

The Microstructure and Biochemistry of Chronic Wounds

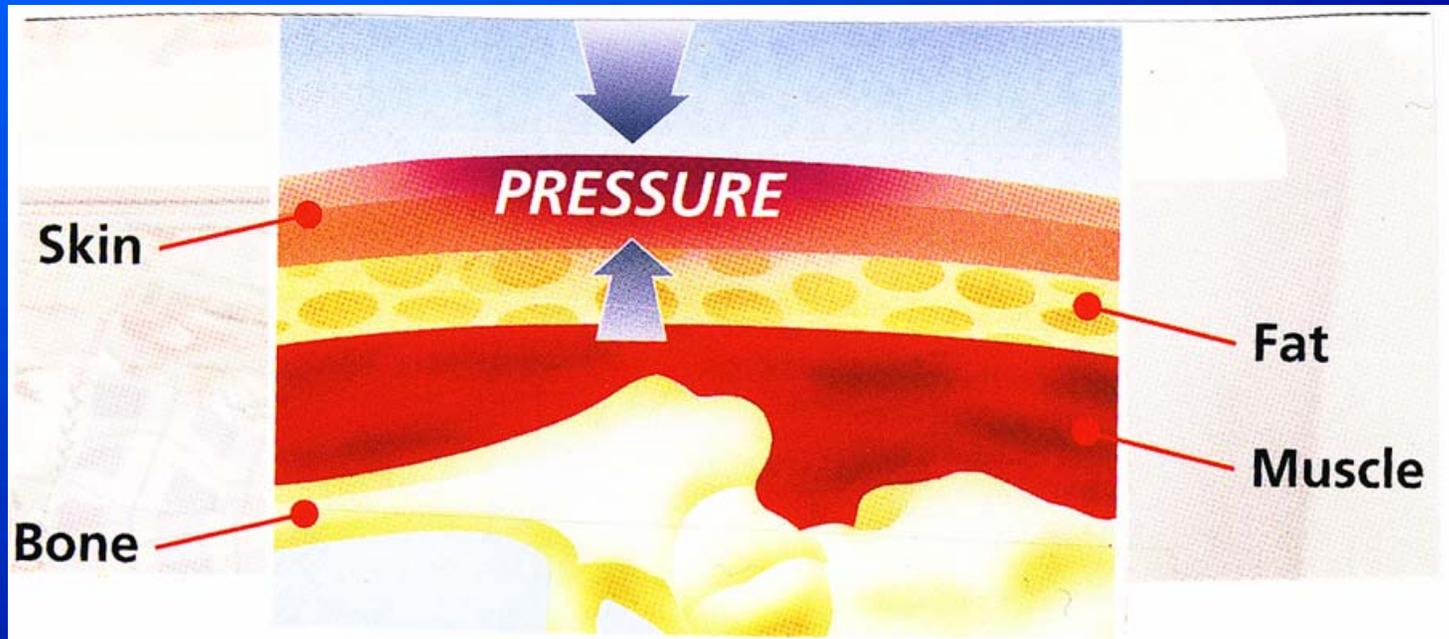
Laura E. Edsberg, Ph.D.



Tissue Microstructure

- **In Vitro**
- **In Vivo**
 - **Animal**
 - **Human**

Pressure



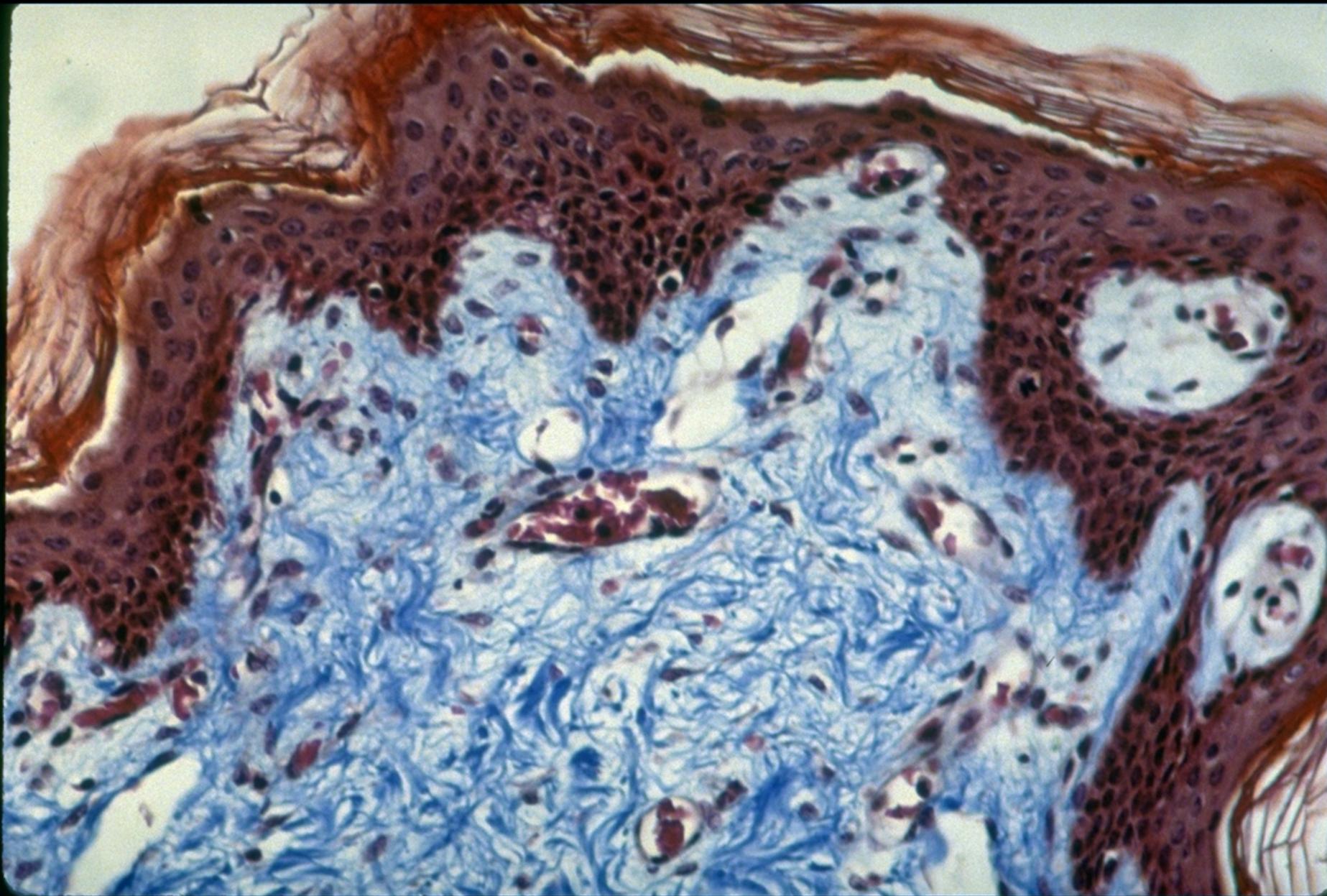
“The perpendicular load or force exerted on a unit of area”

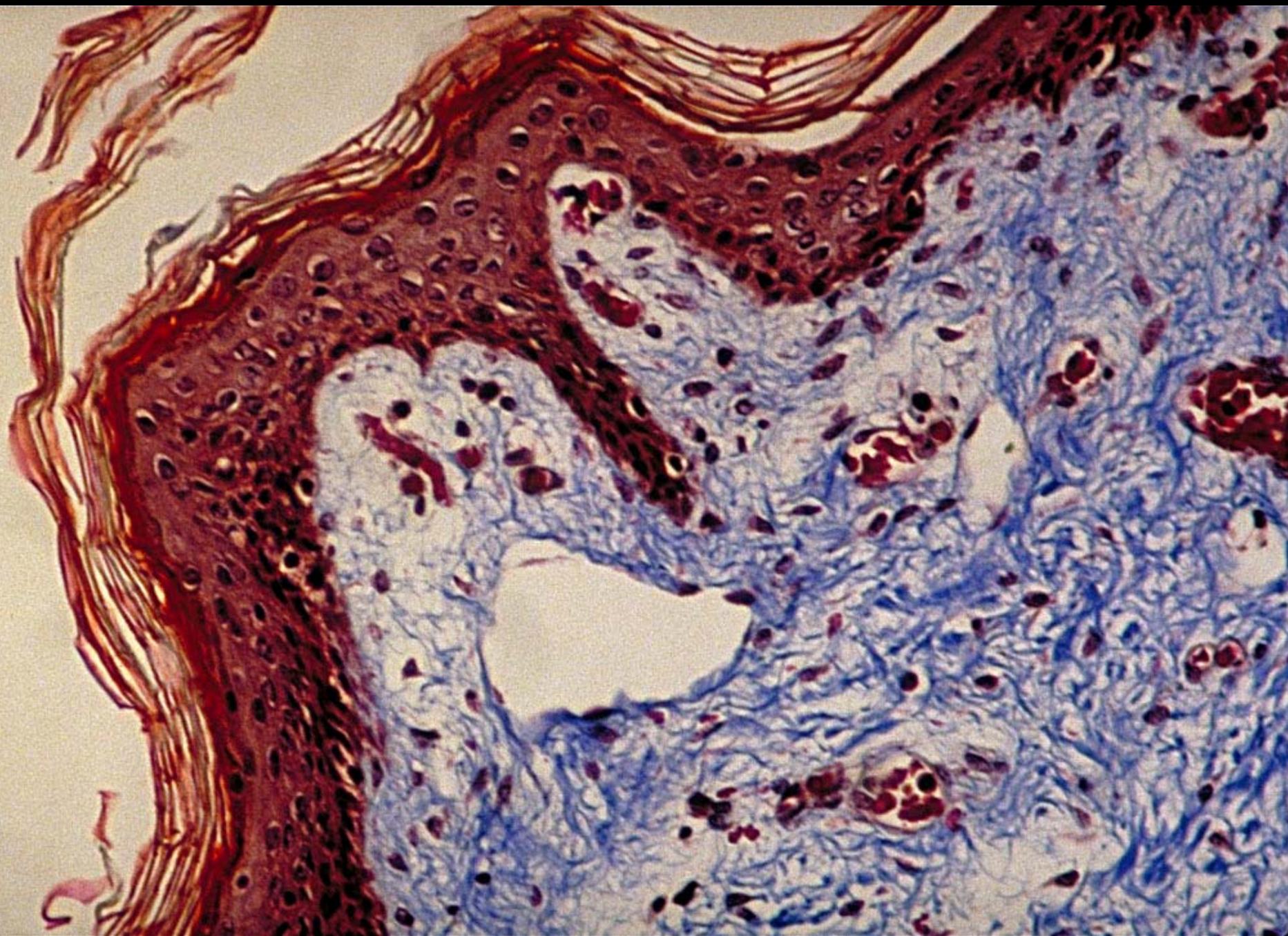
(Collier 1999)

