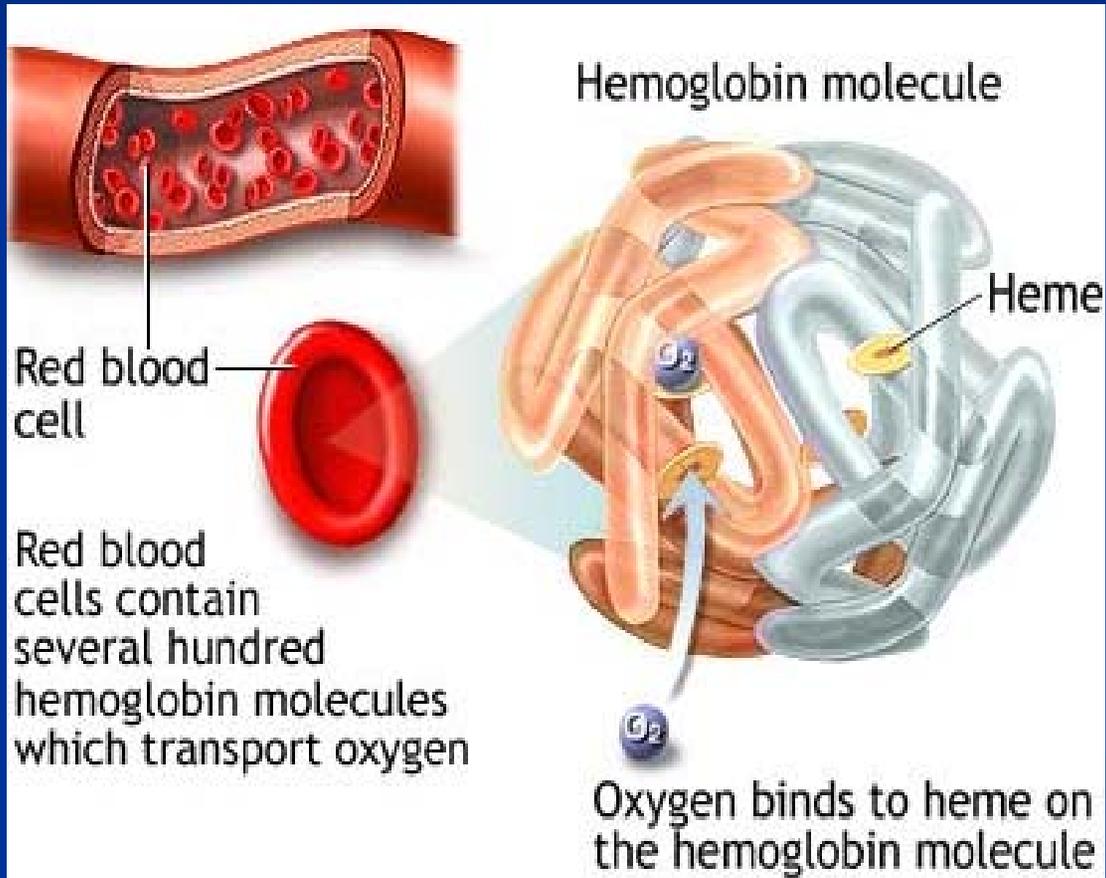


Failure to heal---Why??

- Diabetes: BS, Neuro, Vasc
- Diabetes: Immunopathy
- Tobacco Use: O₂ Delivery
- Hx of Cancer
- Over 70 years of age
- Nutrition: Generally poor
 - Etoh use
 - No DM diet

