

Factors That Influence Tissue Repair

Mechanisms, impaired healing, and clinicopathologic correlations

Inflammation • perfusion • matrix synthesis • mechanical integrity

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Learning objectives

- Classify systemic, local, extrinsic, and tissue-intrinsic influences on repair.
- Explain why infection, impaired perfusion, malnutrition, and mechanical stress delay healing.
- Relate repair defects to chronic ulcers and wound dehiscence.
- Distinguish resolution, organization, and scar formation in tissue spaces.

Two possible outcomes after tissue injury

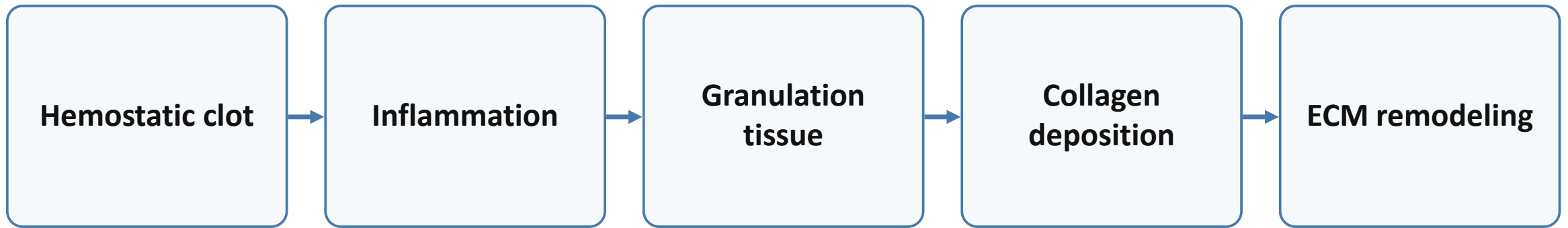
Regeneration

- Lost cells are replaced by viable tissue cells.
- Requires proliferative capacity and an adequate matrix scaffold.
- May restore architecture and function.

Scar formation

- Connective tissue replaces tissue that cannot regenerate adequately.
- Predominates after severe framework injury or in nondividing tissue.
- Restores continuity, not the original architecture.

Wound repair is a coordinated sequence



Interference at any stage can compromise the final scar or delay wound closure.

Macrophages coordinate inflammatory resolution and repair

Macrophages remove microbes and necrotic material



They produce cytokines and growth factors



Fibroblasts, epithelial cells, and vascular cells participate in tissue repair

Granulation tissue and mature scar are distinct

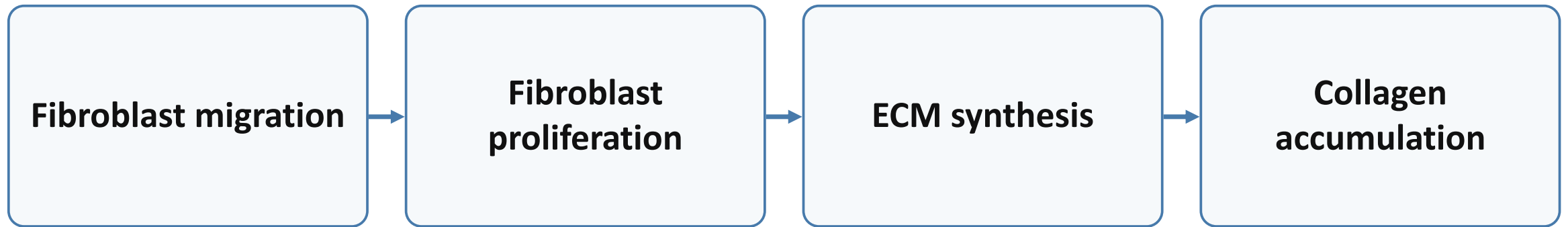
Granulation tissue

- New capillary network and proliferating fibroblasts.
- Loose extracellular matrix with inflammatory cells.
- Typical of actively repairing defects.

Mature scar

- Increased dense collagen deposition.
- Progressive vascular regression.
- Fewer proliferating fibroblasts and vessels.

Connective-tissue deposition requires two linked activities



PDGF, FGF-2, and TGF- β participate in fibroblast recruitment and matrix deposition.

TGF- β favors connective-tissue accumulation

Growth factor signaling, notably TGF- β



Fibroblast activation + collagen and fibronectin synthesis



Greater extracellular matrix deposition

Scar remodeling depends on opposing processes

Matrix formation

- Fibroblast activity
- Collagen and fibronectin synthesis
- Supported by profibrogenic signals

Matrix degradation

- Matrix metalloproteinases digest ECM.
- Proteases activate MMP precursors.
- TIMPs restrain active MMPs.