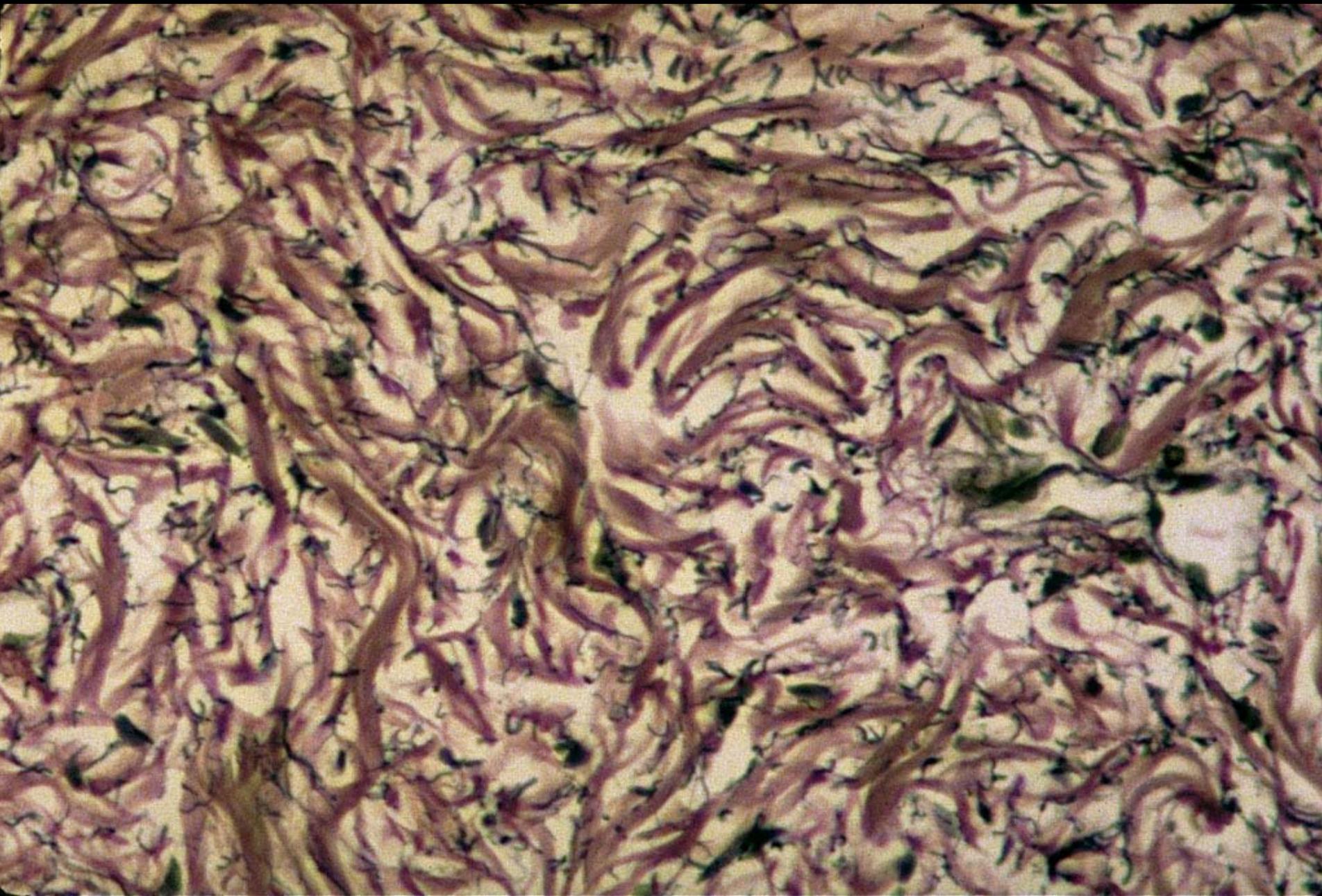
In Vitro Study

- **Human foreskin tissue**
- **Static pressure applied at 50 mm Hg**
- **Static pressure applied at 170 mm Hg**

Edsberg LE et al. Microstructural characteristics of human skin subjected to static versus cyclic pressure. Journal of Rehabilitation Research and Development 2001;38(5):477-486.