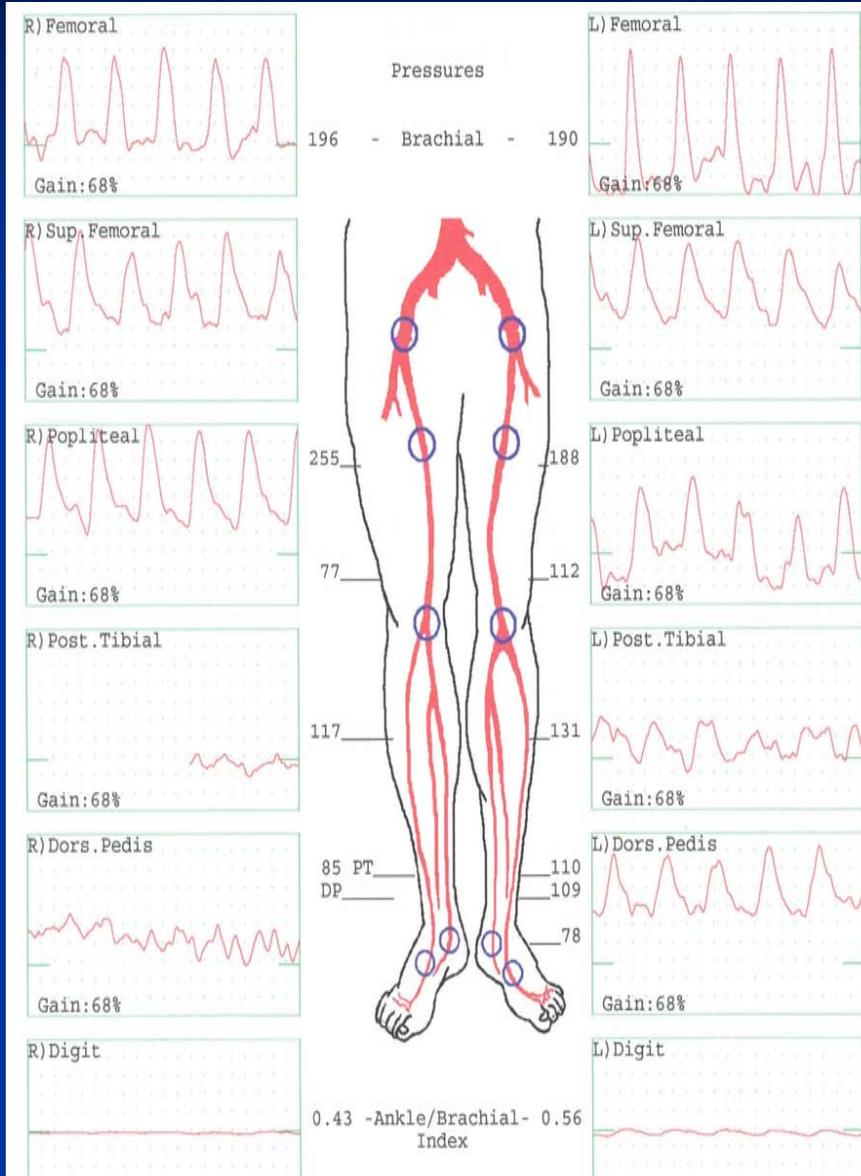


PE: Vascular Compromise

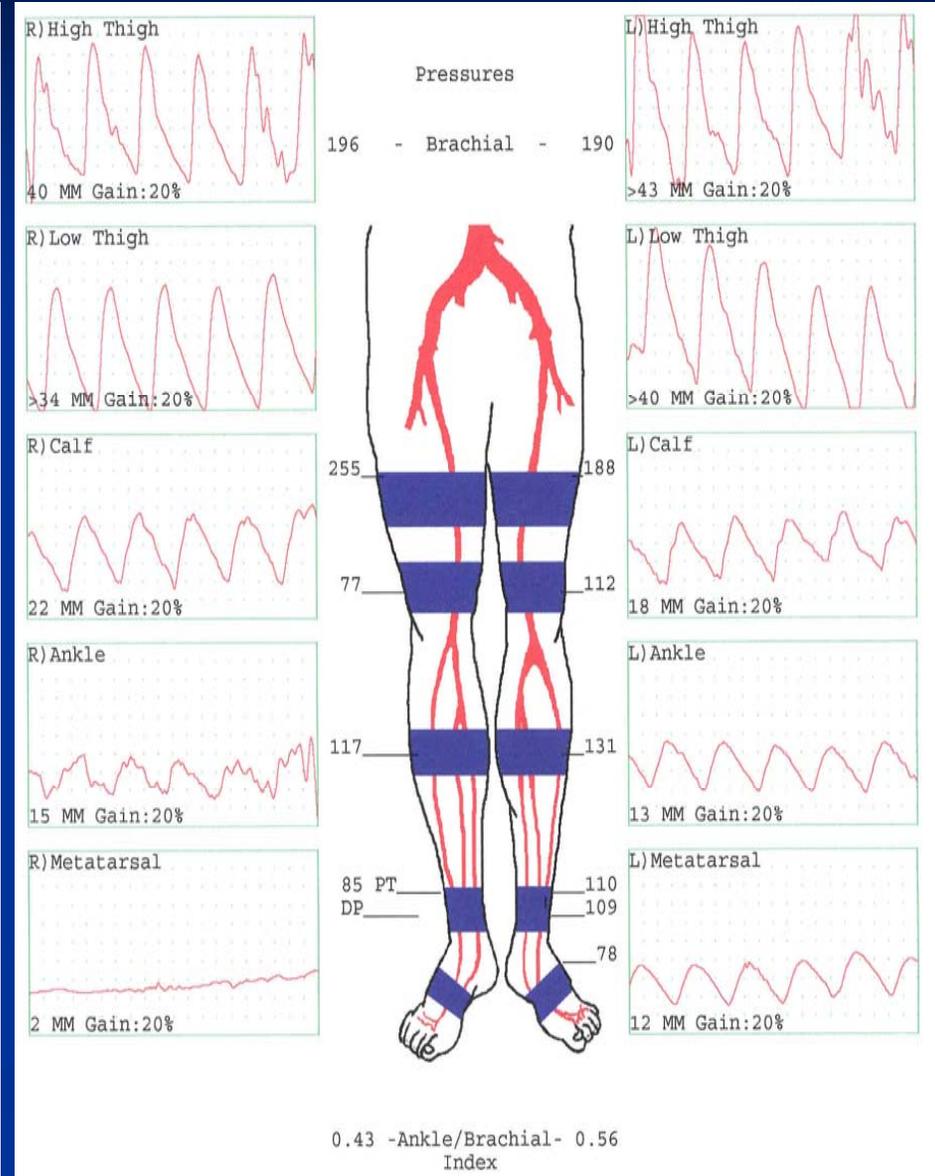


Non Invasive Vascular Studies

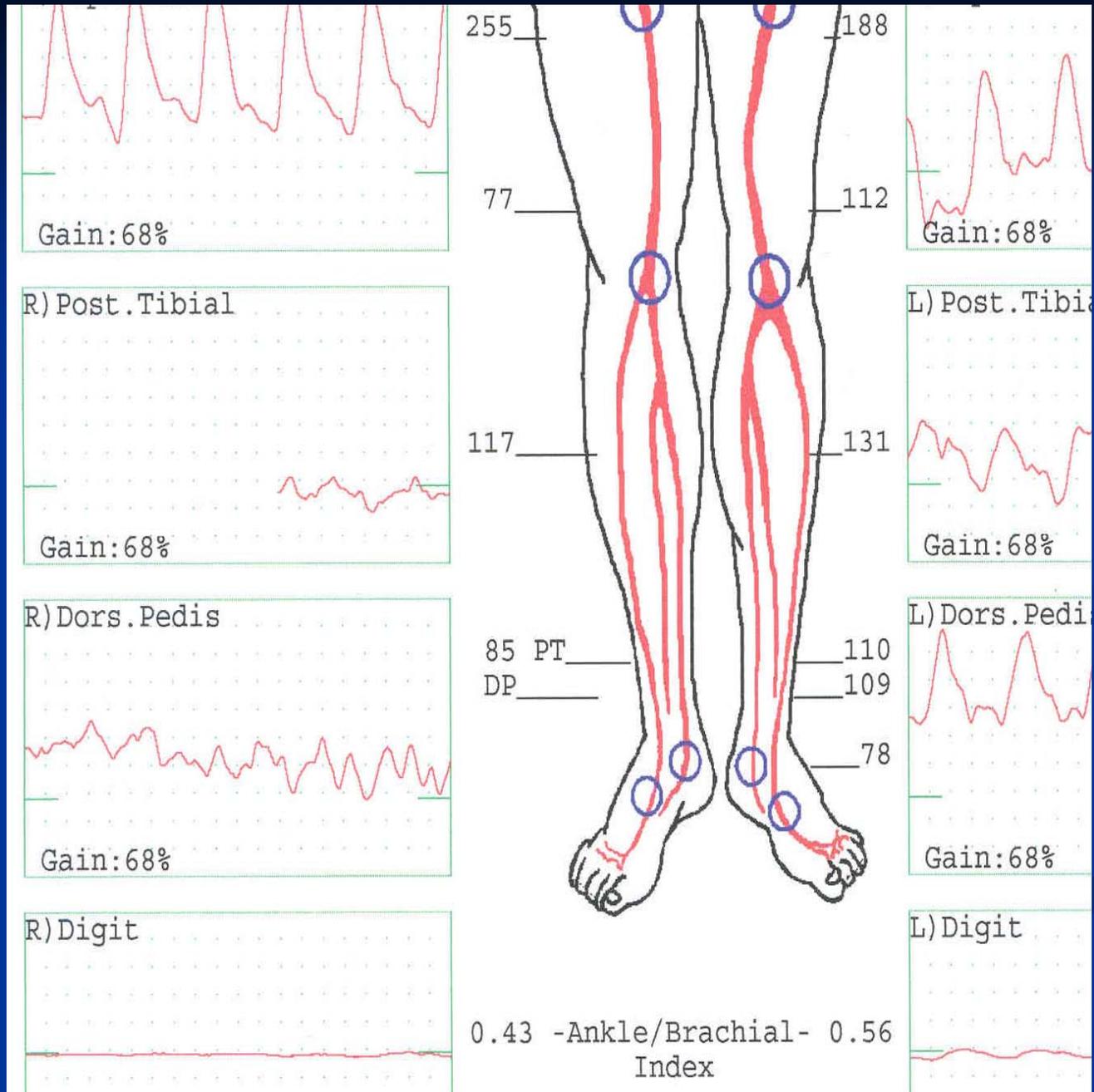
