Macroscopic forces generated by cell-matrix interactions

I. Cells generate forces after becoming attached to a matrix.

II. How do cells attach to a matrix?

III. Cell-matrix interactions control the spontaneous closure of wounds in organs.

IV. What happens when wound closure occurs by induced regeneration?

III. Cell-matrix interactions control the spontaneous closure of wounds in organs.

- **Outline.**
- **What are the different types of tissue and organ injury? How does the organism respond to injury?**
- **The irreversibility of injury**
- **Mechanism of contraction and scar formation**
- **Quantitative measurement of healing modes: The defect closure rule**

Description of response to injury: Contraction and scar formation following trauma

A. Sources of trauma: energy sources.

- **mechanical: deep cut, laceration, surgery**
- **thermal: fire, hot water.**
- **electromagnetic: UV, electrical discharge**
- **nuclear: radiation therapy.**

Contraction and scar formation following trauma (cont.)

B. Outcome of trauma, scar formation and contraction

- **on finger joint it prevents movement ("contracture")**
- **in peripheral nerves (neuroma) it prevents conduction of electric signals (paralysis)**
- **in neck of face it creates serious problems of social acceptance**
- **around suture points (e.g., following caesarian section)**
- **surgical adhesions prevent normal function of intestines**

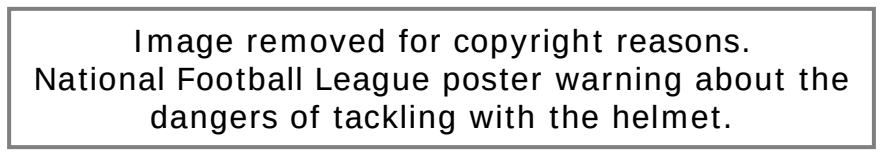
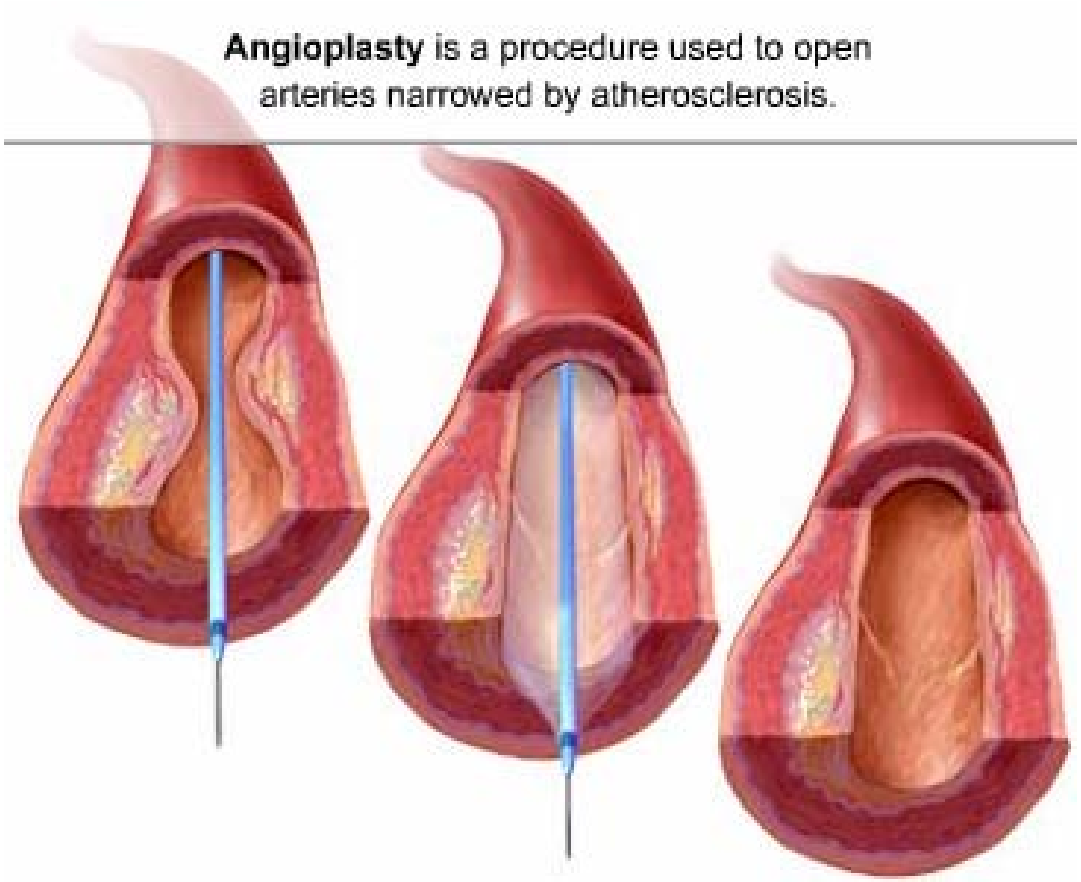


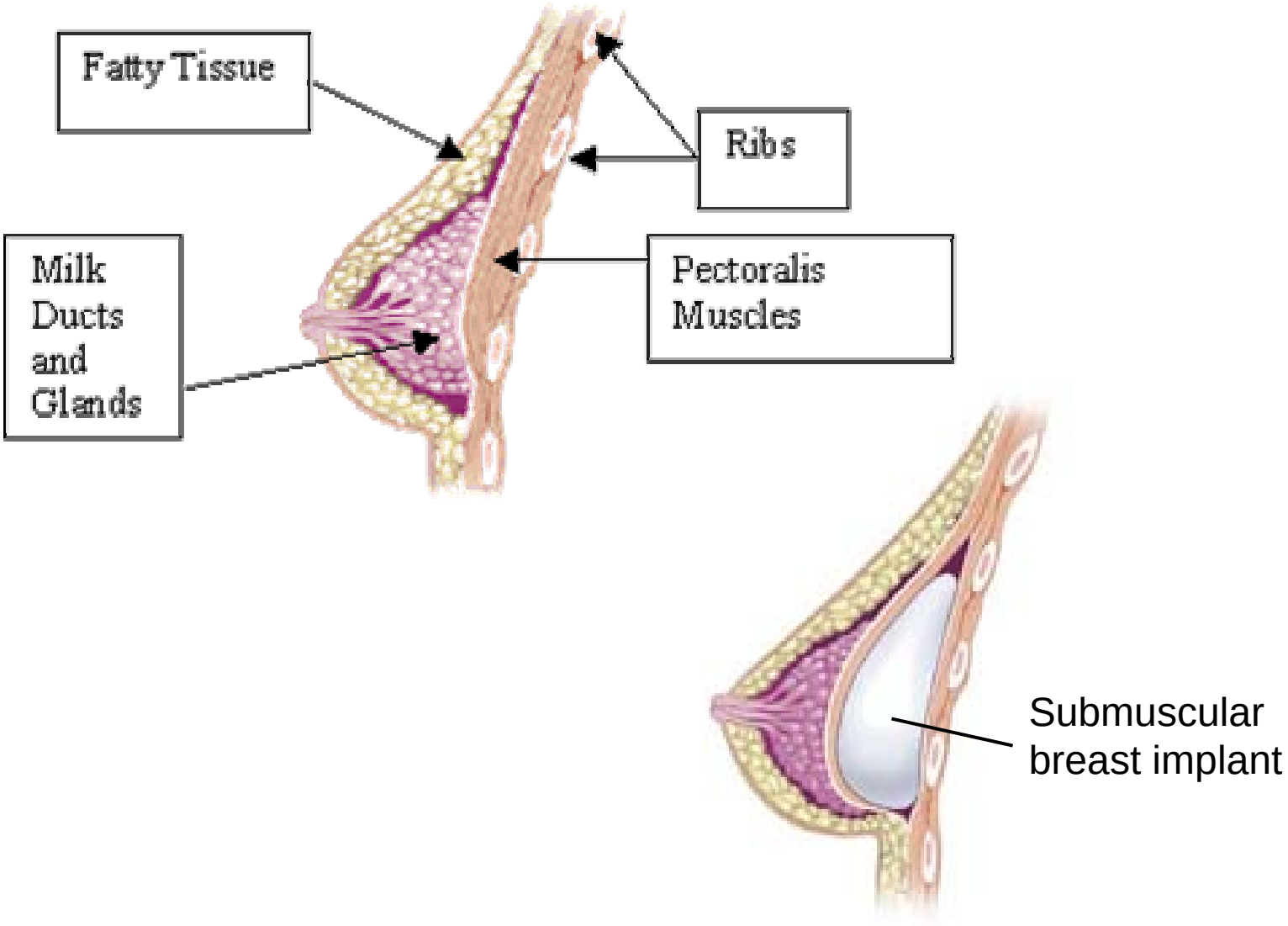
Image removed for copyright reasons.
National Football League poster warning about the dangers of tackling with the helmet.