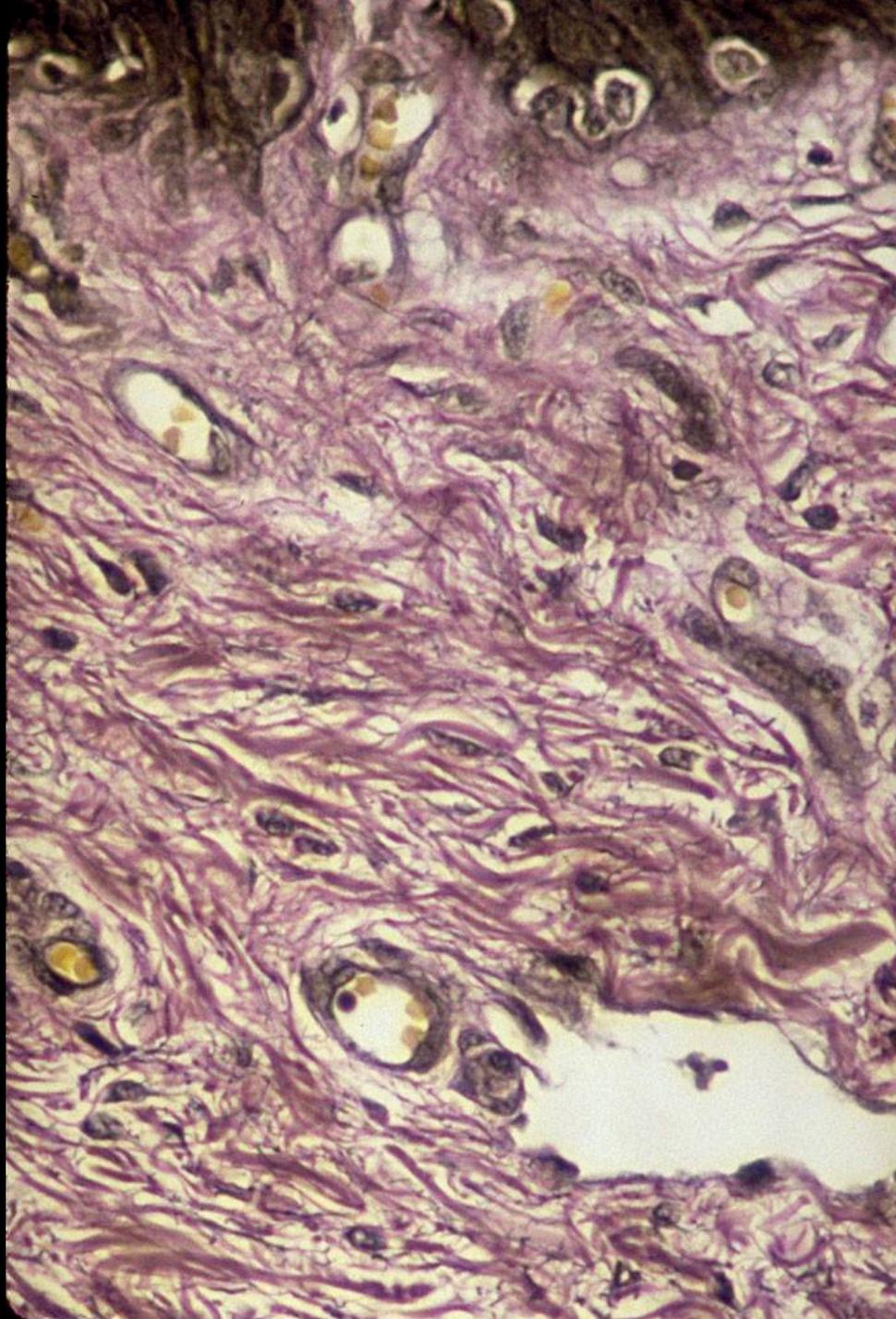


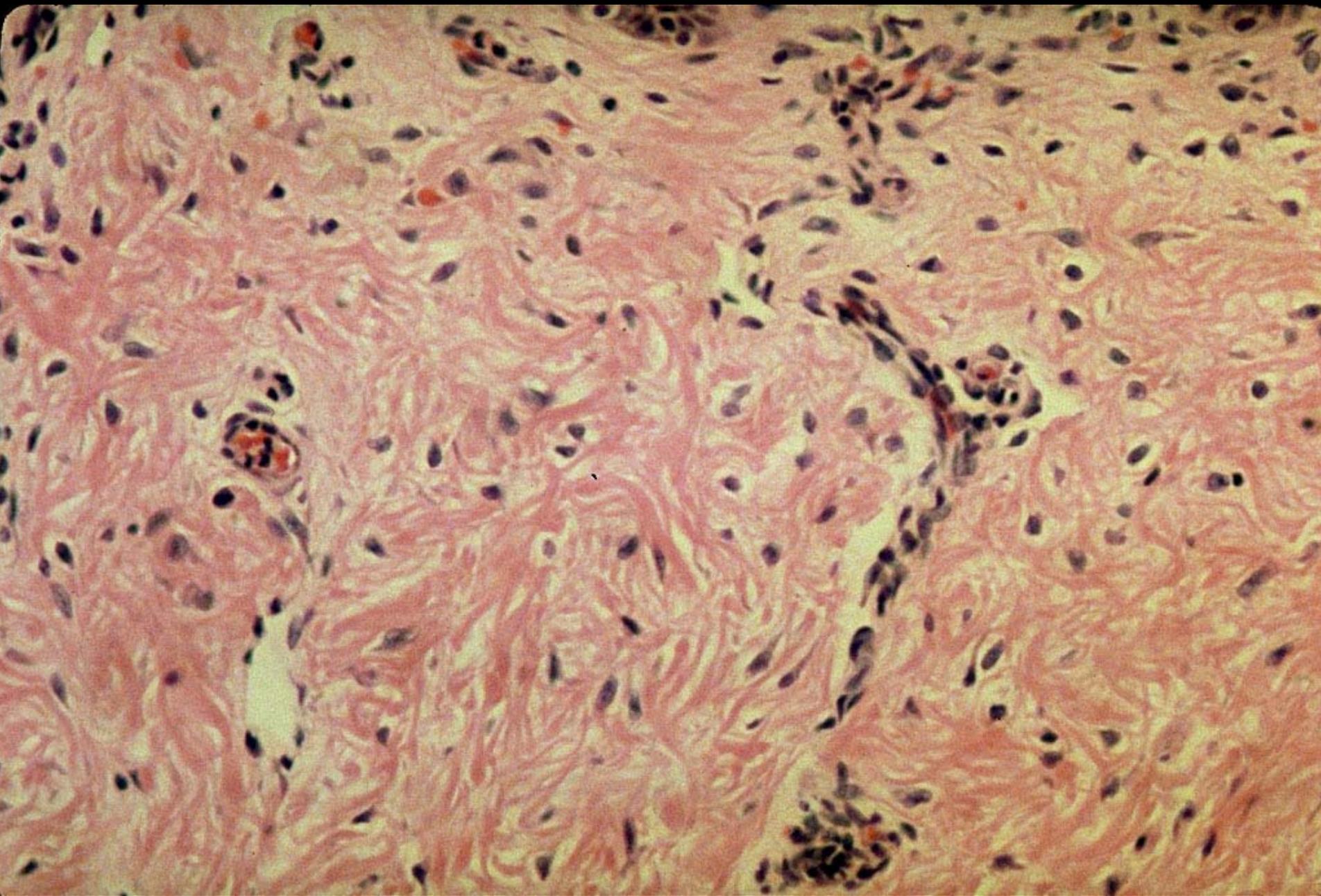




Static Pressure

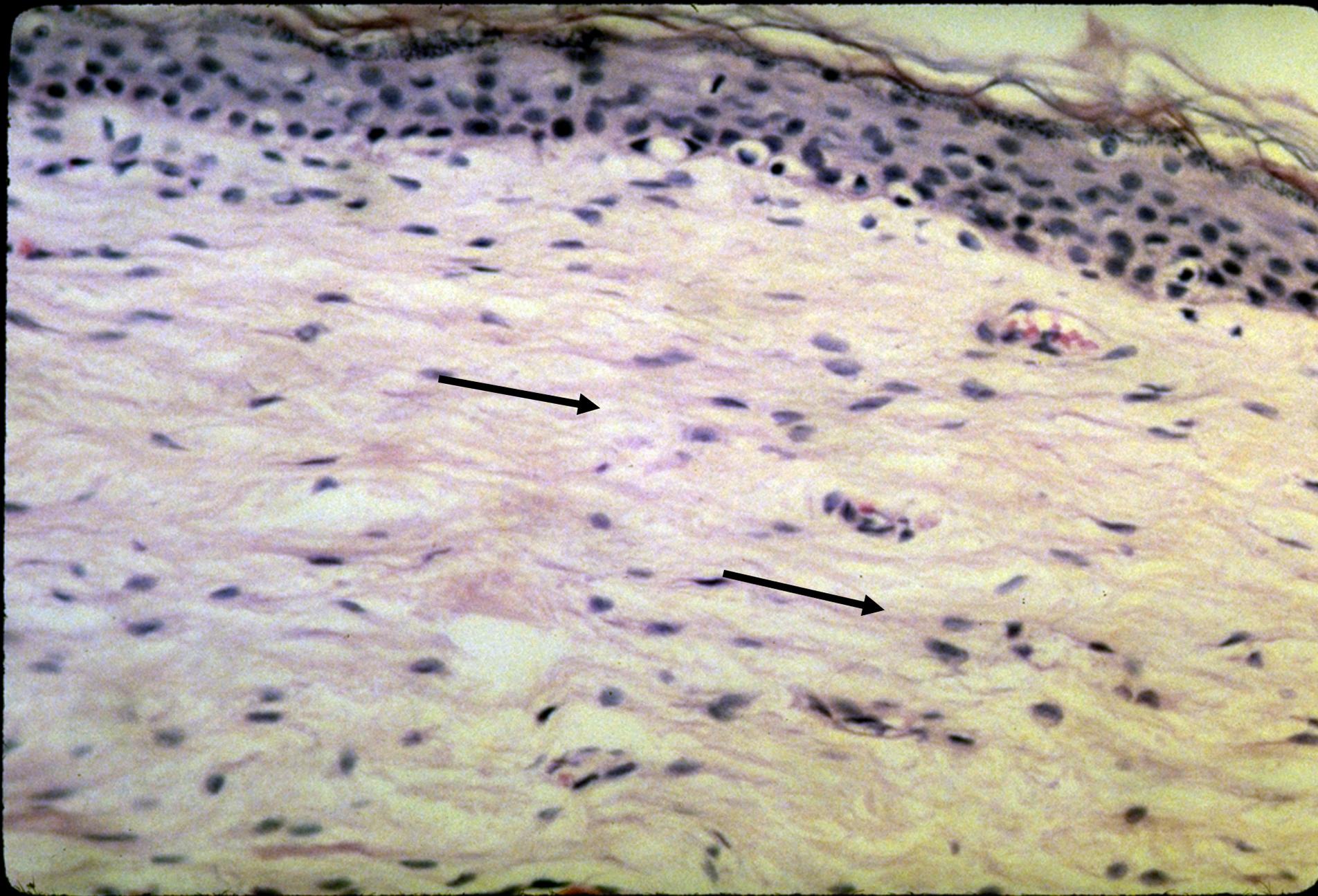
- 50 mm Hg
- 4 hour duration

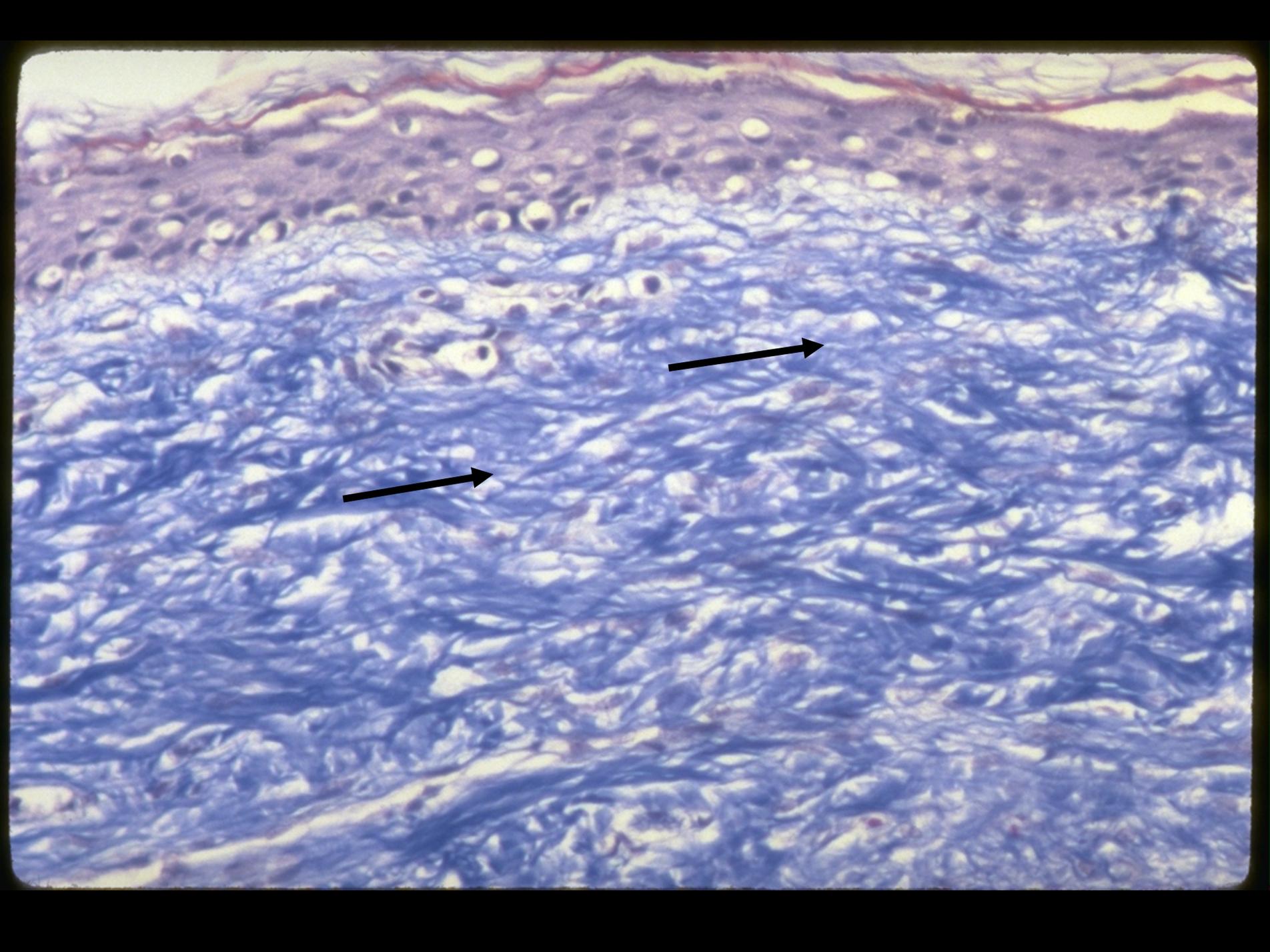




Static Pressure

- 170 mm Hg
- 4 hour duration



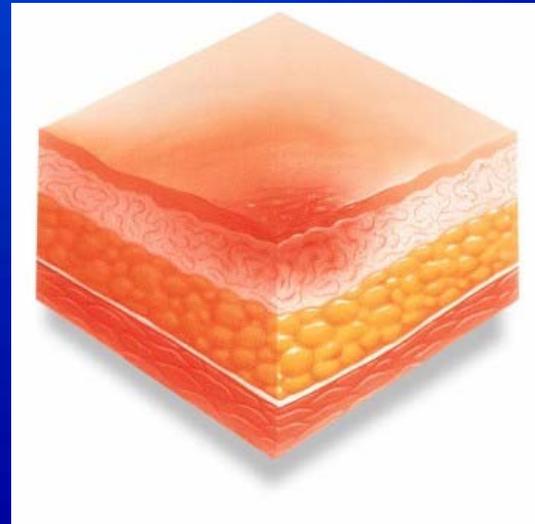


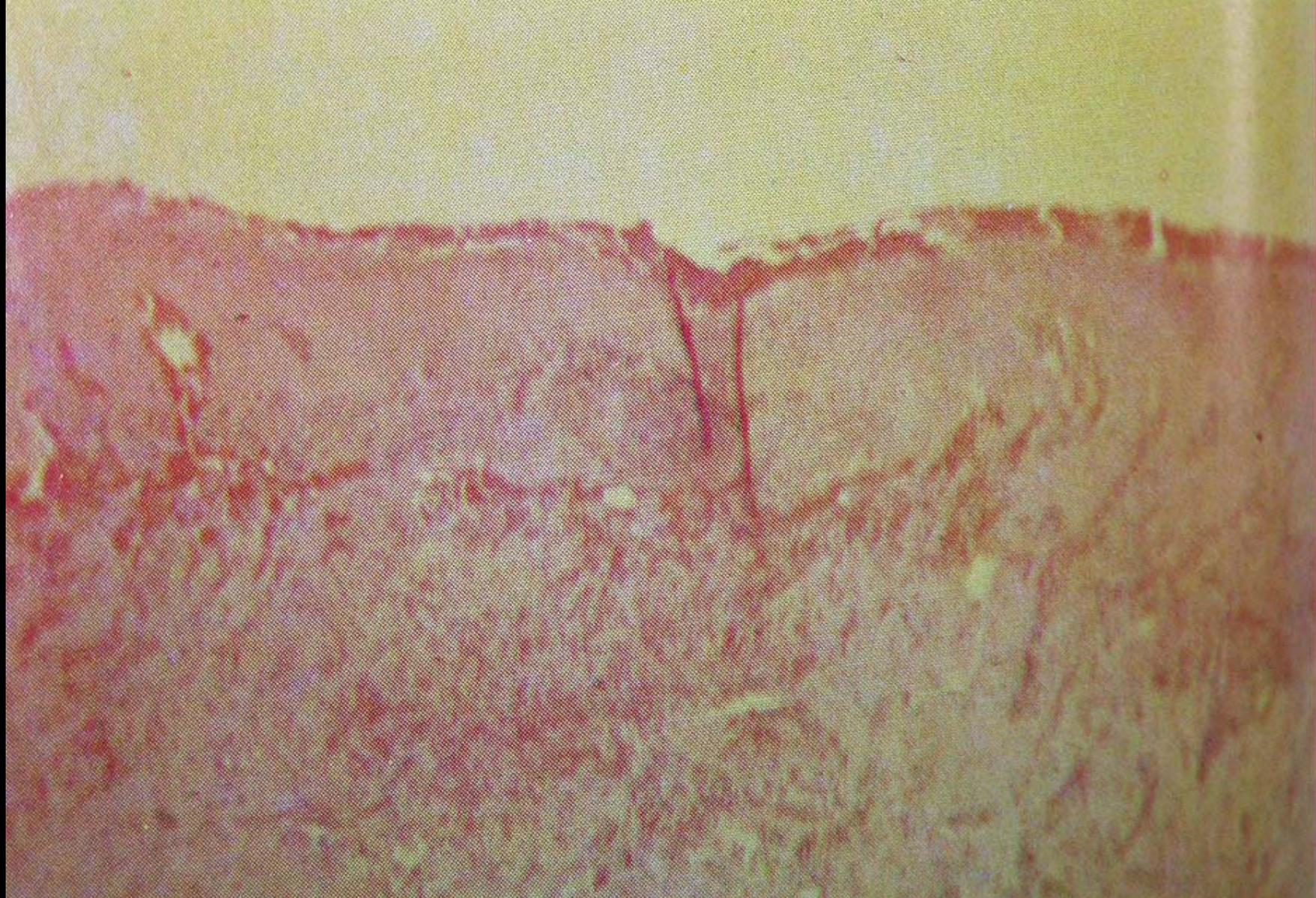
Limitations

- **Tissue utilized**
- **In vitro model**