Doppler



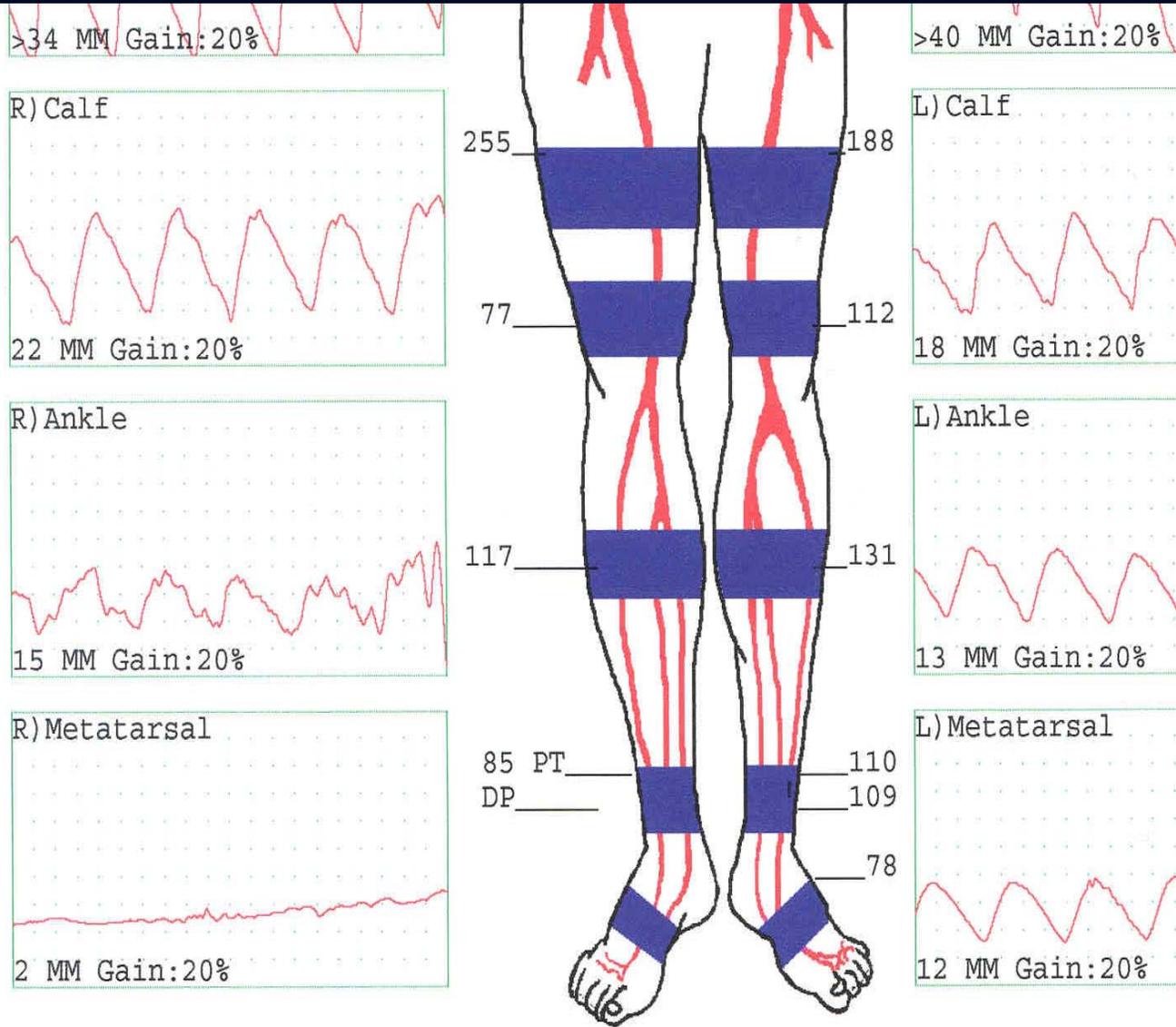
PVR



Doppler

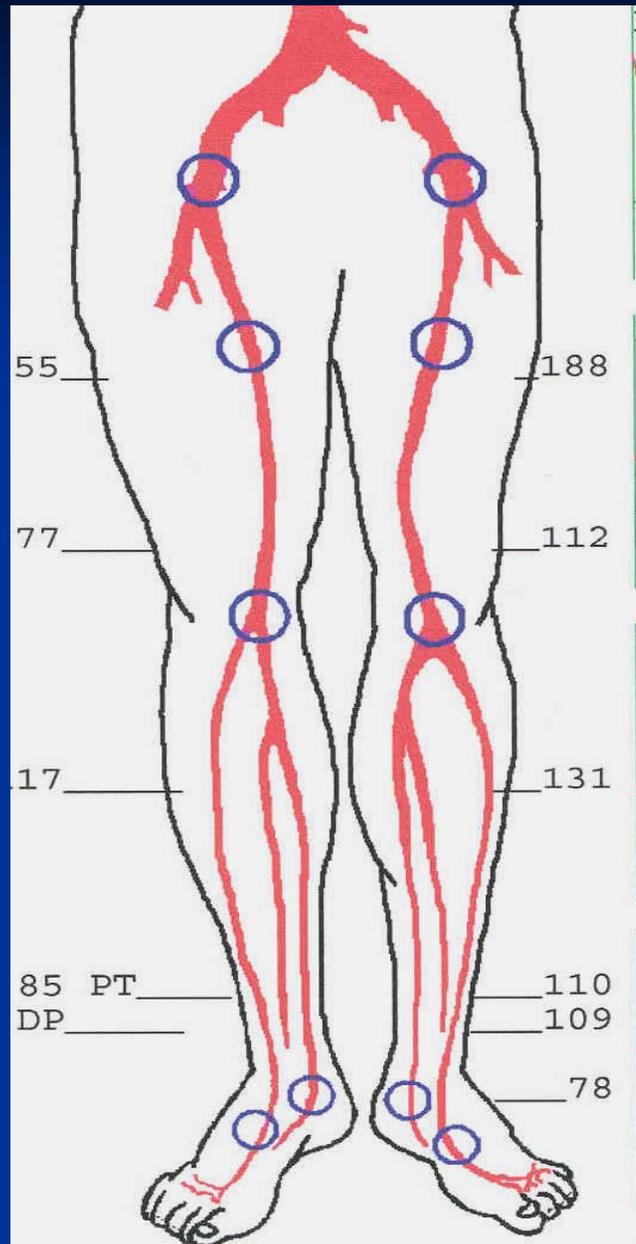


PVR



0.43 -Ankle/Brachial- 0.56
Index

Angiograms



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



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



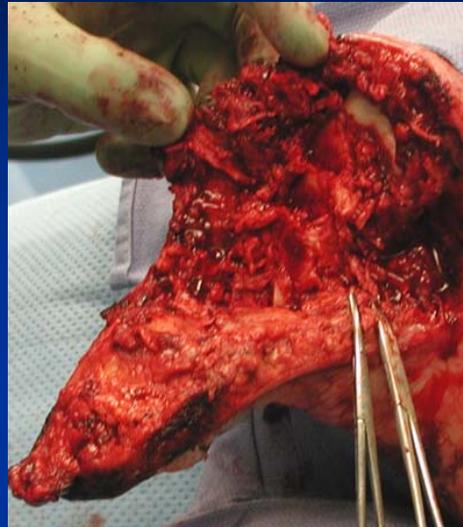
From this...