Source: U.S. FDA. “Cardiac Angioplasty Device.”
http://www.fda.gov/hearthealth/treatments/medicaldevices/angioplasty.html

C. Scar formation around “inert” implant

1. Scarring following implantation of any nondegradable prosthesis (e.g., silicone, polyethylene)
2. Constrictive scar tissue (fibrous capsule) around implant causes chronic pain and implant deformation
3. Implantation of nonporous, biodegradable sheet under skin (subcutaneous) leads to encapsulation of implant by fibrotic tissue. No capsule formation around identical implant, except for being porous.
4. Implants are often supported mechanically by contraction and scar formation around them.



Source: U.S. FDA. “Making an Informed Decision: Saline-Filled Breast Implant Surgery – 2004 update.” http://www.fda.gov/cdrh/breastimplants/labeling/inamed_patient_labeling_5900.html

D. Chronic scar formation

- **Scar formation and contraction result from chronic trauma; or from acute or chronic inflammation caused by various agents**
- **Scar takes different names depending on medical specialty**
- **Examples: 1. Scarred heart valve due to incidence of rheumatic fever leads, e.g., to valve stenosis or to leakage.**

  2. Necrosis (death) of myocardium (infarct)

  due to interruption of oxygen supply (clogged arteries) interferes with electrical conduction of heart muscle

  3. Obstruction of intestinal tract, due to chronic inflammation, leads to digestive problems (e.g., duodenal ulcer with gastric outlet obstruction)

  4. Fibrotic liver (cirrhosis) prevents liver function

scarred heart muscle (heart attack)

scarred liver (cirrhosis)

scarred kidney (infection)

Diagram removed due to copyright considerations.
See Figure 1.3 in [Yannas 2001]: Yannas, I. V. *Tissue and Organ Regeneration in Adults*. New York: Springer, 2001.

scarred cornea (infection)

scarred heart valve (rheumatic fever)

The irreversibility of injury

Amphibian: reversible injury

Spontaneous regeneration of amputated limb in the newt (a small amphibian) occurs independently of severity of injury

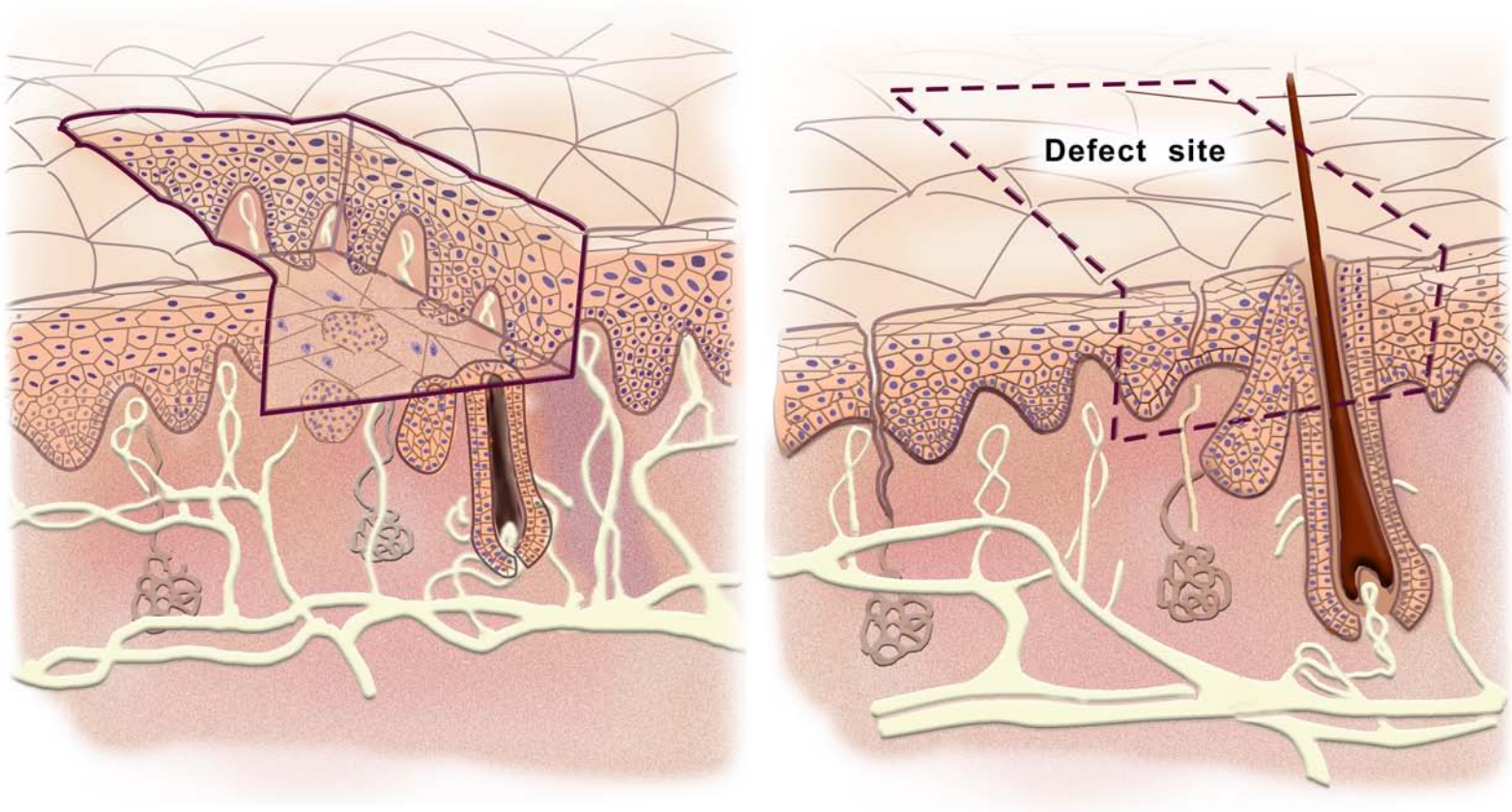
Diagram removed for copyright reasons.
See Figure 1.1 in [Yannas 2001].