Stage I Pressure Ulcer Definition

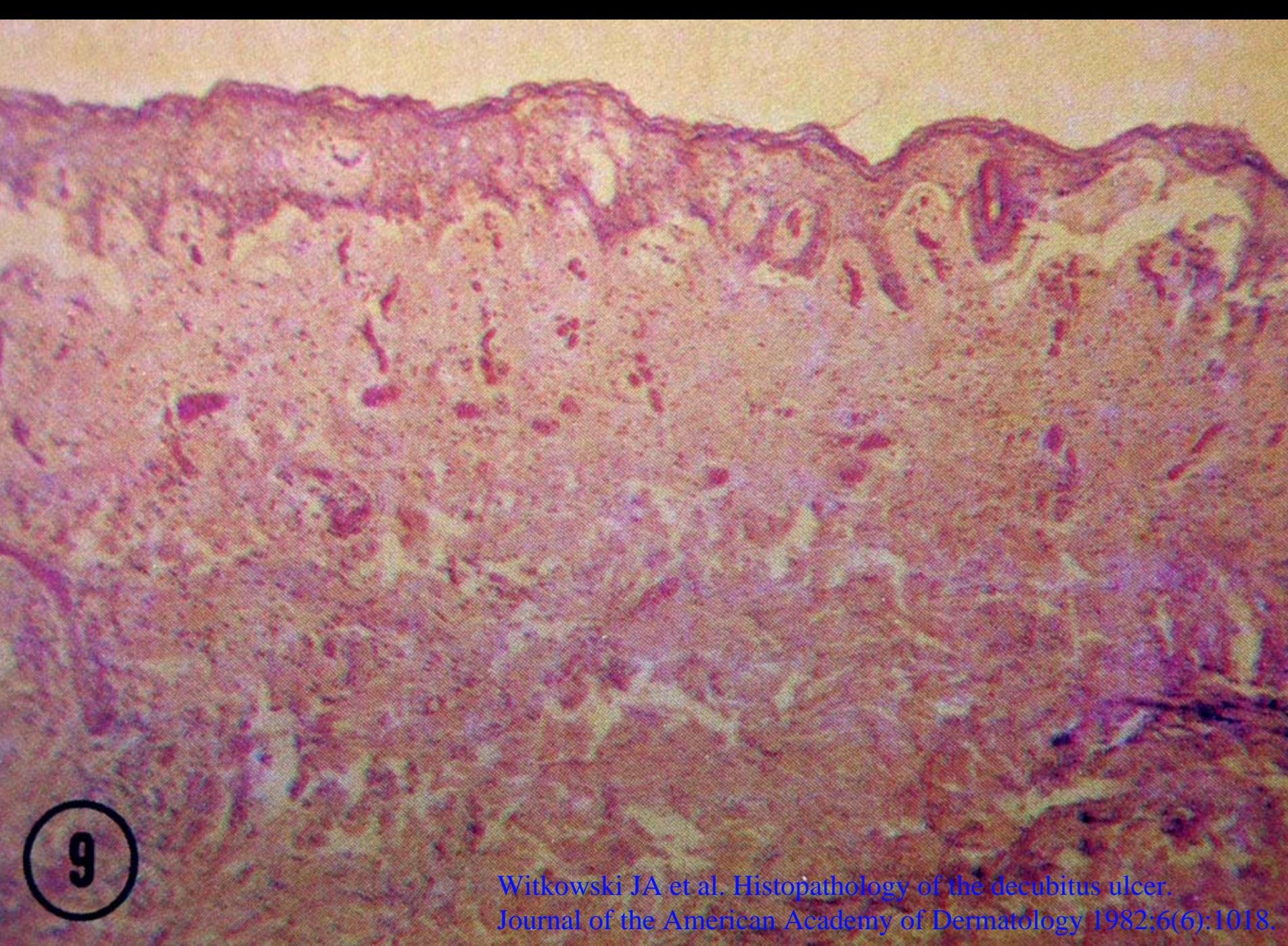
- A defined area of persistent redness (does not blanch) in lightly pigmented skin
- May appear with persistent red, blue, or purple hues in persons with darker skin tones. (NPUAP 2002)
- Compared to surrounding skin, area may also be
 - Warmer or cooler
 - Firm or boggy
 - Painful or itchy
- There is no open area in the skin