Healing by primary versus secondary intention

Feature	Primary intention	Secondary intention
Wound margins	Well apposed; small gap	Larger defect; irregular edges
Inflammation	Relatively limited	More extensive
Granulation tissue	Less abundant	More abundant
Contraction	Less pronounced	Significant
Outcome	Neat linear scar	Contracted, irregular scar

Skin wound healing follows an ordered timeline

Immediate

Clot

24 h

Neutrophils

24–48 h

Epithelium bridges edges

Day 3

Macrophages; Early
granulation

Day 5

Marked new vessel formation

Days 14–30

Collagen-rich scar

Representative sequence for uncomplicated cutaneous healing Table 3.11.

When tissue repair becomes abnormal

Inadequate repair

Persistent defect, chronic ulcer, or wound separation

Excessive repair

Excess collagen or exuberant granulation

Exaggerated contraction

Contracture and distortion of adjacent tissue

Factors act at different biological levels

Systemic milieu	Local wound conditions	Intrinsic tissue properties
Diabetes, nutrition, age, glucocorticoids	Infection, perfusion, pressure, foreign material	Cell proliferation and supporting architecture

Several modifiers converge on four failure mechanisms

Inflammation persists

Microbes and foreign bodies

Blood supply is inadequate

Arterial, venous, or pressure-related impairment

Collagen deposition is reduced

Protein or vitamin C deficiency; Steroids

Wound edges do not remain apposed

Mobility, tension, pressure, or torsion

Infection is a major cause of delayed wound healing

Infection in an injured site

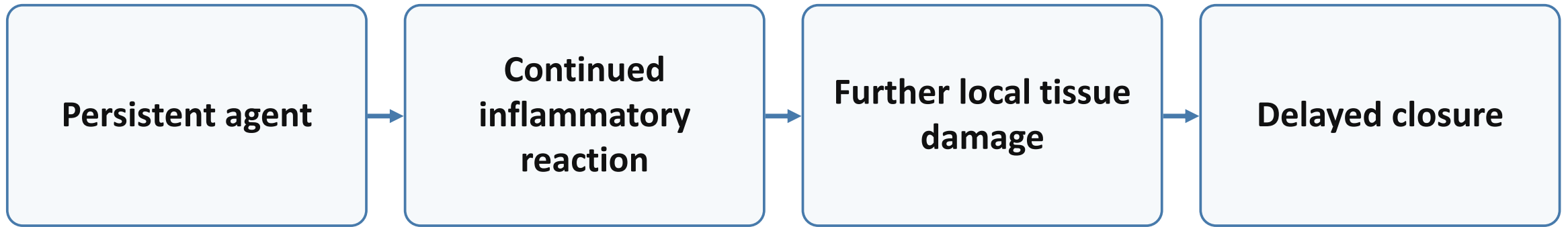


Prolonged inflammation + possible additional tissue injury



Delayed progression to effective repair

Why sustained inflammation impedes repair



The wound remains exposed to the cause of injury rather than advancing through uncomplicated repair.

Diabetes compromises healing by multiple mechanisms

Vascular disease

Perfusion can be impaired.

Neuropathy

Contributes to diabetic lower-extremity ulcers.

Secondary infection

Adds further injury and inflammation.

Tissue necrosis

Sustains nonhealing ulceration.