Liver: Reversible or irreversible injury?

The healed liver has the same mass, but a different shape (resected lobes are not regenerated), than the intact organ

Diagram removed for copyright reasons.
See Figure 1.2 in [Yannas 2001].

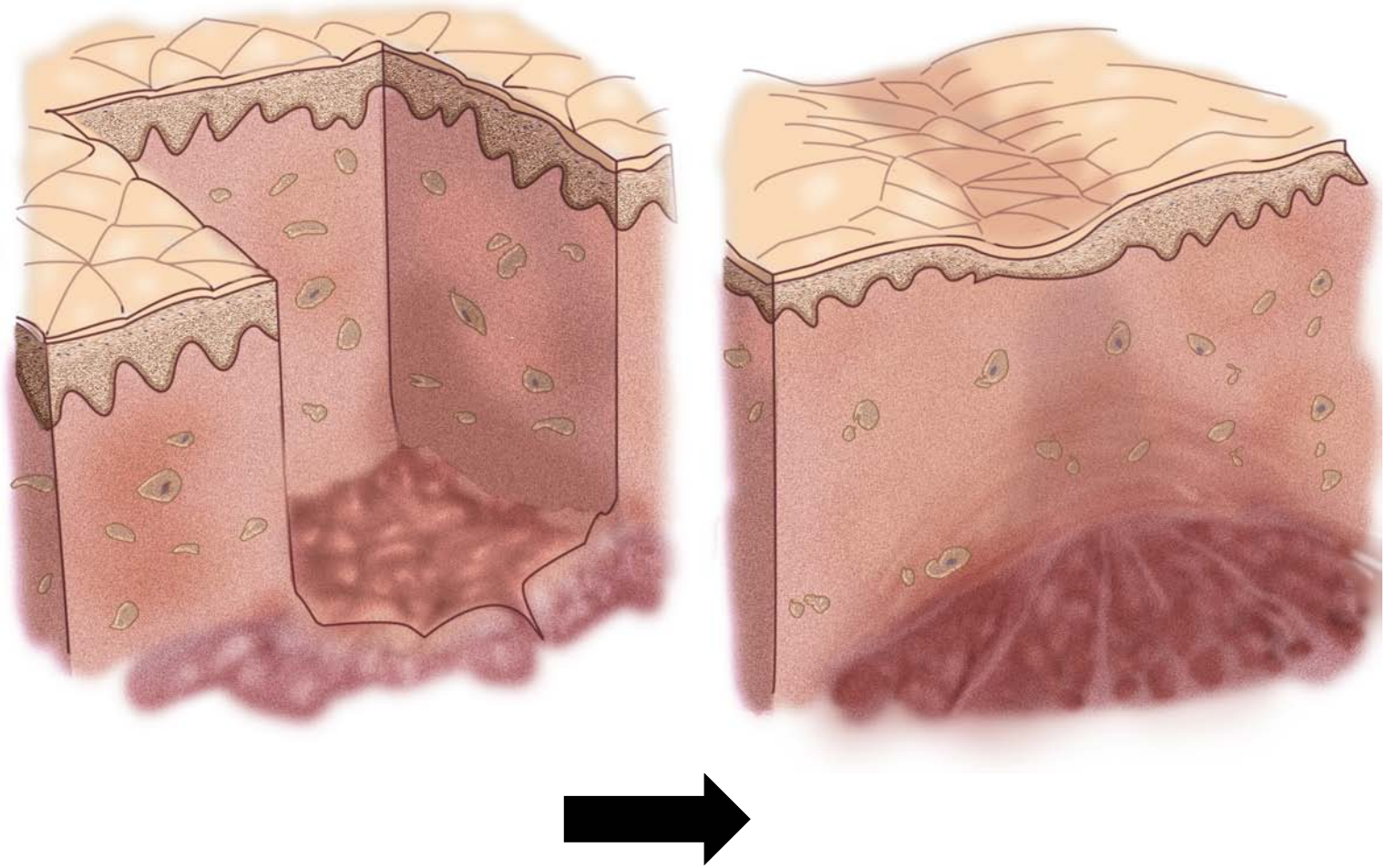
Skin: reversible injury



Spontaneous regeneration of excised epidermis

Figure by MIT OCW. After Figure 2.1 in [Yannas 2001].

Skin: irreversible injury



Spontaneous healing of skin excised to full thickness by contraction and scar formation. The dermis does not regenerate.

Figure by MIT OCW. After Figure 2.2 in [Yannas 2001].