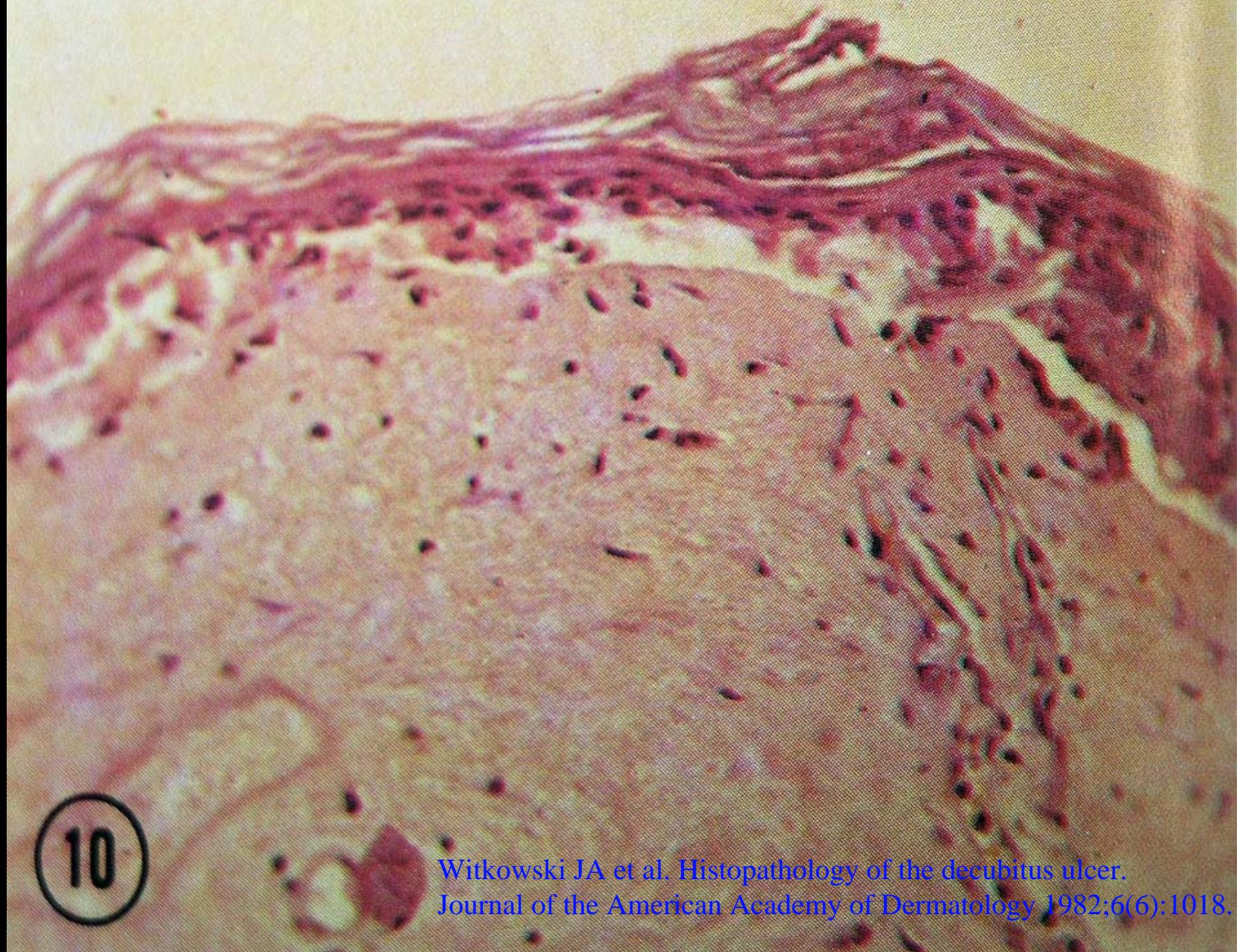
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Witkowski JA et al. Histopathology of the decubitus ulcer.
Journal of the American Academy of Dermatology 1982;6(6):1018.



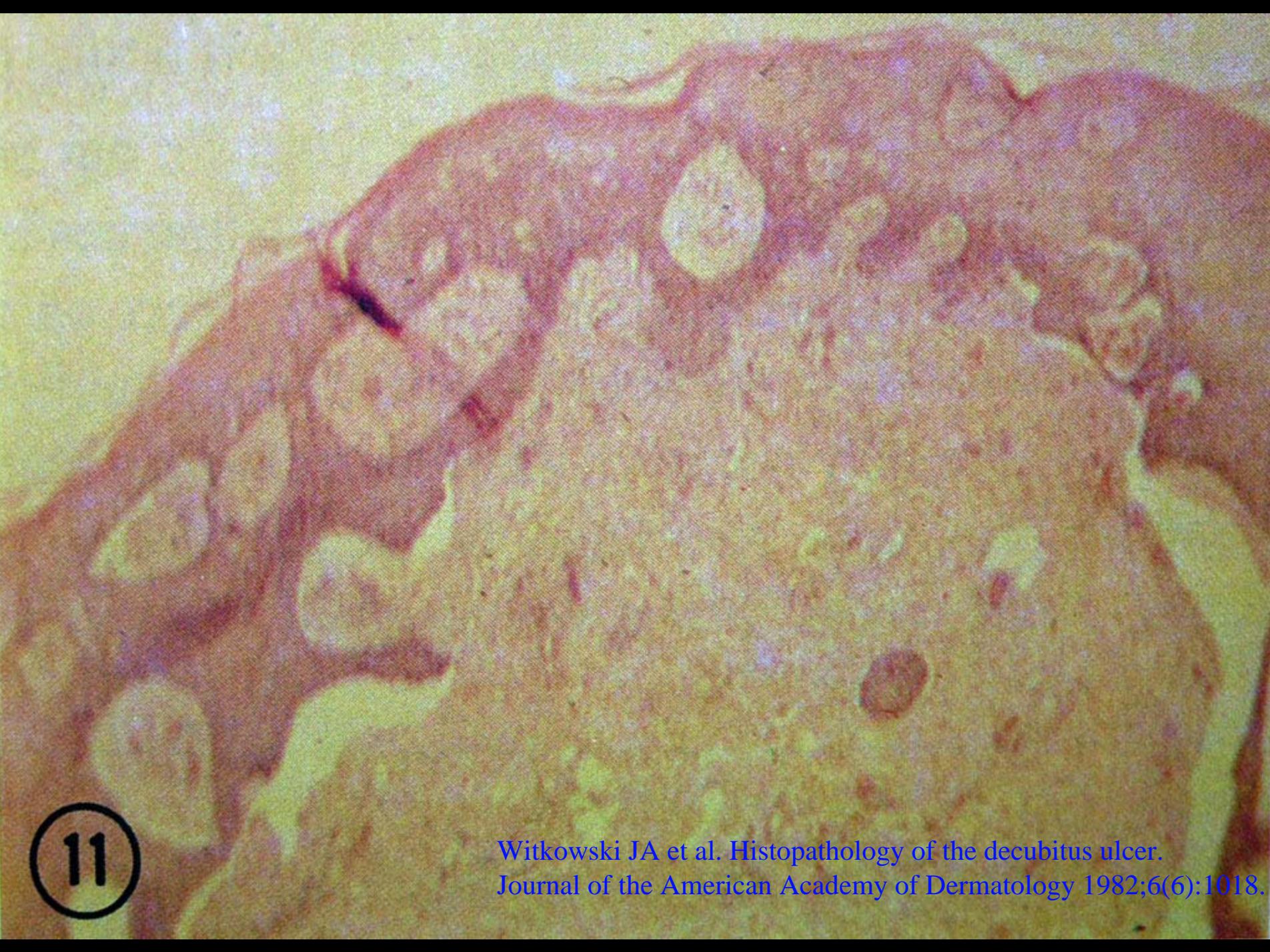
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Witkowski JA et al. Histopathology of the decubitus ulcer.
Journal of the American Academy of Dermatology 1982;6(6):1018.



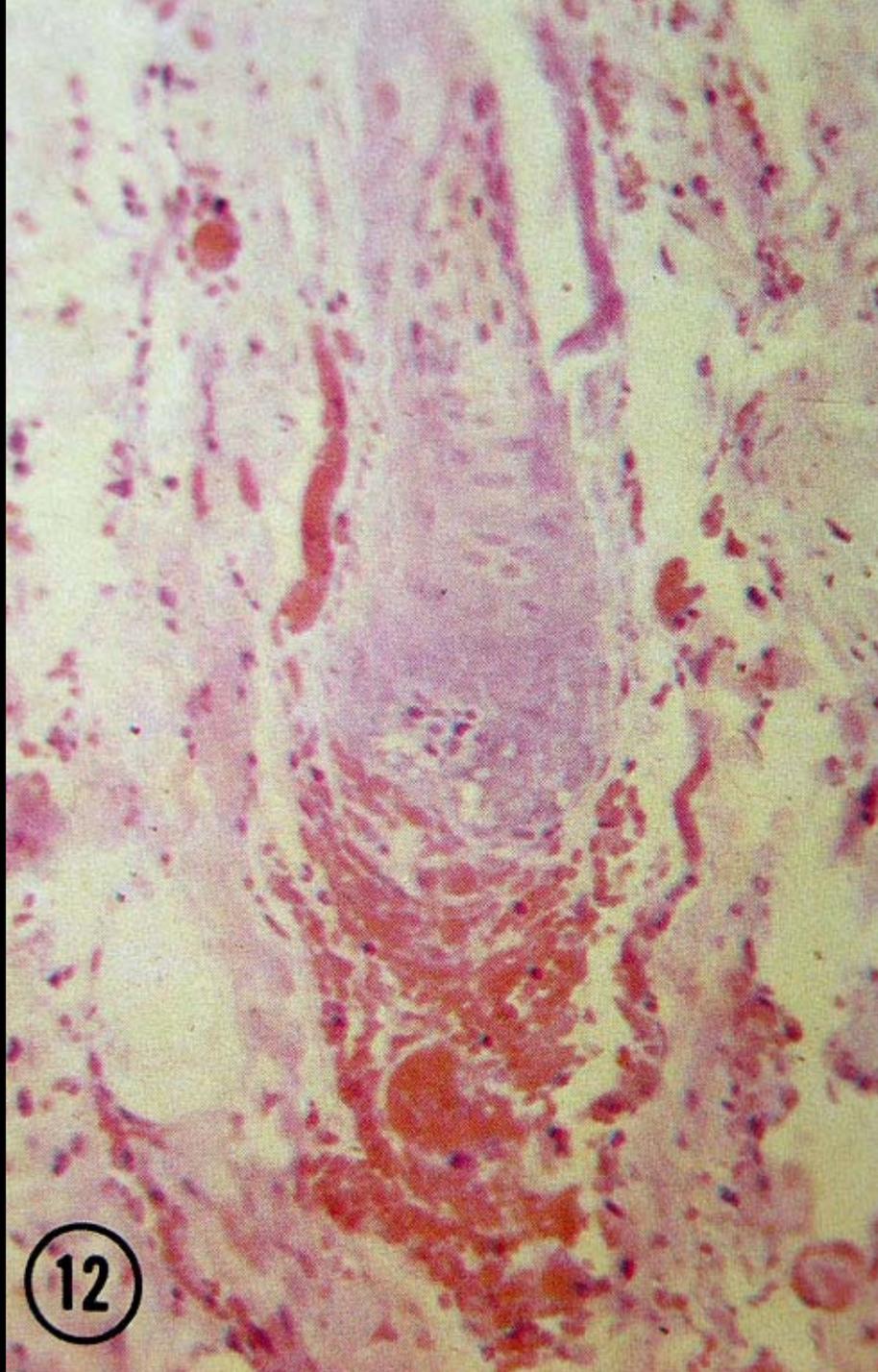
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Witkowski JA et al. Histopathology of the decubitus ulcer.
Journal of the American Academy of Dermatology 1982;6(6):1018.