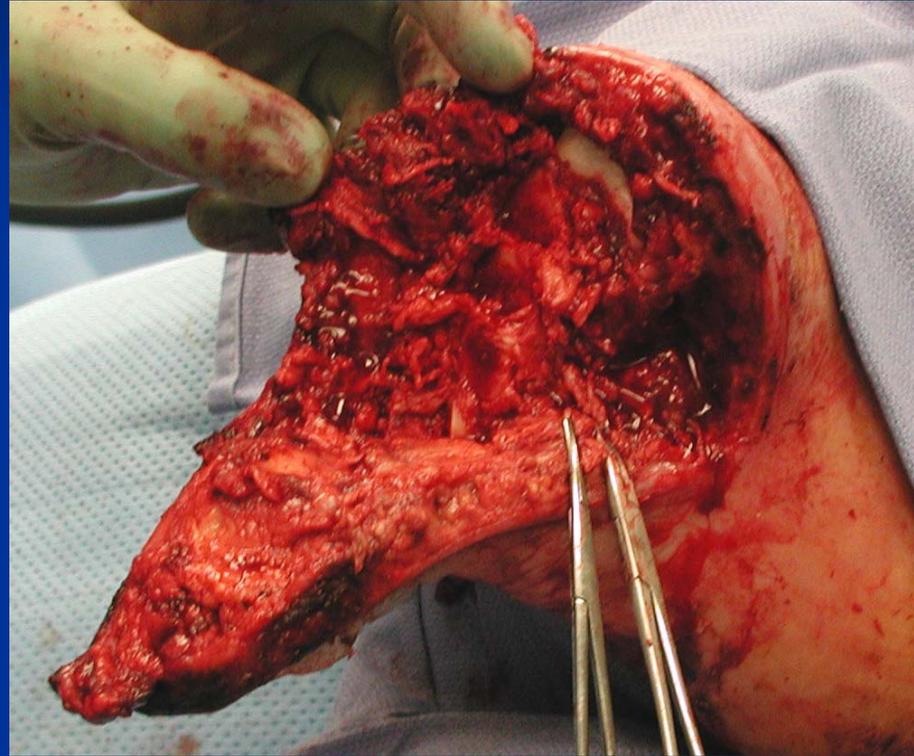
To this



Wound Healing Chronology



Wound Healing: Phase 1 Inflammatory Phase



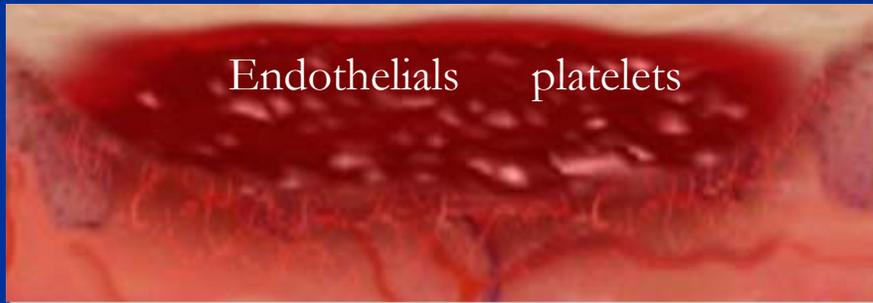
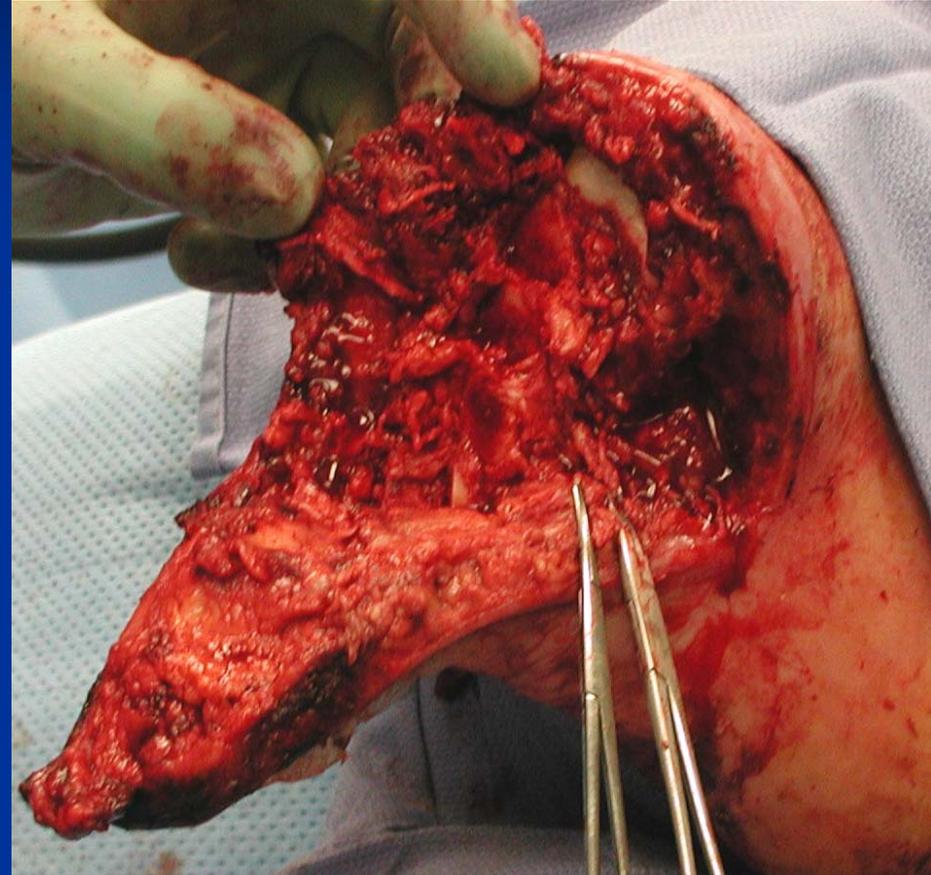
Phase 1: Inflammatory Phase First few days post inj/sx
Inflammatory cells, macrophages, platelets, pmns