Vascular disease is central to diabetic wound failure

Diabetes-associated vascular disease



Ischemia and injury to lower-extremity tissues



Necrosis and failure of ulcers to heal

Neuropathy contributes to diabetic foot ulcers

Diabetic neuropathy

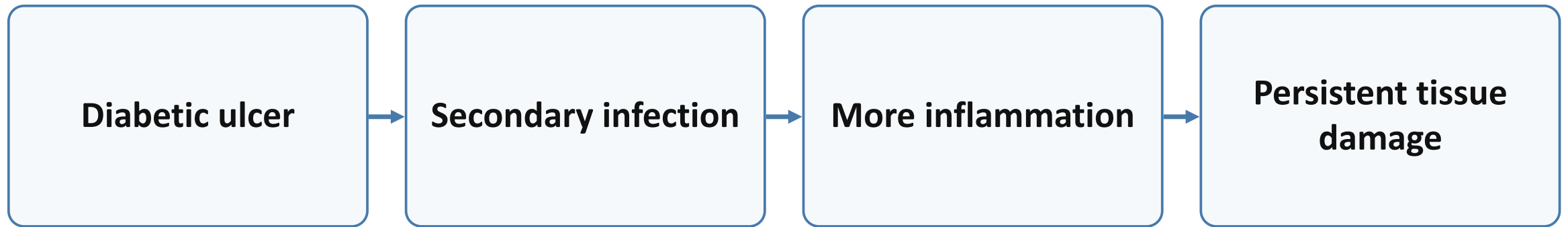


Combined with vascular disease and secondary infections



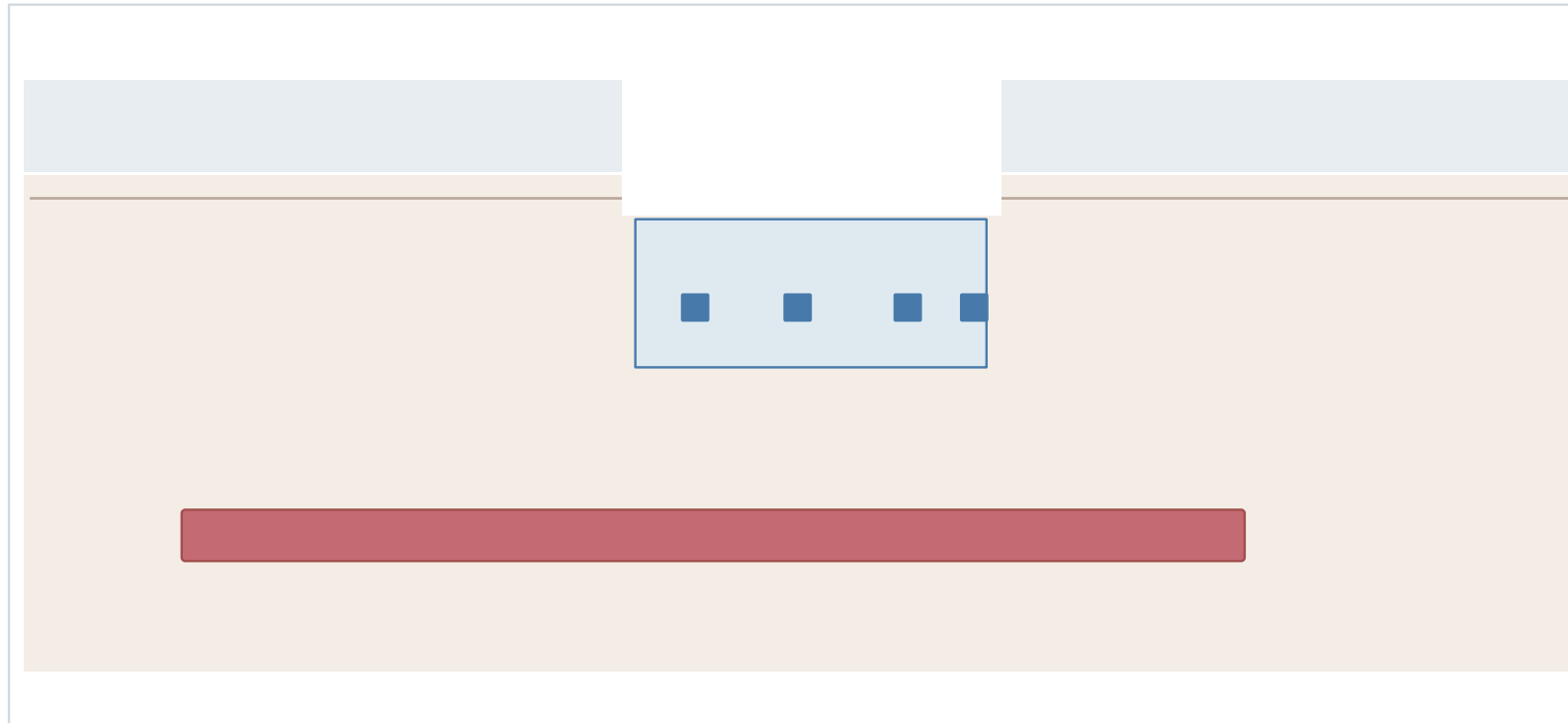
Ulceration and persistent tissue injury

Secondary infection worsens diabetic ulceration



This schematic represents a possible exacerbating mechanism, not an inevitable sequence in all diabetic ulcers.