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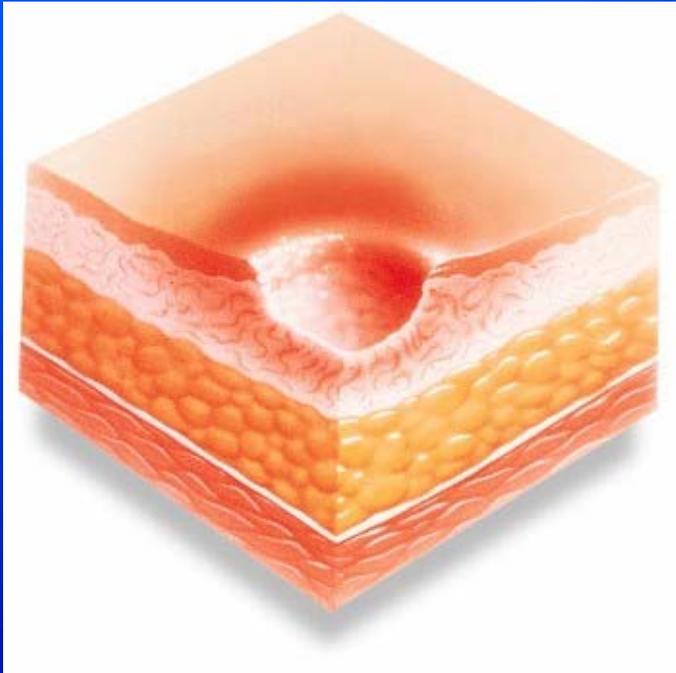
Witkowski JA et al. Histopathology of the decubitus ulcer.
Journal of the American Academy of Dermatology 1982;6(6):1018.



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Witkowski JA et al.
Histopathology of
the decubitus ulcer.
Journal of the
American Academy
of Dermatology
1982;6(6):1018.

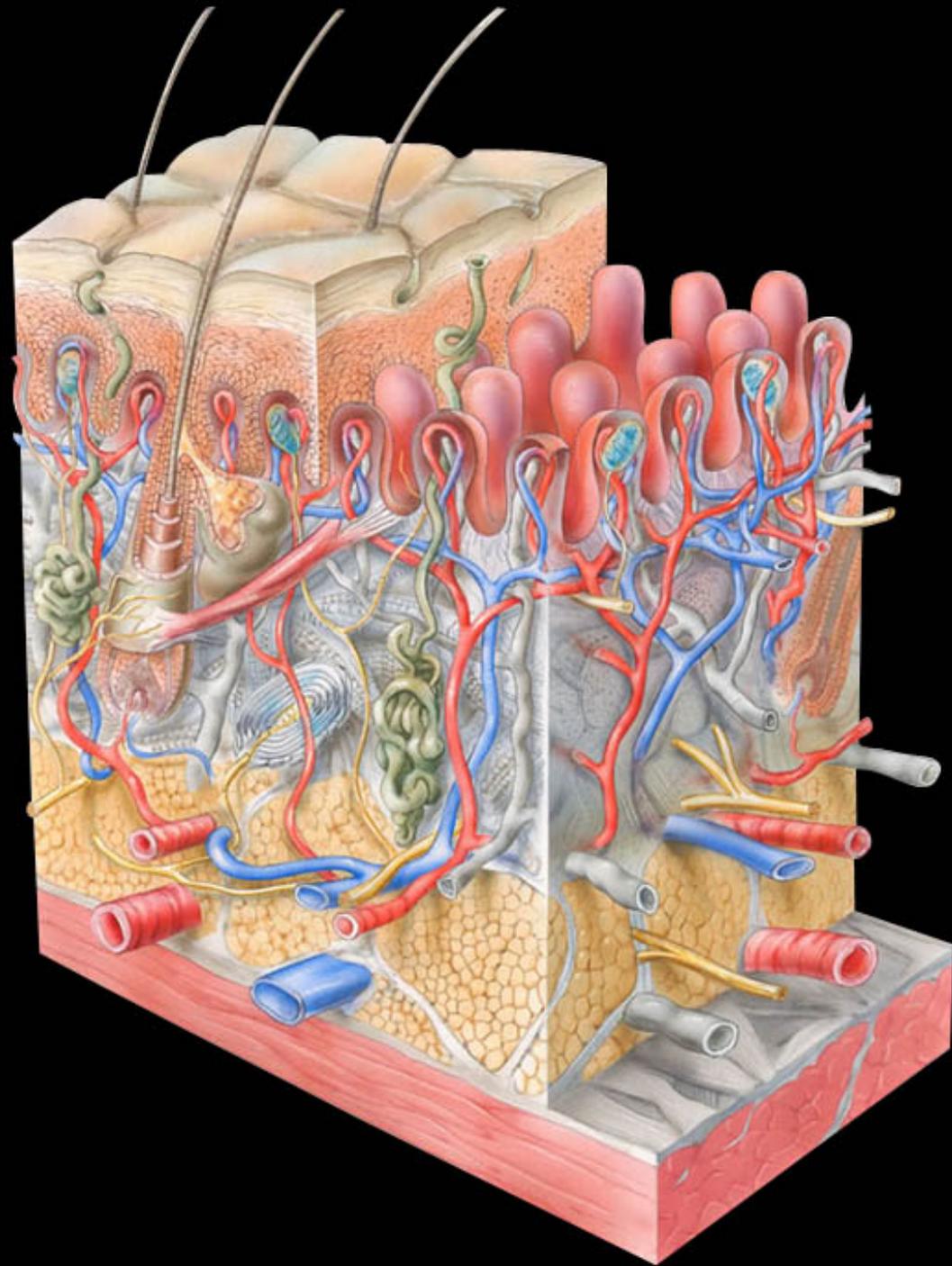
Stage II Pressure Ulcer Definition



**Partial thickness skin
loss involving
epidermis and/or
portions of dermis**

Ulcer is superficial

NPUAP (1989)