Peripheral nerve: reversible injury

Mildly crushed nerve heals spontaneously by regeneration

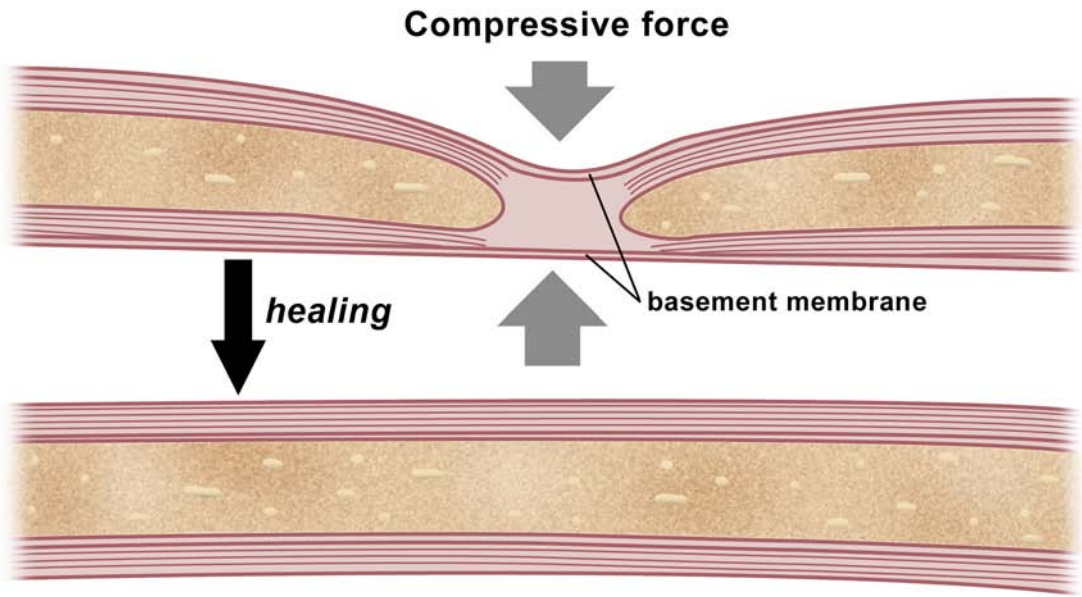
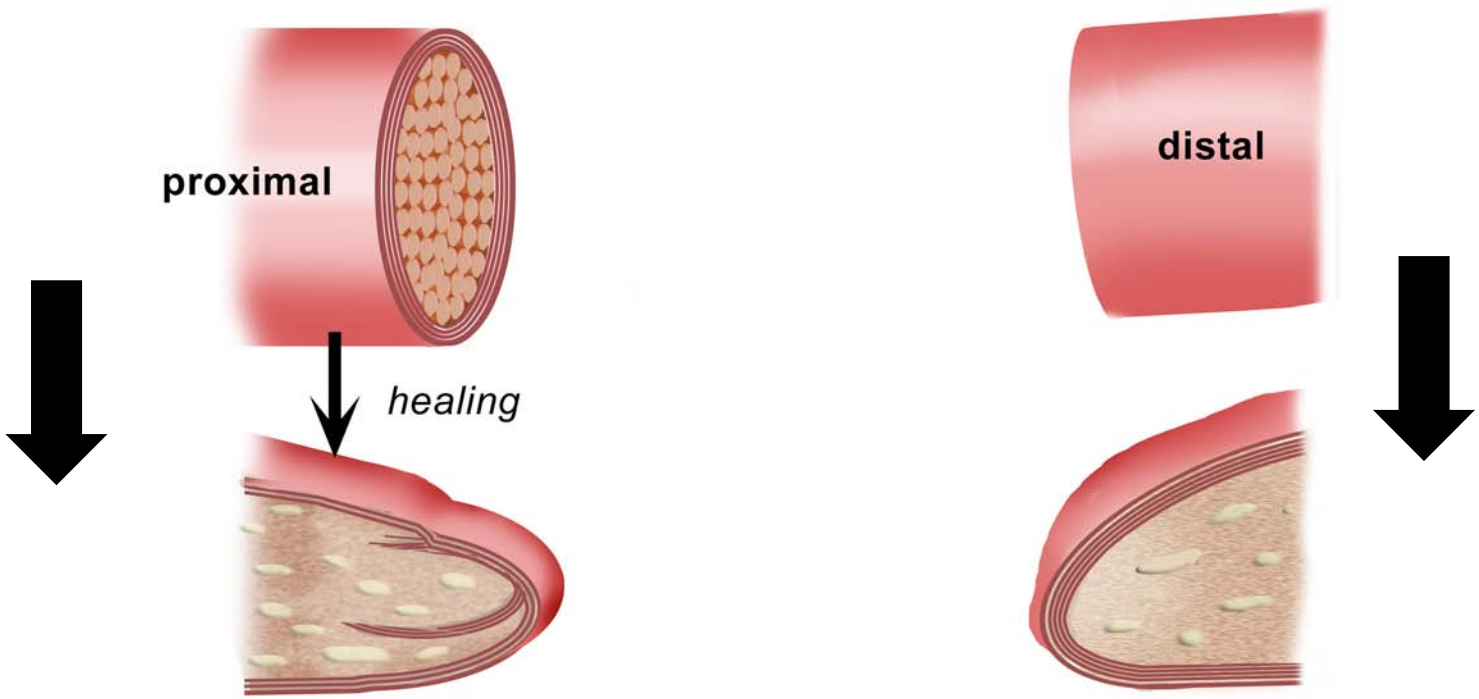


Figure by MIT OCW. After Figure 2.3 in [Yannas 2001].

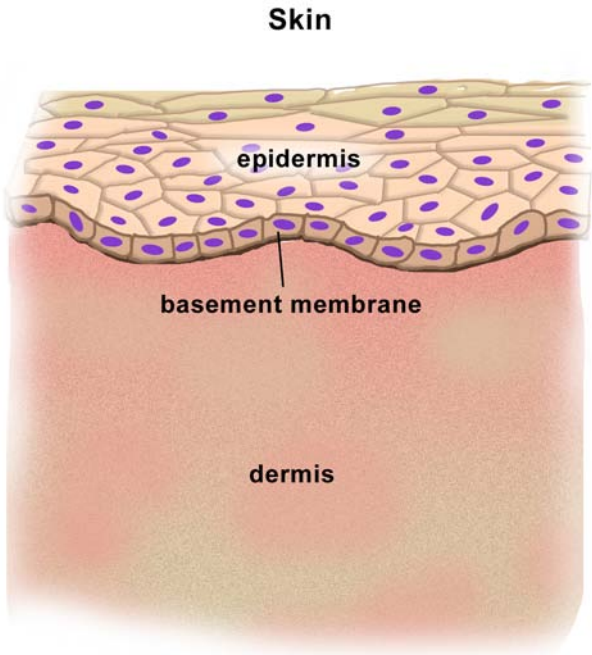
Peripheral nerve: irreversible injury

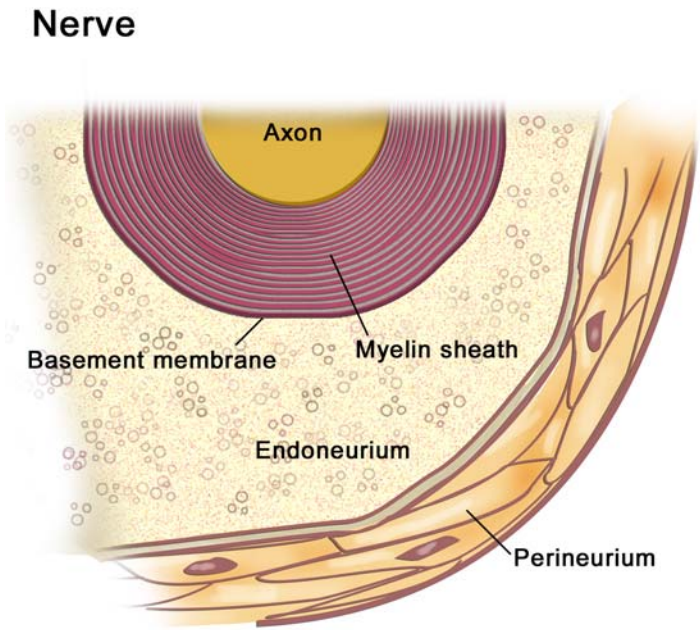


Transected nerve heals spontaneously by contraction and neuroma (neural scar) formation. No reconnection of stumps.

Figure by MIT OCW. After Figure 2.4 in [Yannas 2001].

Generalized view of reversibility of injury based on rule of tissue triad





Cartoon of "organism" shows that basement membrane (thick solid line) appears In almost all organs

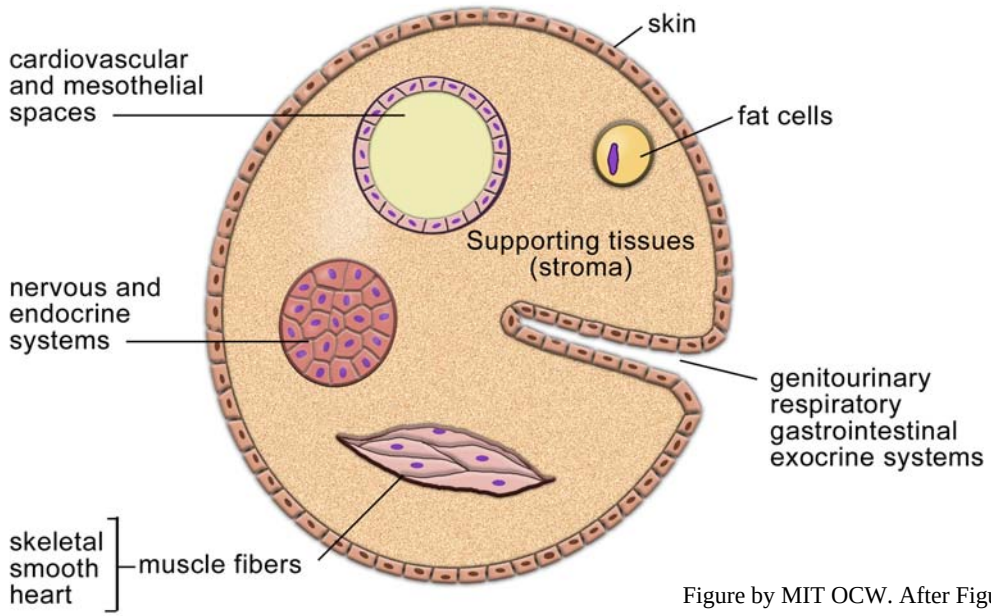


Figure by MIT OCW. After Figure 2.7 in [Yannas 2001].