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

KEY Cells:

Endothelial cells
Macrophages, PMNs
Platelets

KEY Cellular Components

Integrins

KEY Elements

Hypoxia, lactate, acidity
Monos become macrophages
FGF-2
PDGF-BB
VEGF
MMPs
Phagocytosis



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

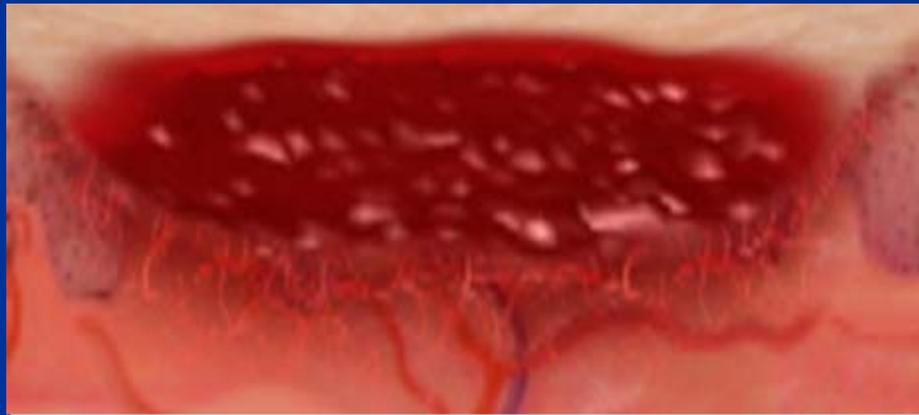
- Endothelial cells
- Macrophages
- Fibroblasts

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



Growth Factors

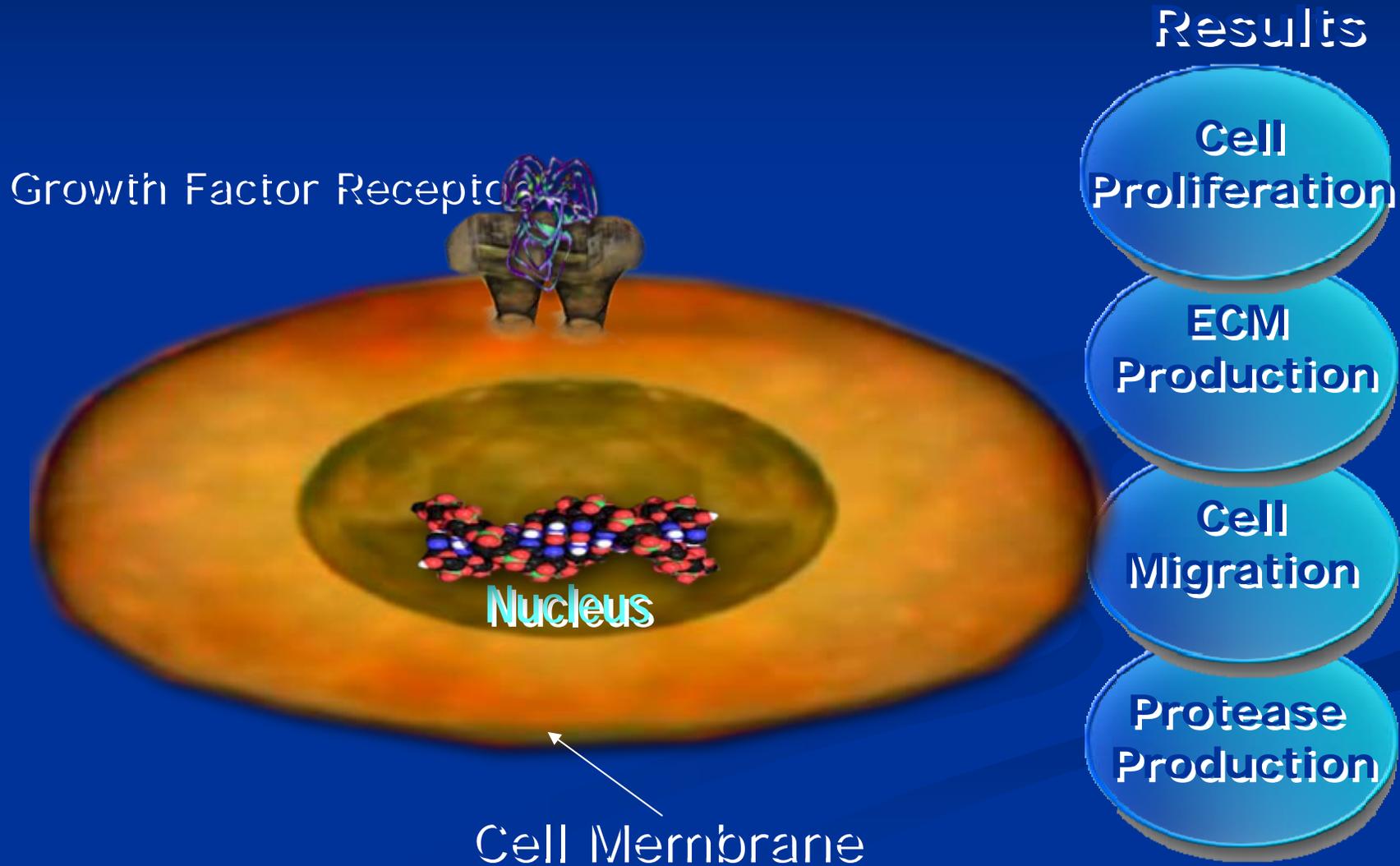


Receptors



Target Cells

How Do Growth Factors Work?