Healthy

Border

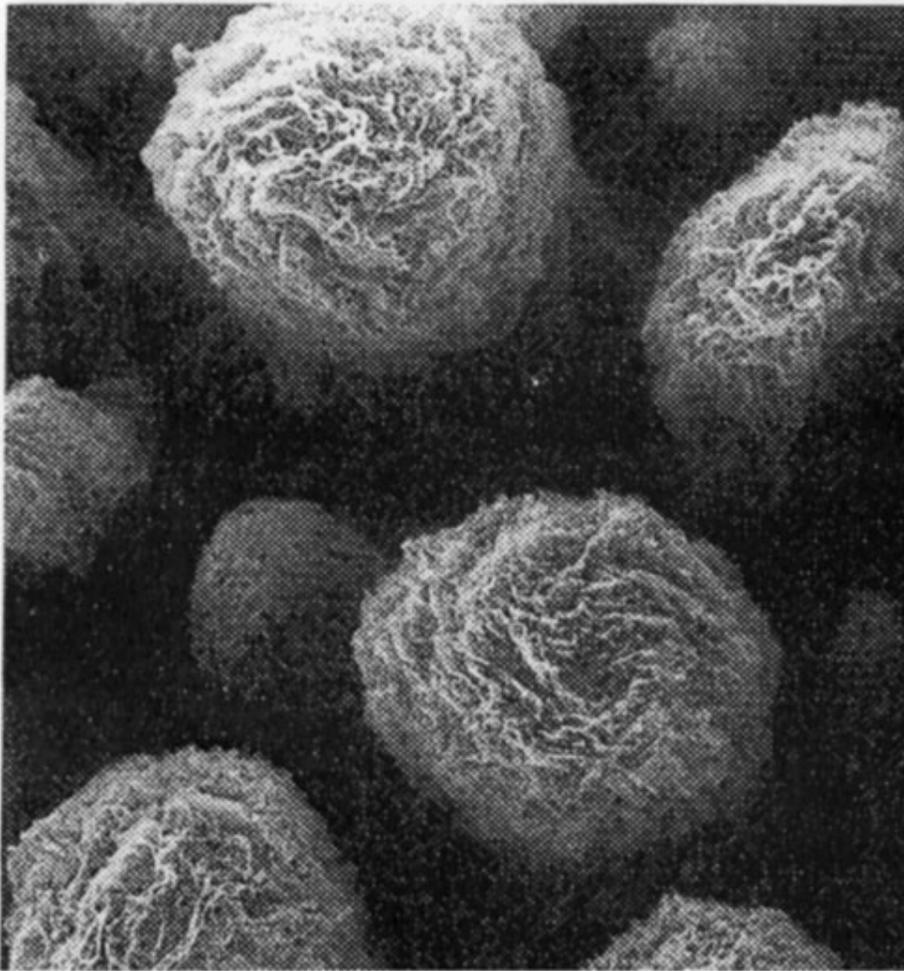
Damaged



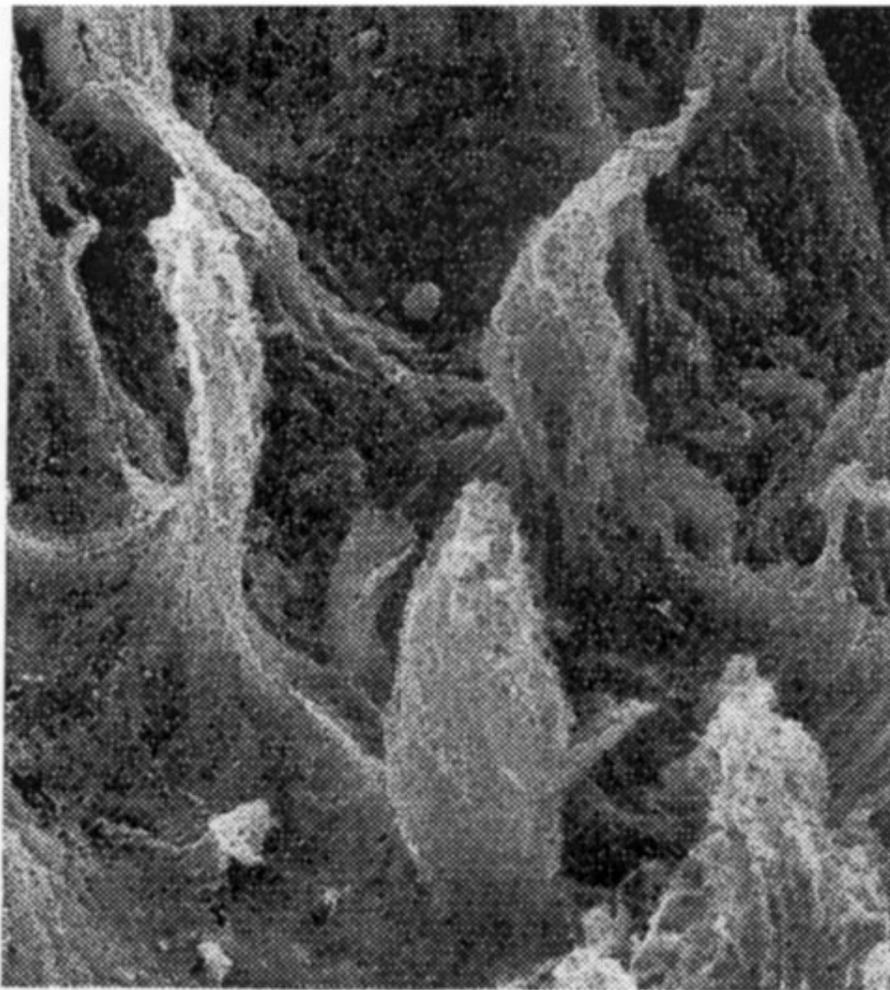
Arao H. et al. Morphological characteristics of the dermal papillae in the development of pressure sores. *Journal of Tissue Viability* 1998;8(3):18.



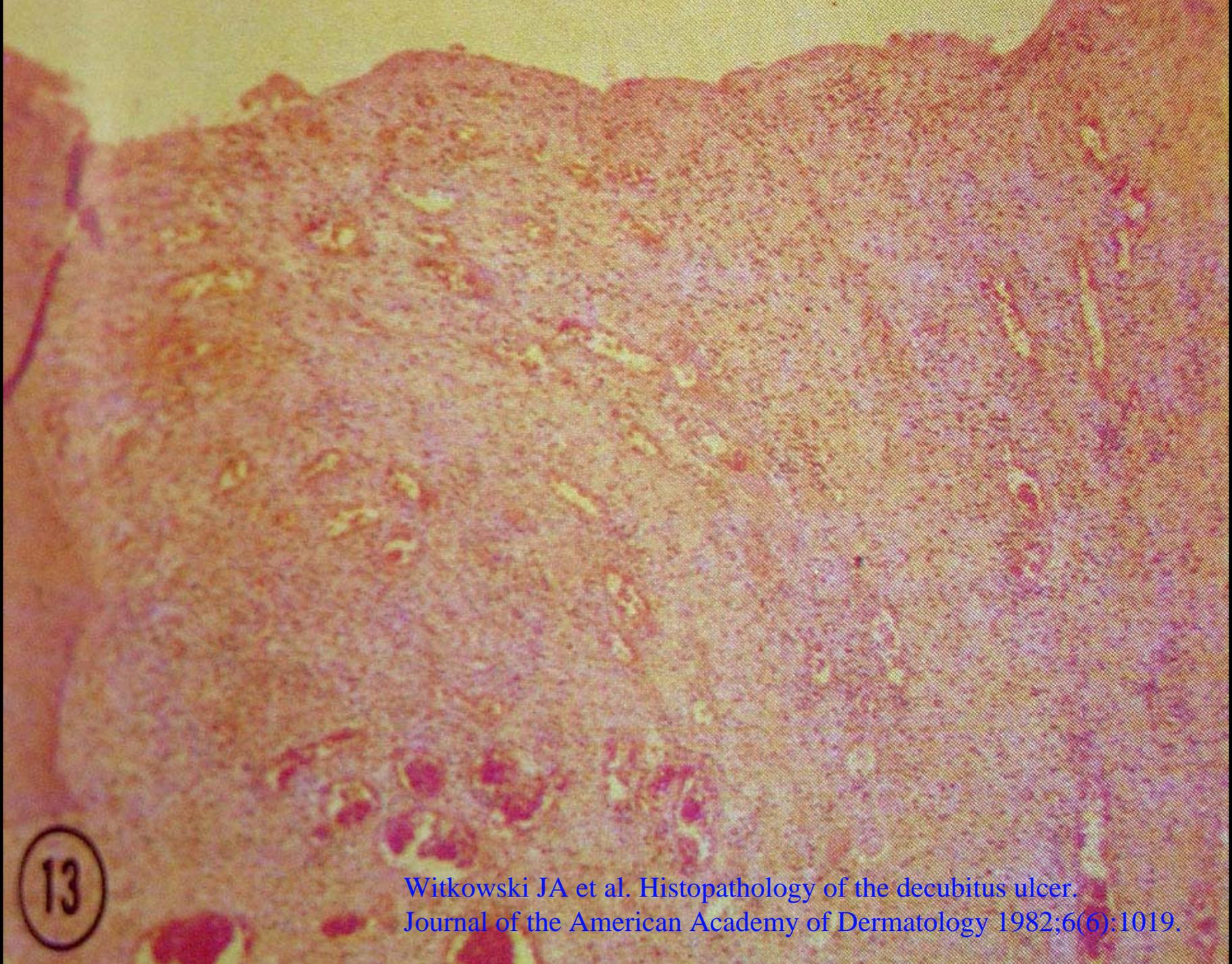
Arao H. et al. Morphological characteristics of the dermal papillae in the development of pressure sores. *Journal of Tissue Viability* 1998;8(3):19.



Arao H. et al. Morphological characteristics of the dermal papillae in the development of pressure sores. *Journal of Tissue Viability* 1998;8(3):20.



Arao H. et al. Morphological characteristics of the dermal papillae in the development of pressure sores. *Journal of Tissue Viability* 1998;8(3):20.