Healing rules: epithelial tissue and BM, spontaneously regenerative; stroma, nonregenerative

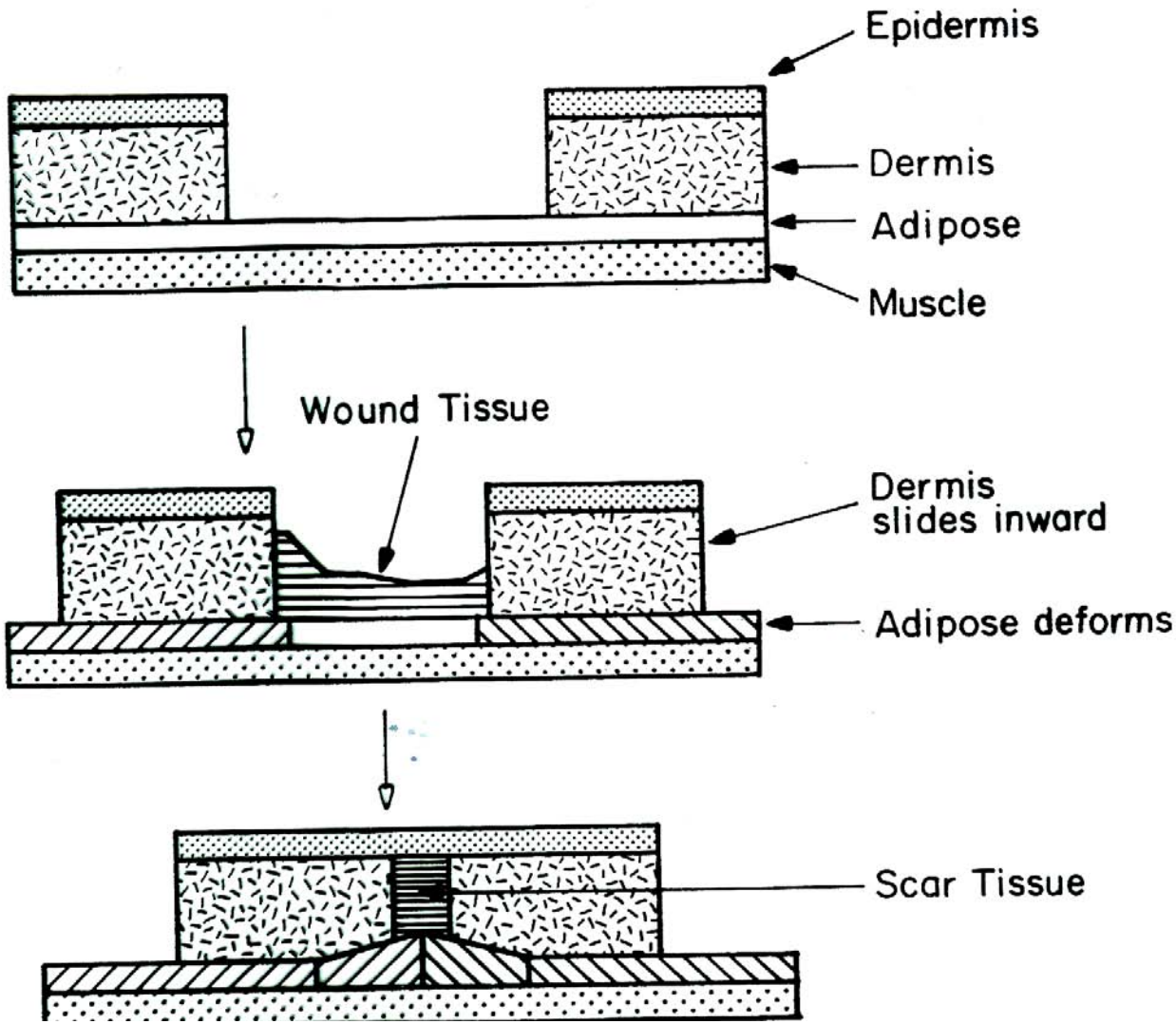
	Regenerative tissues. Reversible injury. No contraction.	Nonregenerative tissues. Irrever-sible injury. Contraction +scar.
SKIN	epidermis	dermis
	BM	
NERVE	myelin	endoneurial stroma
	BM	
GENERAL ORGAN	epithelial tissue BM	stroma

Mechanism of contraction and scar formation

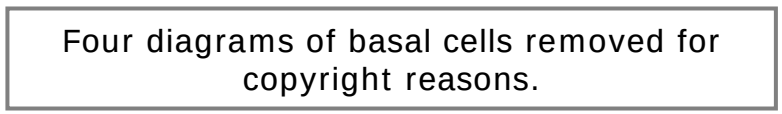
Mechanism of contraction and scar formation

1. Movement of tissue from periphery of wound toward center
2. Contractile fibroblasts (myofibroblasts) may initiate contraction; they almost certainly propagate contraction
3. Collagen fibers in scar are highly oriented in the plane of the wound.
4. Collagen fibers synthesized by FB and extruded outside with fiber axis parallel to long cell axis. Fiber orientation is replica of cell axis orientation during scar synthesis.
5. Collagen fiber orientation in scar is in the plane of the wound, suggesting the presence of a plane stress field during scar synthesis.
6. Regeneration templates cancel out mechanical field, leading to fiber synthesis in random orientation.