What a diabetic ulcer shows histologically



Schematic

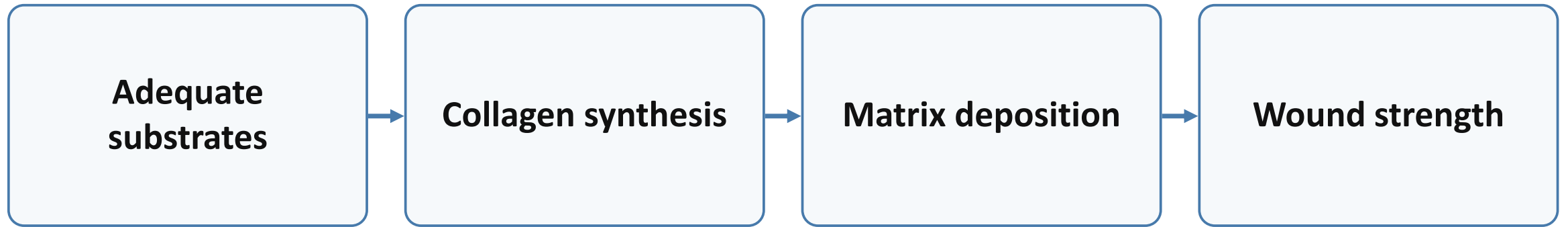
Epithelial ulceration

Underlying granulation
tissue

Chronic inflammatory
infiltrate

Original editable schematic; Not a photomicrograph. Findings are described.

Nutritional status directly affects collagen synthesis



Protein and vitamin C deficiencies interrupt efficient collagen production and delay repair.

Protein deficiency retards tissue repair

Deficient protein nutrition



Reduced capacity for collagen synthesis



Slower and less effective wound repair

Vitamin C deficiency impairs collagen synthesis

Vitamin C deficiency



Impaired collagen synthesis



Delayed tissue repair

Aging is a modifier, not a wound diagnosis

- Healing capacity decreases with increasing age.
- Age-related impairment may coexist with diabetes, malnutrition, vascular disease, and reduced mobility.
- Assess the actual contributing mechanisms rather than attributing every nonhealing wound to age alone.

The last two points are clinical reasoning based on the coexisting factors.

Glucocorticoids affect inflammation and scar strength

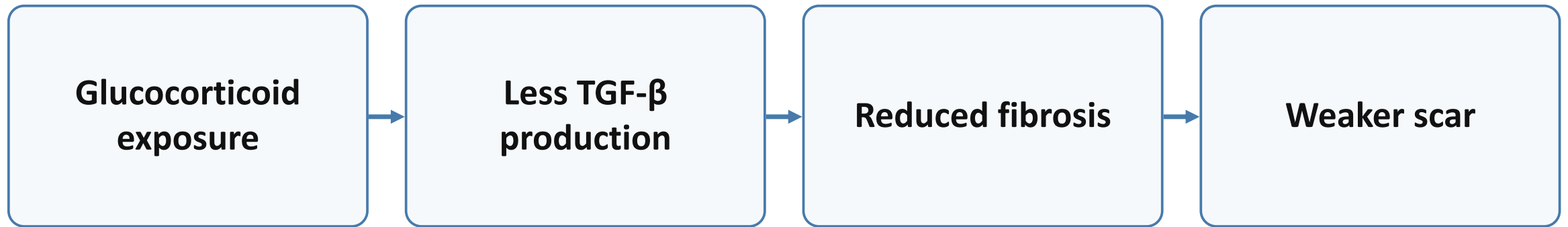
Anti-inflammatory action

- Suppress inflammatory responses.
- May be clinically useful when scarring itself threatens function.

Potential adverse effect on repair

- Decrease TGF- β production.
- Diminish fibrosis.
- Can lead to weaker scars.

How steroids can weaken a scar



A mechanistic example of systemic therapy modifying connective-tissue deposition.