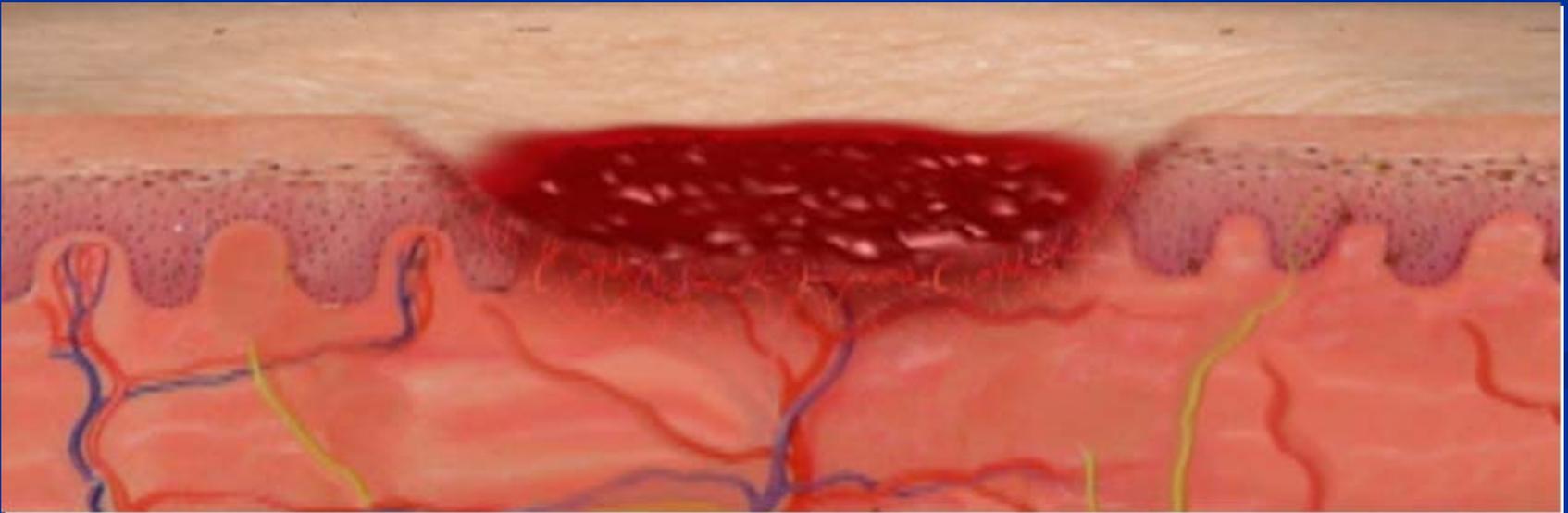
Proliferation/Epithelialization

KEY Cells

- Epithelial cells

KEY Elements

- EGF
- KGF
- MMPs



Proliferation/Epithelialization

KEY Cells

- Epithelial cells
- Keratinocytes
- Fibroblasts

KEY Cellular components

Platelets, Macros initiate

KEY Elements

- MMPs
- EGF
- TGF-*a*
- IL-6
- KGF-1 and 2

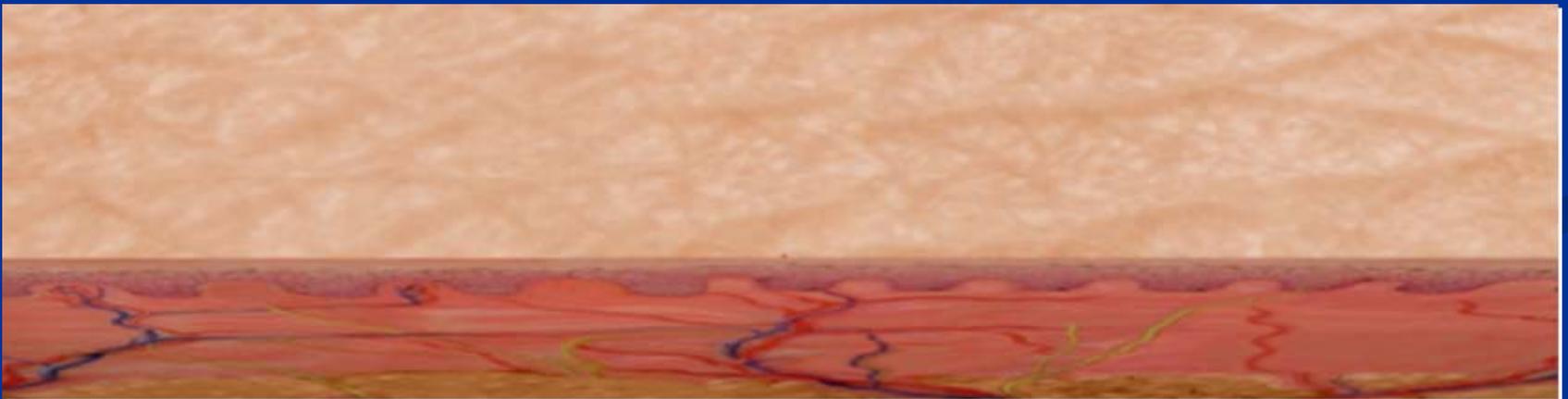


Proliferation/Epithelialization



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 deficiency (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)