Deformation of Perilesional Tissues During Contraction



Source: K. Troxel *MIT thesis*, 1994

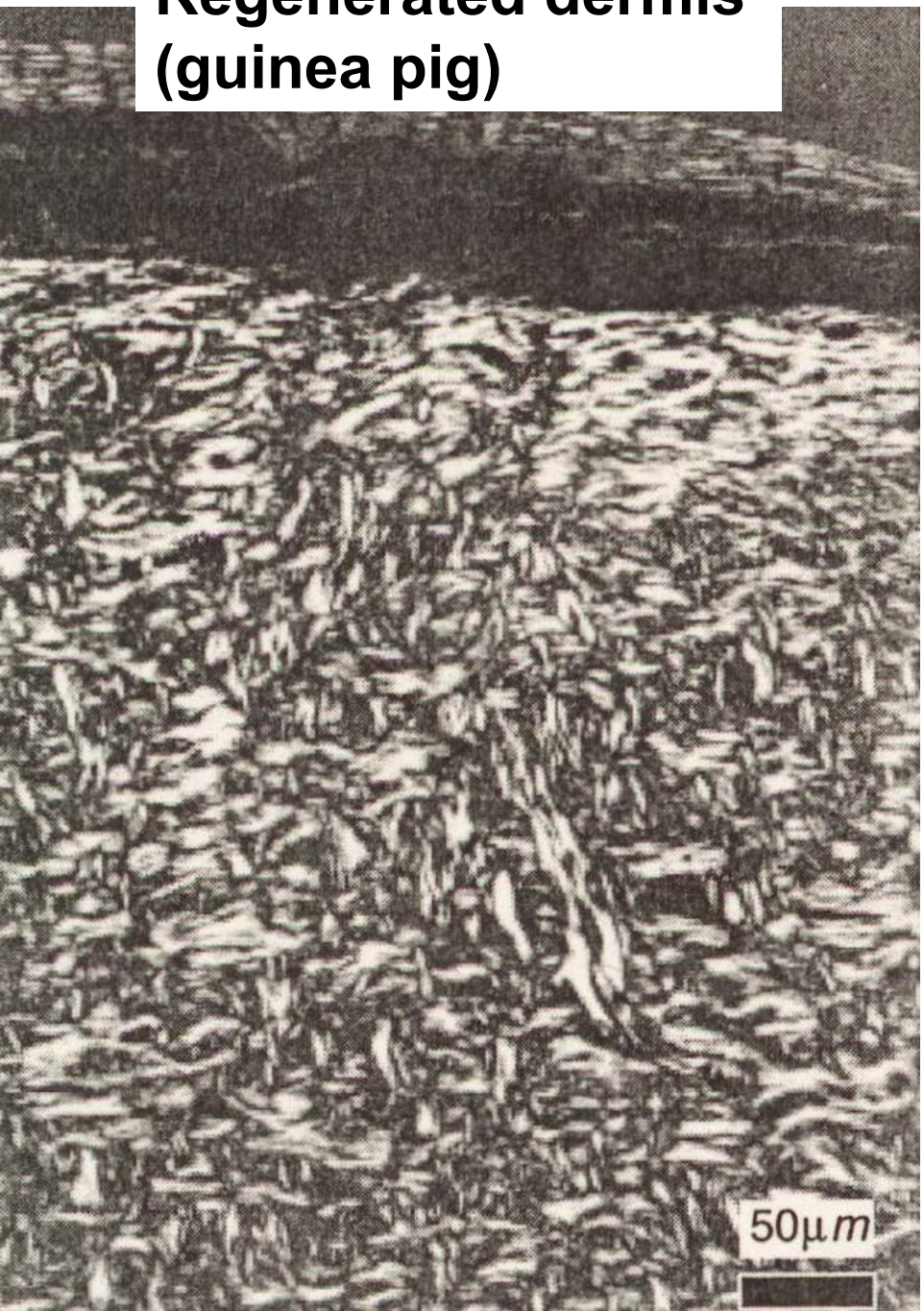


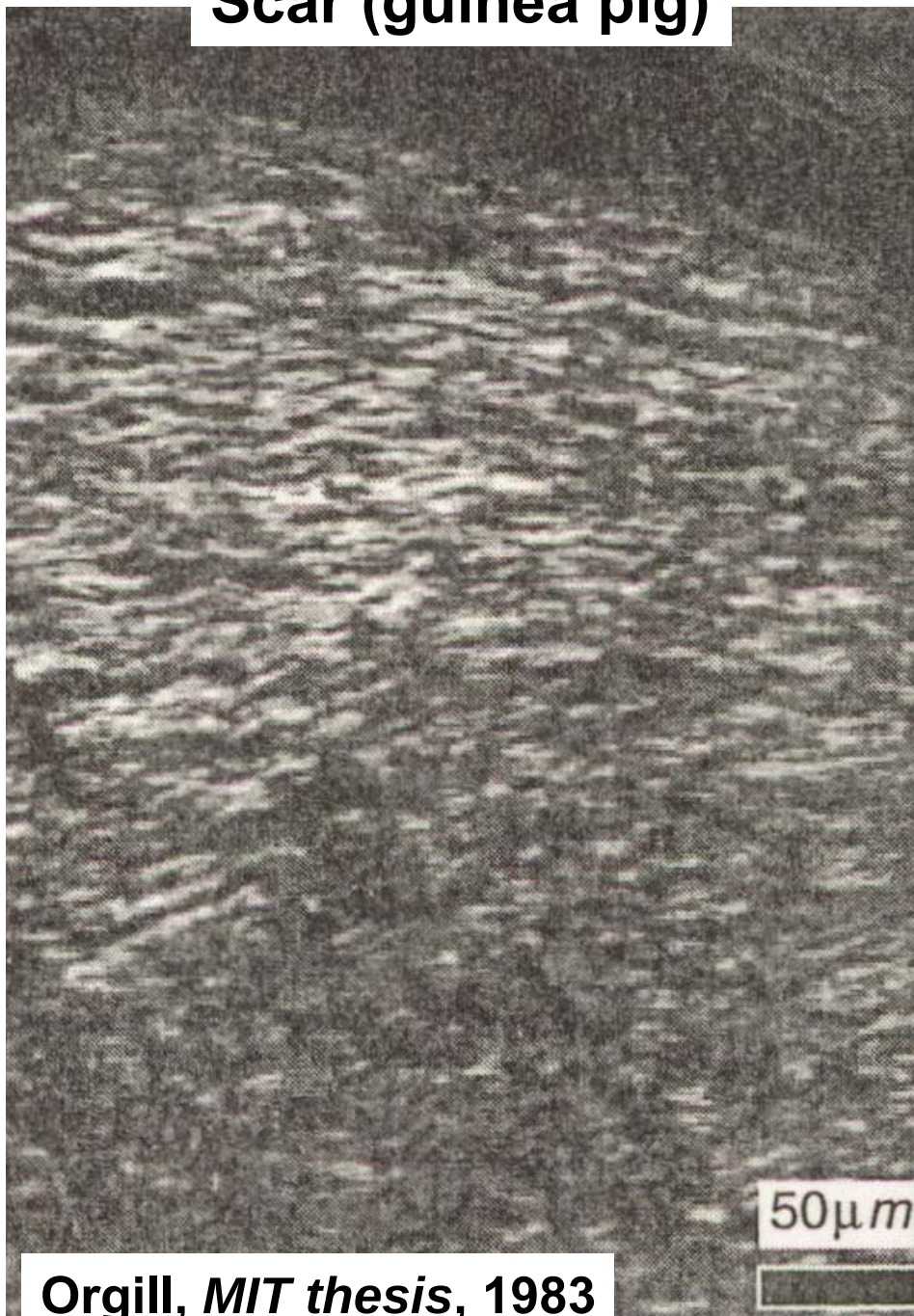
From Asmussen and Sollner,
Lume 29:3, 1993

Myofibroblast detected with antibody to α-SM actin

Diagram removed for copyright reasons.

Tomasek et al., 2000





Orgill, *MIT thesis*, 1983

Measure S (quantitative assay)

Diagram & photo removed for copyright reasons.
See Figure 4.7 in [Yannas 2001]

Original source: Ferdman and Yannas,
J. Invest. Dermatol., 1993

Unit cell processes of scar formation

- **Wound healing can be summed up as a sequence comprising an inflammatory response, fibroplasia, epithelialization, wound contraction and scar maturation. The following sequence of unit cell processes is a hypothetical and highly simplified model of certain aspects of wound healing in the dermal layer. Epithelialization and scar maturation are entirely omitted in the model below:**
- **n Platelets + Quaternary-structured collagen = [Degranulation] = Thrombus + PDGF* (and TGF-b*)**

- **PDGF + Monocyte = [Differentiation] = Macrophage + PDGF**
- **PDGF + Macrophage + ECM = [Collagenase** synthesis] = Solubilized ECM + Regulator**
- **Regulator + Macrophage + Solubilized ECM = [Phagocytosis] = Degraded ECM + Regulator**

Unit cell processes of scar formation (Cont.)