The effect of suppressing fibrosis depends on context

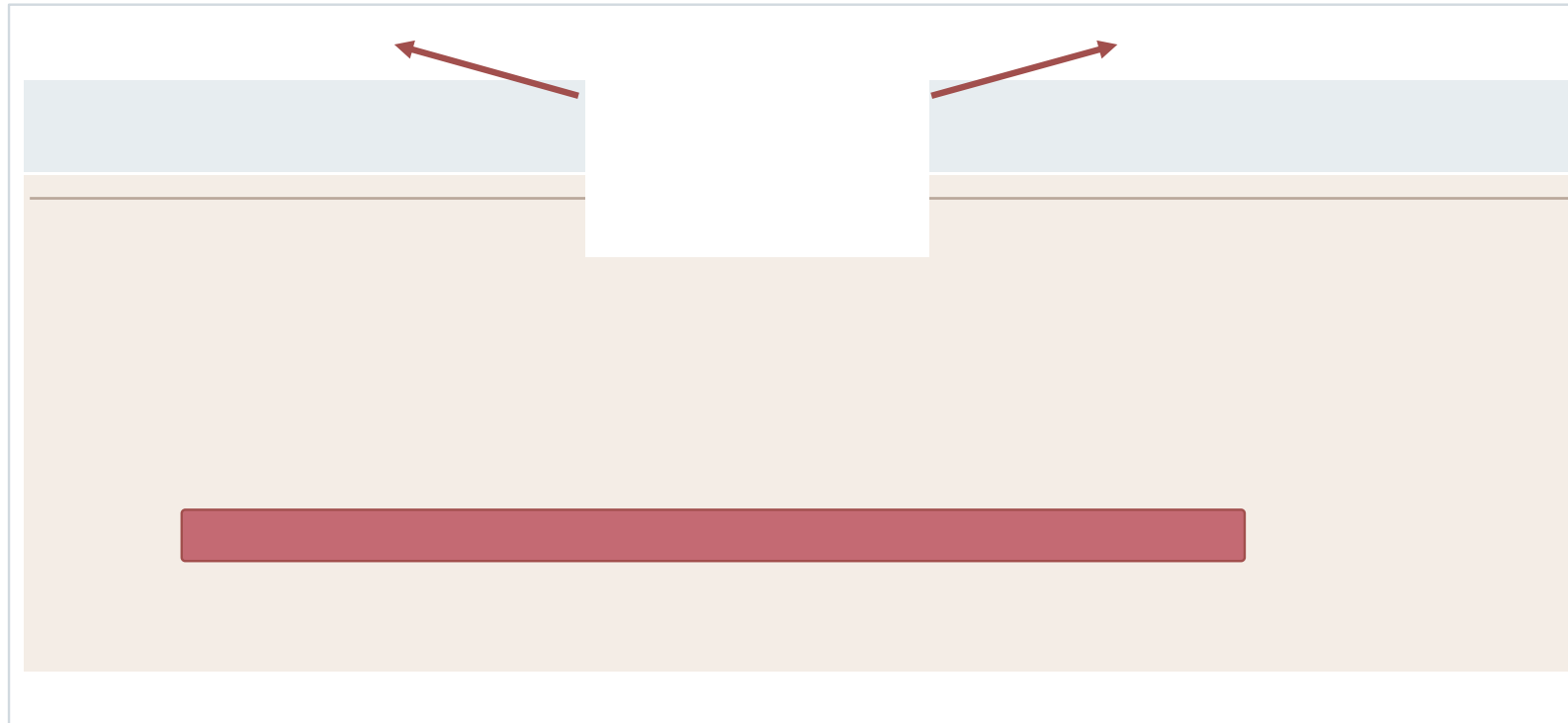
Cutaneous incision

- A mechanically competent collagen scar is desirable.
- Reduced fibrosis can weaken wound repair.

Corneal infection

- Opacity from excessive scarring may impair transparency.
- Selected use of steroids alongside antibiotics.

Mechanical stress can prevent wound apposition



Schematic

Apposed wound edges

Excess movement /
tension

Edges pull apart

Original native-shape schematic. Mechanical strain compromises continued contact between wound margins.

Excessive mobility disrupts healing

Movement across an injured site

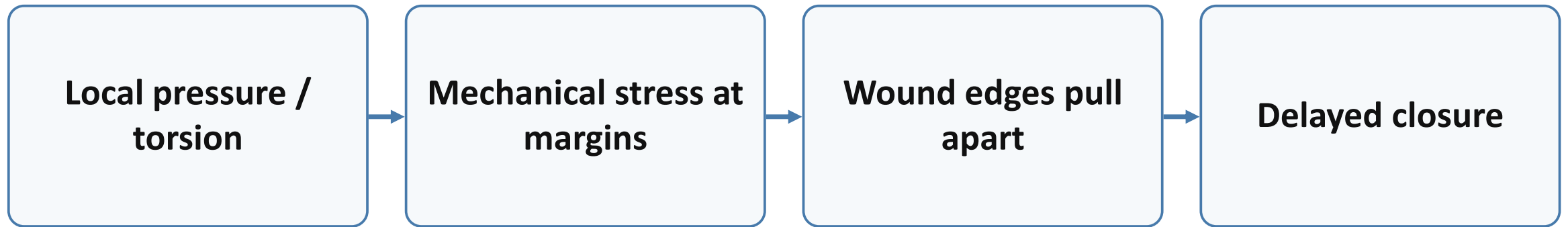


Failure of stable apposition of wound edges



Risk of impaired closure

Pressure and torsion can separate wound margins



Mechanical integrity is a distinct requirement from adequate nutrition and perfusion.