IE: Factors in Delayed Healing

Disturbance or impairment of:

- Vascular system
- Cellular components and/or mediators
- Biochemical components: O₂, Nutr, CO₂
- 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

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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 Anticepsis

C Reyer 1846-1890: Earl, Partial Debridement

Depage 1862-1925 Complete Debridement

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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 Anticepsis

C Reyer 1846-1890: Earl, Partial Debridement

Depage 1862-1925 Complete Debridement

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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 Anticepsis

C Reyer 1846-1890: Earl, Partial Debridement

Depage 1862-1925 Complete Debridement

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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: Ear, Partial Debridement
- Depage 1862-1925 Complete Debridement

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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

History of Wound Healing

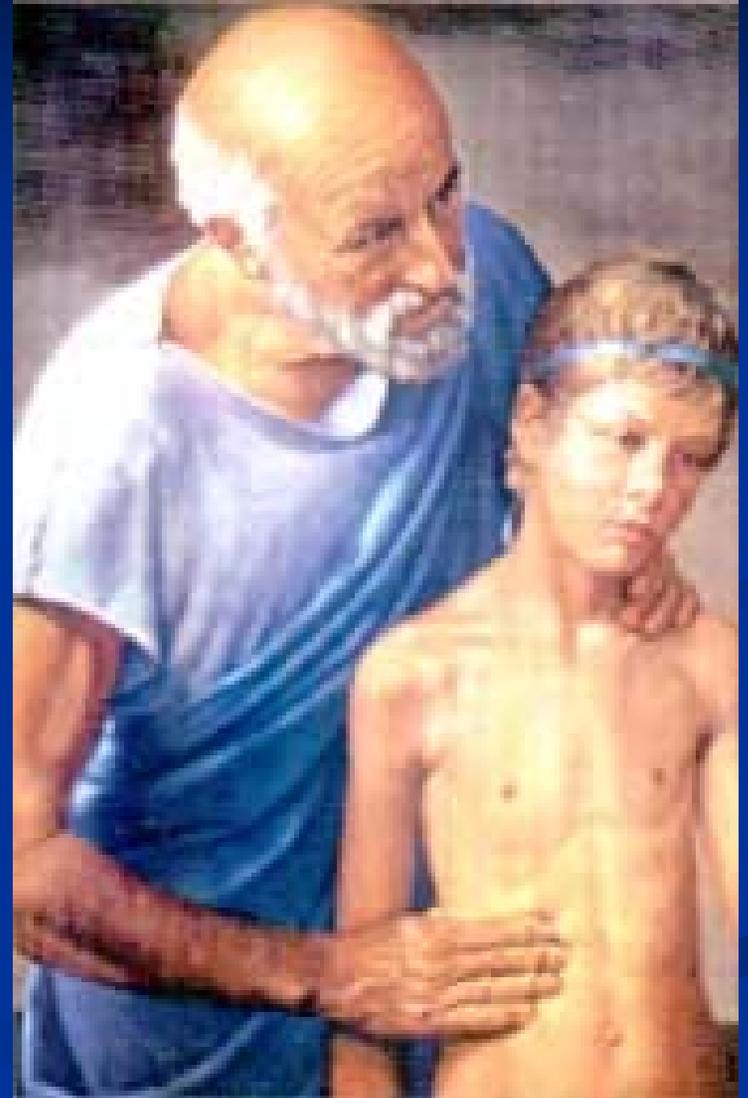
- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & water
 - 2) Application bacteriocidal salve
 - 3) Application of bandages
- 400 BC I&D
- 130-200AD Galen: Hemostasis
- Dark Ages: Hot Oils, Gunpowder
- 1563 Ambroise Pare Reformed Wound Care
- Middle Ages: Allowed to “rot a bit” through Am civil war
- 1865 Lister Antisepsis
- **C Reyer 1846-1890: Earl, Partial Debridement**
- Depage 1862-1925 Complete Debridement

History of Wound Healing

- 2100 BC 1st recorded wound care: 3 gestures
 - 1) Washing wound with alcohol & 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: Ear, Partial Debridement
- Depage 1862-1925 Complete Debridement

History of Wound Healing

What Have We
Learned????



Hippocrates

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

History of Wound Healing

2100 BC 1st recorded wound care: 3 gestures

- 1) Washing wound with alcohol & water
- 2) Application bacteriocidal salve
- 3) Application of bandages

History of Wound Healing

2100 BC 1st recorded wound care: 3 gestures

- 1) **Washing wound with alcohol & water**
- 2) Application bacteriocidal salve
- 3) Application of bandages

History of Wound Healing

2100 BC 1st recorded wound care: 3 gestures

- 1) Washing wound with alcohol & water
- 2) Application bacteriocidal salve
- 3) Application of bandages

History of Wound Healing

2100 BC 1st recorded wound care: 3 gestures

- 1) Washing wound with alcohol & water
- 2) Application bacteriocidal salve
- 3) **Application of bandages**

Thank You