- **PDGF + Fibroblast + ECM = [Mitosis] = Fibroblast proliferation + Regulator**
- **Regulator + Fibroblast + ECM = [Synthesis] = Collagen I and III + Regulator**

- **Composite unit cell process: Collagen synthesis + Angiogenesis = Granulation tissue**

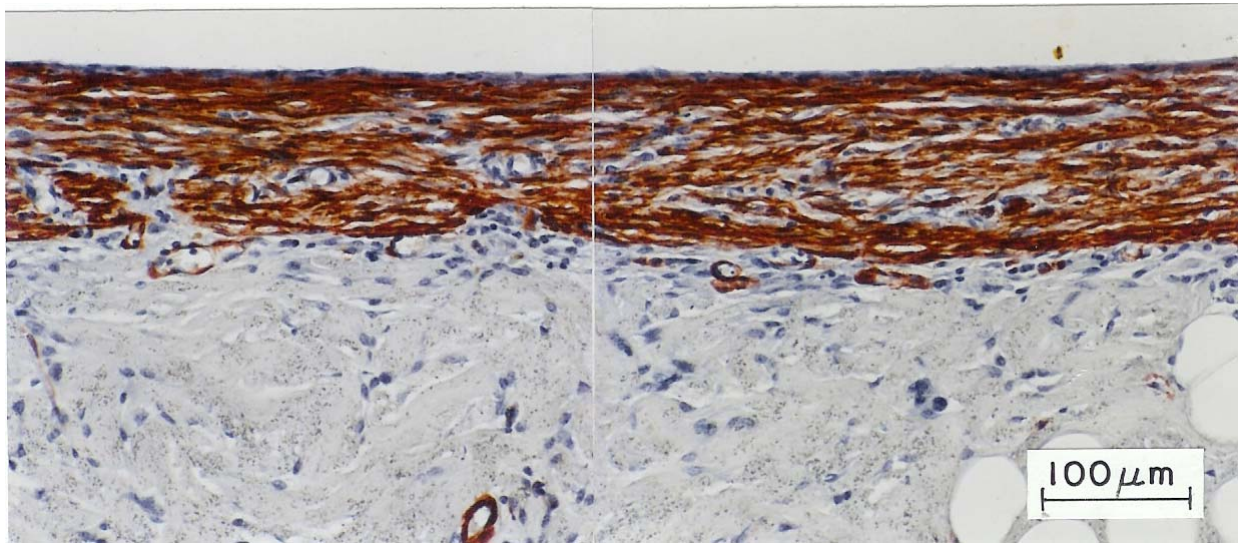
- **Regulator + Fibroblast + ECM = [Synthesis of α-actin] = Contractile fibroblast ("Myofibroblast") + Regulator**
- **Regulator + Myofibroblast + ECM = [Synthesis] = Scar tissue + Regulator**
- **Regulator + Myofibroblast + ECM = [Contraction] = Closed wound + Regulator**

- **Wound closes up. Myofibroblasts dedifferentiate to stable fibroblasts.**

Contraction blocked by scaffold (bottom)

Ungrafted. <u>Contracting vigorously</u>.

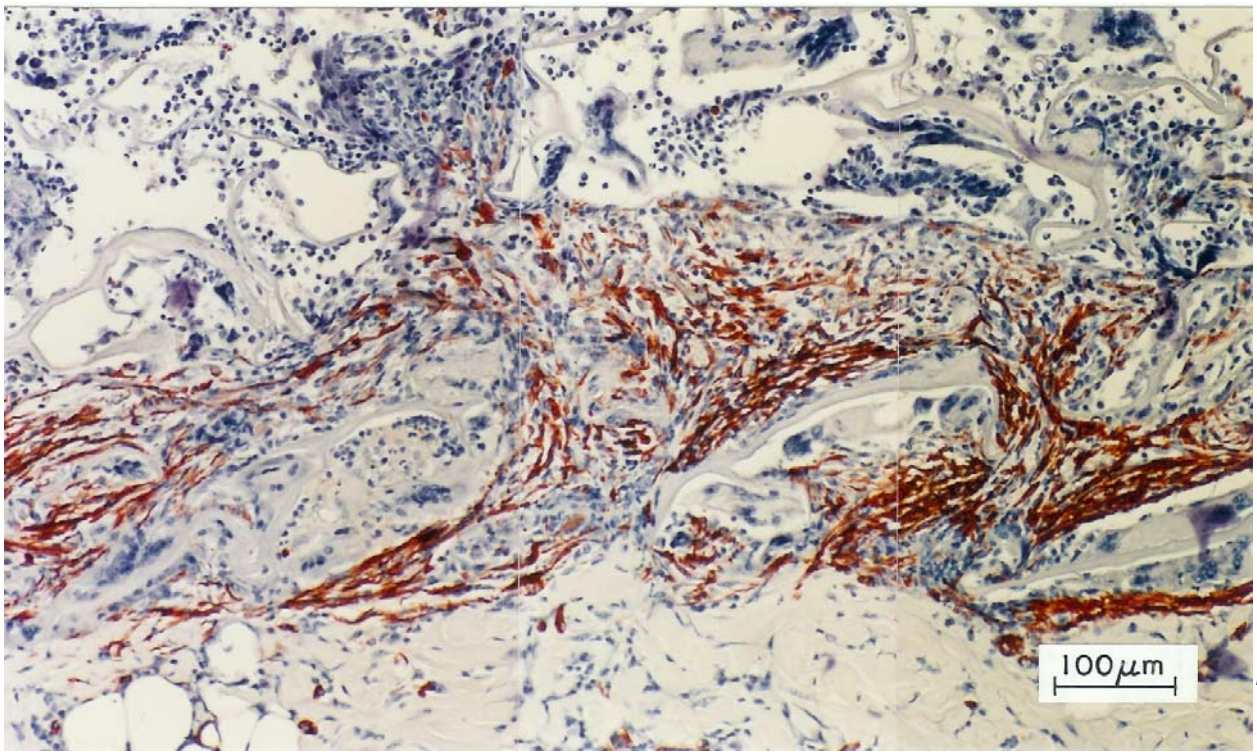
→



Red-brown: stained with antibody to α-SM actin. 10 d

Grafted with DRT. <u>No contraction</u>.