Poor perfusion is a major local impediment

Arterial inflow impaired

- Peripheral arterial disease / atherosclerosis.
- Reduced delivery to injured tissue.
- Ischemia may culminate in necrosis.

Venous drainage obstructed

- Varicose veins and other venous disorders.
- Venous hypertension impairs healing.
- Venous ulceration may follow.

Arterial insufficiency causes ischemic injury

Atherosclerosis of peripheral arteries



Local ischemia, tissue atrophy, and necrosis



Painful arterial ulceration can develop

Obstructed venous drainage also impairs repair

Chronic venous hypertension

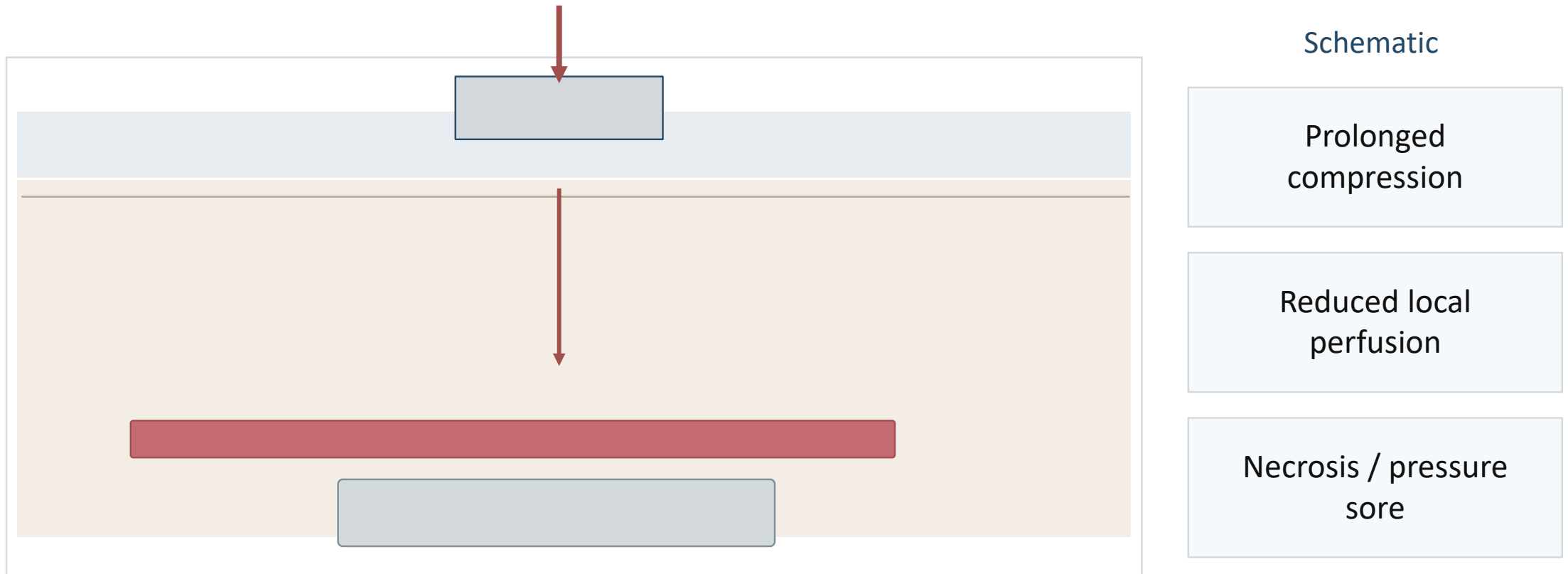


Poor effective oxygen delivery in the ulcer bed



Persistent venous leg ulcer

Sustained pressure causes ischemic tissue damage



Original editable schematic showing compression of tissue against bone, not a clinical photograph.