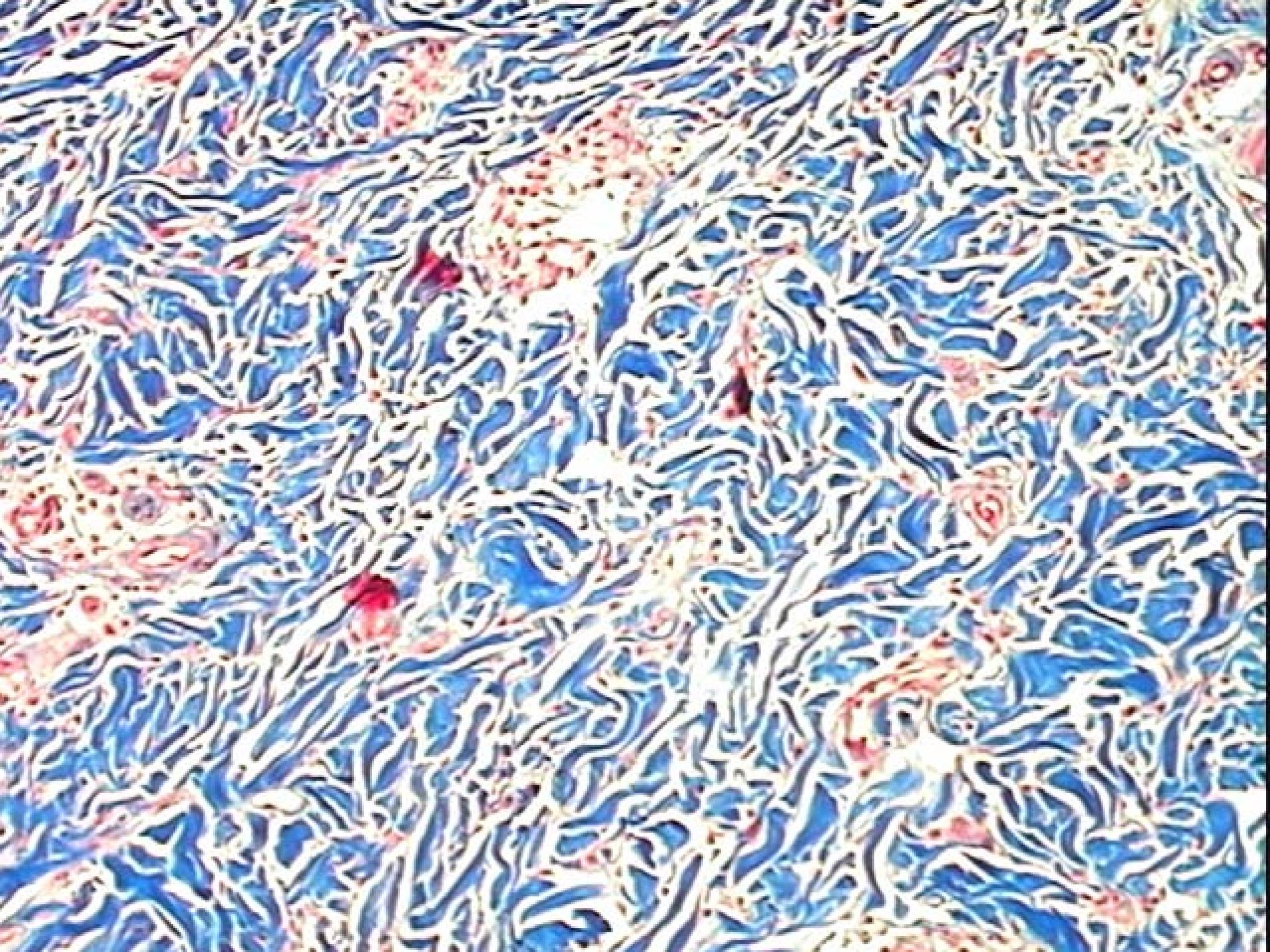


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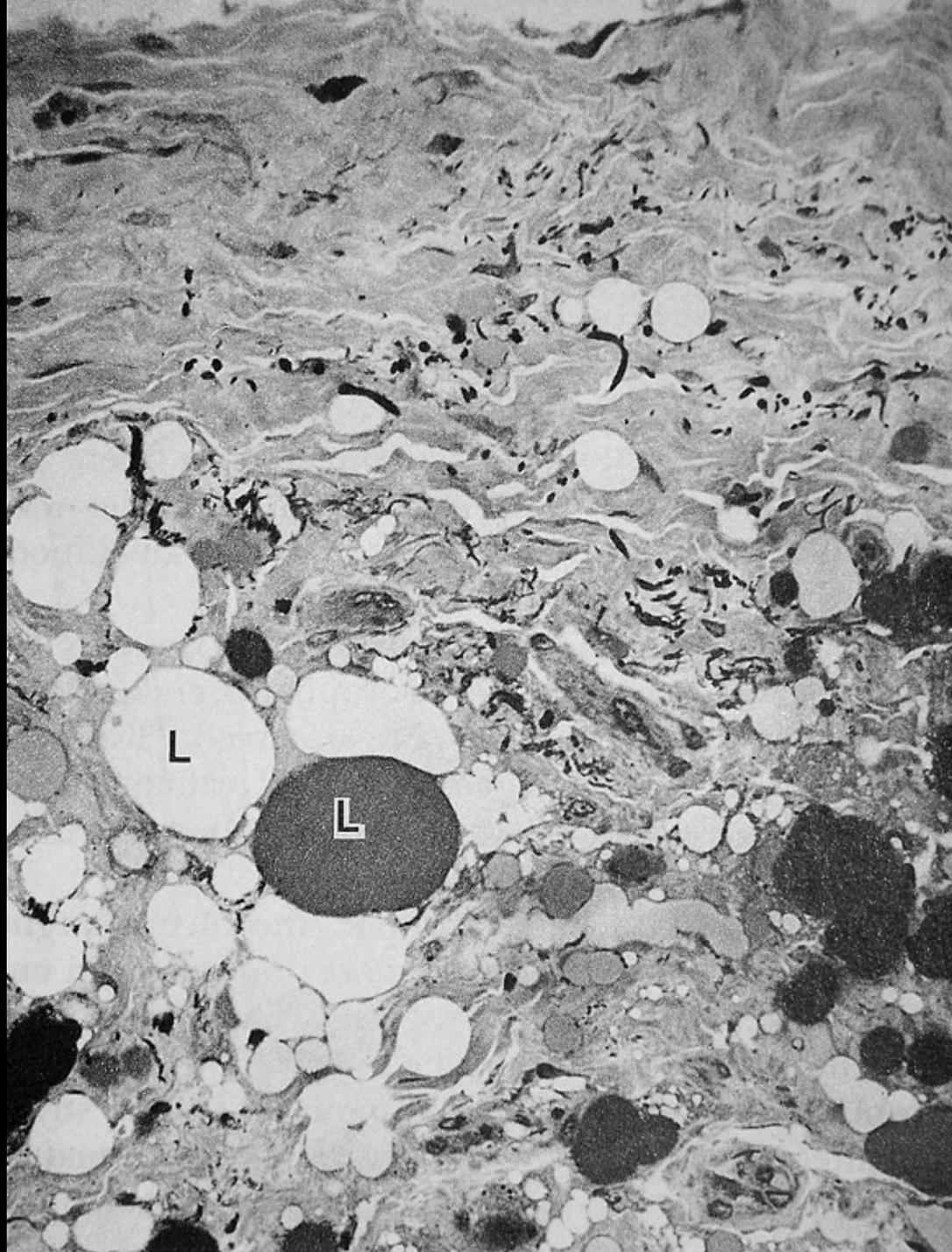
Witkowski JA et al. Histopathology of the decubitus ulcer.
Journal of the American Academy of Dermatology 1982;6(6):1019.

Tissue adjacent to pressure ulcers versus normal control tissue

Edsberg LE, Cutway R, Anain S, Natiella JR. Microstructural and mechanical
Characterization of human tissue at and adjacent to pressure ulcers.
Journal of Rehabilitation Research and Development 2000;37:463-471.







Vande Berg JS et al. Pressure (decubitus) ulcer: Variation in histopathology - a light and electron microscope study. *Human Pathology* 1995;26(2):198.



Vande Berg JS et al.
Pressure (decubitus)
ulcer: Variation in
histopathology
- a light and electron
microscope study.
Human Pathology
1995;26(2):198.



In Vivo Animal Studies

- **Tissue subjected to pressures > 60 mm Hg for durations > 1 hour**
 - Muscular necrosis, hyaline degeneration, venous thrombosis, etc
- **Tissue subjected to pressures > 115 mm Hg for durations > 3 hours**
 - More than 10% of the muscle fibers had signs of inflammation

Kosiak M. Etiology and pathology of ischemic ulcers. Archives of Physical Medicine and Rehabilitation 1959;40:62-69.

Kosiak M. Etiology of decubitus ulcers. Archives of Physical Medicine and Rehabilitation 1961;42:19-29.

In Vivo Animal Studies

- **Tissue subjected to pressures of 100 mm Hg for 2 hours**
 - Muscular necrosis, subcutaneous edema, etc
- **Tissue subjected to pressures of 100 mm Hg for 6 hours**
 - Compressed muscle with large numbers of inflammatory cells

In Vivo Animal Studies

- **Ischemic loading**
 - Changes were reversible
- **Compressive loading**
 - Changes irreversible

Stekelenburg A, Oomens CWJ, Strijkers GJ, Bader DL, Nicolay K. The relative contributions of deformation and ischaemia to deep tissue injury.

-
- **Other Factors???**

Wound Healing

- **Stages**
 - **Coagulation**
 - **Inflammation**
 - **Proliferation**
 - **Remodeling**

Coagulation Phase

- **Clotting process initiated immediately following tissue injury**
 - Wounds that extend past the epidermis
- **Platelets**
 - Aggregation
 - Hemostasis
 - Degranulation
 - Fibrin clot

Inflammation Phase

- **Initiated by several growth factors released from platelets**
 - PDGF, IGF-I, EGF, TGF- β , TNF- α
 - Migration of Neutrophils and Macrophages
- **Secretion of pro-inflammatory cytokines and proteases**
 - Elastase and collagenase
 - Degrade and remove damaged ECM components

Elevated Proteases

- **Neutrophil elastase (degrades fibronectin)**
 - **Greatly elevated in chronic wounds**
 - Yager DR, Chen SM, Ward BS, Olotoye O, Diegelmann RF, Cohen IK. Ability of wound fluid to degrade peptide growth factors is associated with increased levels of elastase activity and diminished levels of proteinase inhibitors. *Wound Repair and Regeneration* 1997;5:23.
- **MMP-2, 9 Elevated in chronic wounds**
 - Wysocki AB, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9. *Journal of Investigative Dermatology* 1993 Jul; 101(1):64-8.
 - Wysocki AB, Kusakabe AO, Chang S, Tuan TL. Temporal expression of urokinase plasminogen activator, plasminogen activator inhibitor and gelatinase-B in chronic wound fluid switches from a chronic to acute wound profile with progression to healing. *Wound Repair and Regeneration* 1999 May-Jun; 7(3):154-65.

Inflammation Phase

- **Macrophages**
 - **Secrete pro-inflammatory cytokines and growth factors**
 - **Stimulate migration of fibroblasts, vascular endothelial cells, and endothelial cells**

Proliferative Phase

- **Keratinocytes proliferate, migrate, and differentiate**
- **Endothelial cells from damaged blood vessels generate capillary buds**
- **Fibroblasts migrate and proliferate**

Fibroblasts

- **Synthesis ECM**
- **Source of matrix metalloproteinases (MMP's)**
 - Matrix degrading enzymes
- **Source of tissue inhibitors of metalloproteinases (TIMP's)**

TIMP Changes

- **TIMP's neutralize MMP's**
- **TIMP 1,2,3,4**
 - **decreased levels in chronic wounds**
- **Vaalamo M, Leivo T, Saarialho-Kere U. Differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing. Human Pathology 1999 Jul; 30(7):795-802.**
- **Bullen EC, Longaker MT, Updike DL, Benton R, Ladin D, Hou Z, Howard EW. Tissue inhibitor of metalloproteinases-1 is decreased and activated gelatinases are increased in chronic wounds. Journal of Investigative Dermatology 1995 Feb; 104(2):236-40.**

Remodeling Phase

- **Initial scar is in the process of synthesizing new components and degrading other components**
- **Matrix degrading enzymes - MMP's involved**
- **May last years**

Collagen Synthesis vs. Lysis

- **Balance**
- **Synthesis impeded**
 - **Decreased tensile strength**
- **Lysis decreased**
 - **Hypertrophy or keloid formation may occur**

Wound Fluid

- **Chronic wound fluid inhibits proliferation of**
 - **Fibroblasts**
 - **Keratinocytes**
 - **Endothelial cells**
- **Acute wound fluid stimulates**
- **EGF added to chronic wound fluid had significant degradation (28.6%) versus acute wound fluid (0.6%)**
 - **Trengove NJ, et al. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair and Regeneration 1999;7:442-452.**

Discussion Points

- **Growth factors often enhance healing in acute experimental animal models more than in human trials of chronic wounds**
- **Single growth factors**
- **Wound bed preparation**



QUESTIONS?