→



From Troxel, *MIT thesis*, 1994

Quantitative measurement of healing response: The defect closure rule

Defect closure rule

Original wound area = A_o

Wound area closed by contraction = A_c

Wound area closed by scar formation = A_s

Wound area closed by regeneration = A_r

$$A_c + A_s + A_r = A_o \qquad [1]$$

Dividing both sides of Equation [1] by A_o (normalization) we get the sum of the fractional areas:

$$A_c/A_o + A_s/A_o + A_r/A_o = 1 \qquad [2]$$

Replacing the fractional areas with the symbols C, S and R, and multiplying by 100, we get the wound closure rule:

$$C + S + R = 100 \qquad [3]$$

Spontaneously healing defect	**Configuration of final state**
general case	**[C, S, R]**
ideal fetal healing	**[0, 0, 100]**
dermis-free skin--adult rodents	**[96, 4, 0]**
dermis-free skin--adult human	**[37, 63, 0]**
peripheral nerve–adult rat	**[96, 4, 0]**
conjunctiva--adult rabbit	**[45, 55, 0]**

Burn patient has closed severe skin wounds in neck partly by contraction and partly by scar

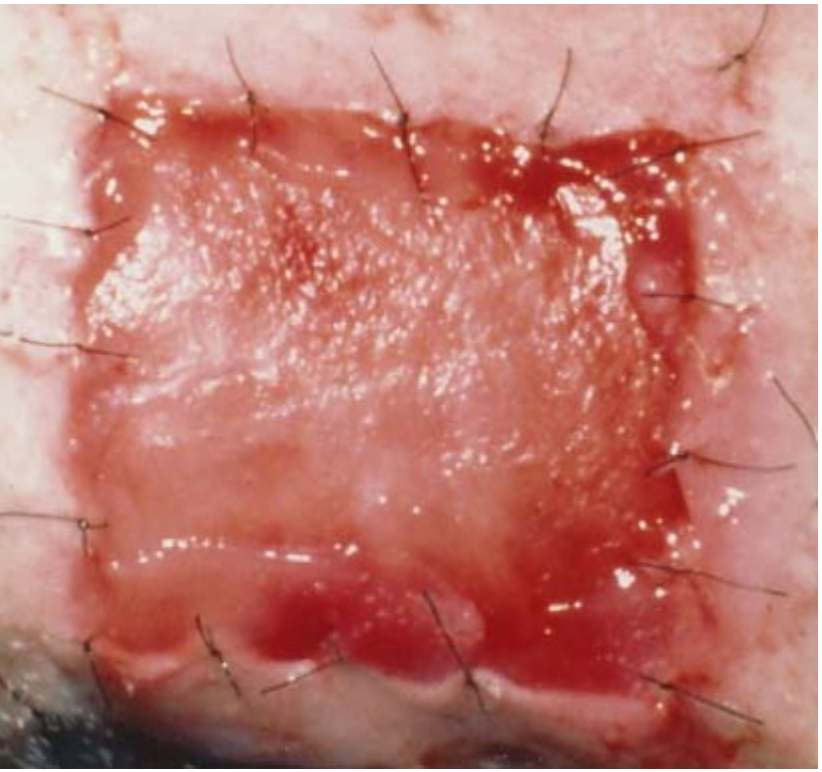
Photo removed for copyright reasons.

Final state of healing of full-thickness skin wound in the human.

Reference not recalled

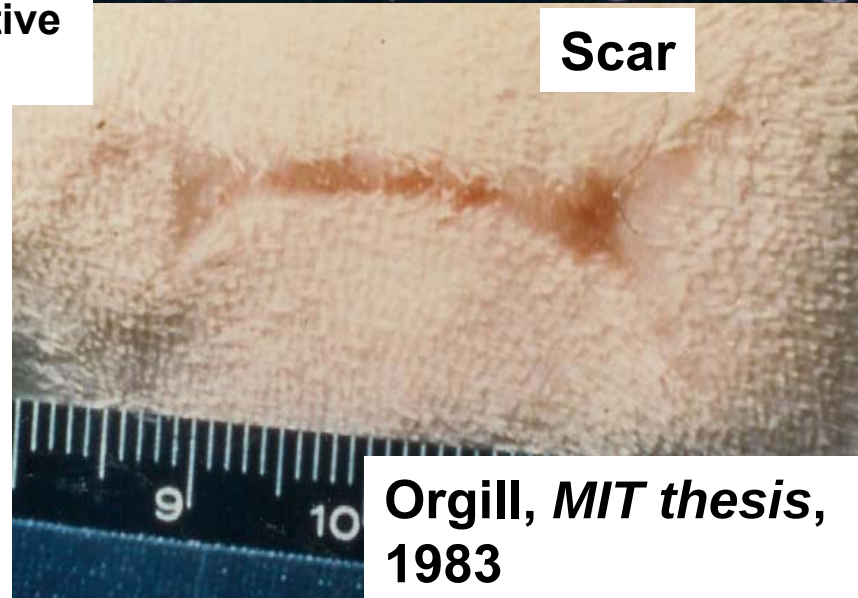
Final state of healing of full-thickness skin wound in the guinea pig.

Orgill, *MIT thesis*, 1983



KC + DRT

KC + inactive scaffold



Full-thickness skin wound (guinea pig) grafted with keratinocytes (KC) and either dermis regeneration template (DRT) or inactive scaffold

Orgill, *MIT thesis*, 1983

Measure C

Graph removed for copyright reasons.
See Figure 4.1 in [Yannas 2001]

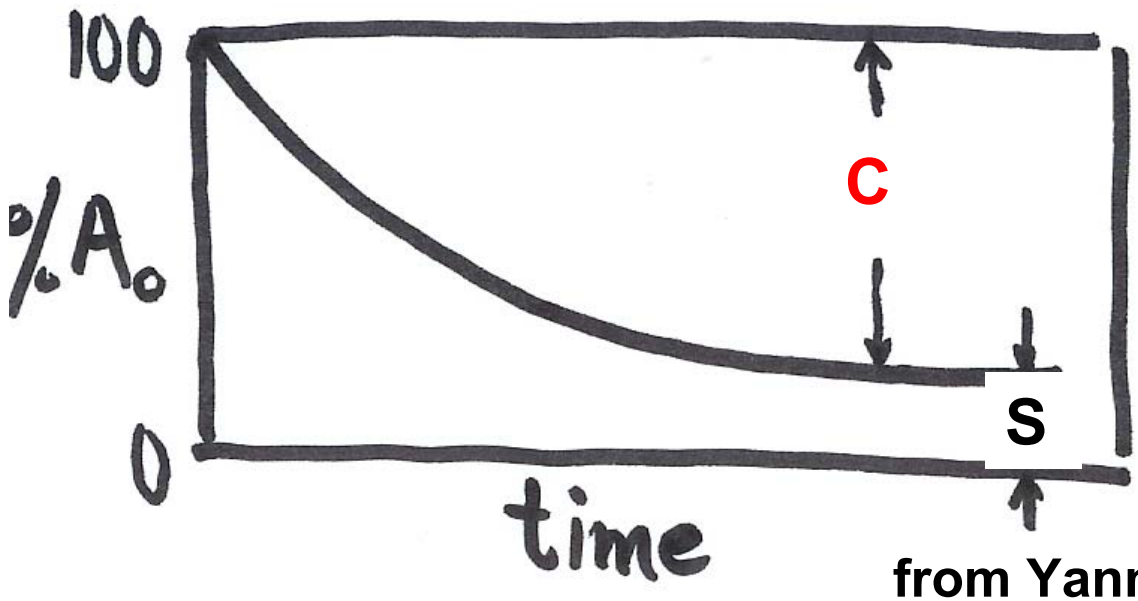
From Kennedy and Cliff, 1979

Kinetics of change in C

Graph removed for copyright reasons.
See Figure 4.2 in [Yannas 2001]

Measurement of C, S and R in full-thickness skin wounds after wound has closed. Use only "final state" data!

Graph removed for copyright reasons.
See Figure 4.3 in [Yannas 2001]



from Yannas' book, 2001

Figure removed for copyright reasons.
See Table 4.1 in [Yannas 2001]