Foreign bodies perpetuate inflammation

Retained foreign material



Ongoing chronic inflammatory reaction



Impaired or delayed tissue healing

The tissue type limits regenerative capacity

Cell population	Examples	Implication for repair
Labile	Surface epithelia; hematopoietic cells	Continuously renewed; regeneration possible
Stable	Most parenchymal tissues	Proliferation possible when stimulated
Permanent	Neurons; cardiac and skeletal muscle	Limited cell replacement; injury often scars

An intact extracellular scaffold matters

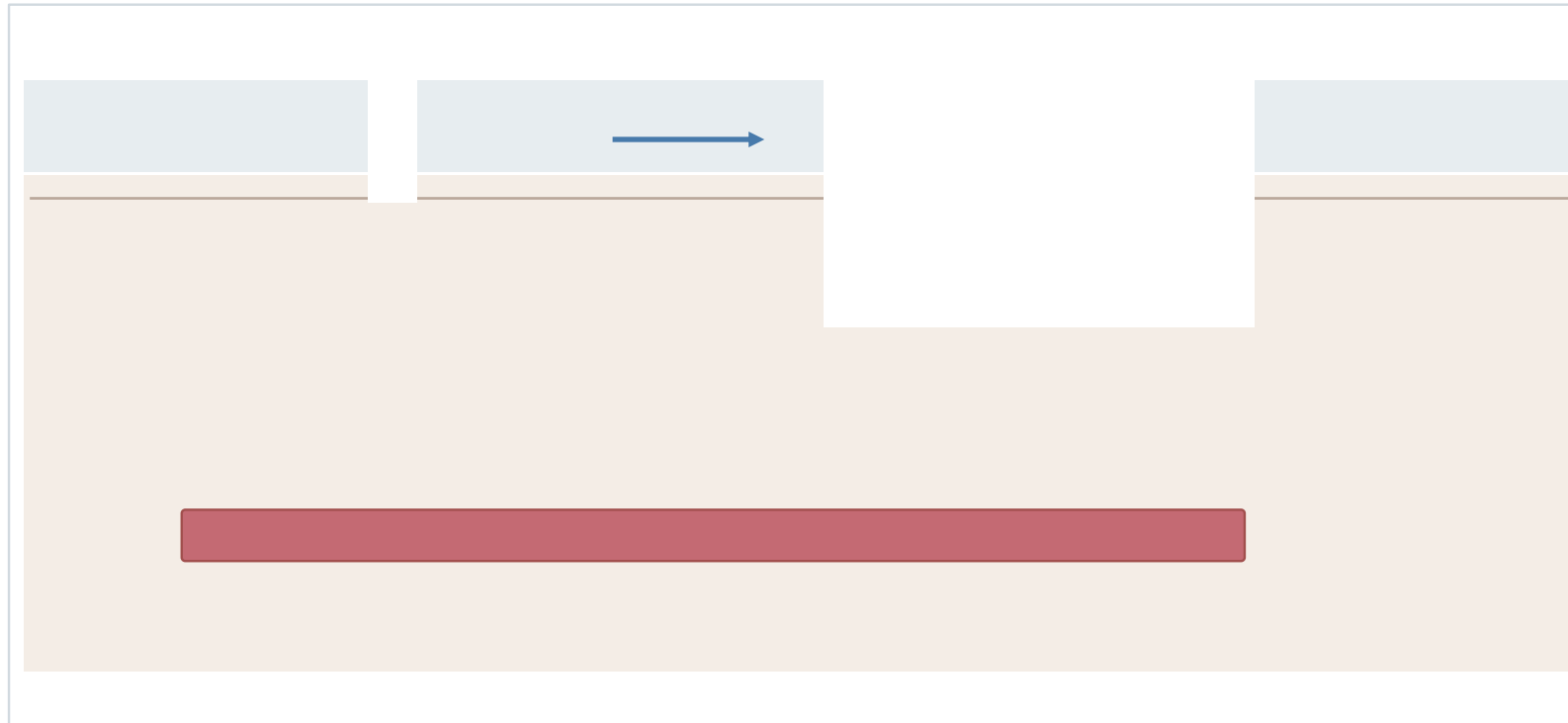
Scaffold preserved

- Regenerating cells retain a structural framework.
- More complete tissue restoration can occur.

Scaffold destroyed

- Normal tissue organization cannot be reconstituted readily.
- Repair shifts toward connective-tissue replacement.

Extent of tissue injury affects the outcome



Schematic

Small, aligned incision

Large tissue defect

Greater need for scar formation

Editable schematic contrasts injury geometry; It does not claim a quantitative threshold.

Anatomic location changes the repair pathway

Cutaneous defect

Closure, granulation, epithelialization, and scar

Pleural cavity

Exudate may undergo resolution or organization

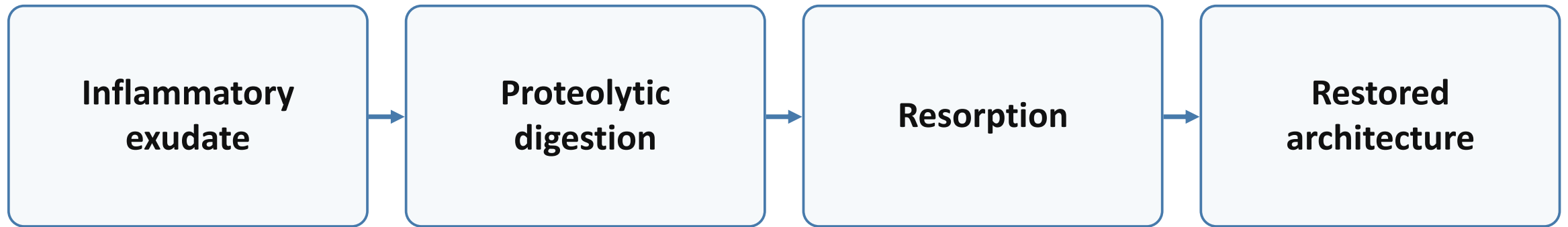
Peritoneal cavity

Large exudates may organize

Synovial cavity

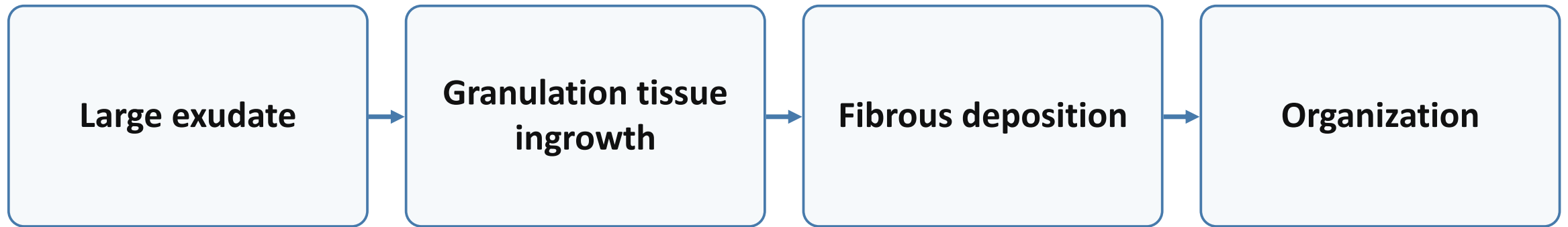
Repair also depends on exudate clearance

Resolution removes inflammatory exudate



Typically possible in the absence of cell necrosis when the exudate can be cleared.

Organization converts retained exudate into scar



The reparative pathway changes when an exudate is not effectively resolved.

Resolution and organization differ fundamentally

Resolution

- Leukocyte enzymes liquefy exudate.
- Resorption removes inflammatory material.
- Architecture generally returns if necrosis is absent.

Organization

- Granulation tissue grows into retained exudate.
- Connective tissue replaces the material.
- A fibrous scar remains.

Chronic wound patterns illustrate failed repair

Venous leg ulcer

Venous hypertension

Arterial ulcer

Ischemia due to arterial disease

Diabetic foot ulcer

Ischemia, neuropathy, and infection

Pressure sore

Pressure-related local ischemia

Venous leg ulcers reflect venous hypertension

Severe varicose veins or congestive heart failure

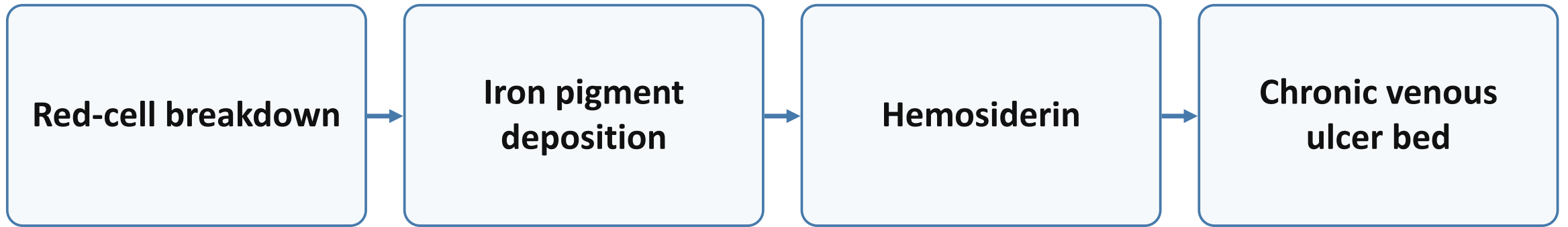


Chronic venous hypertension and poor oxygen delivery



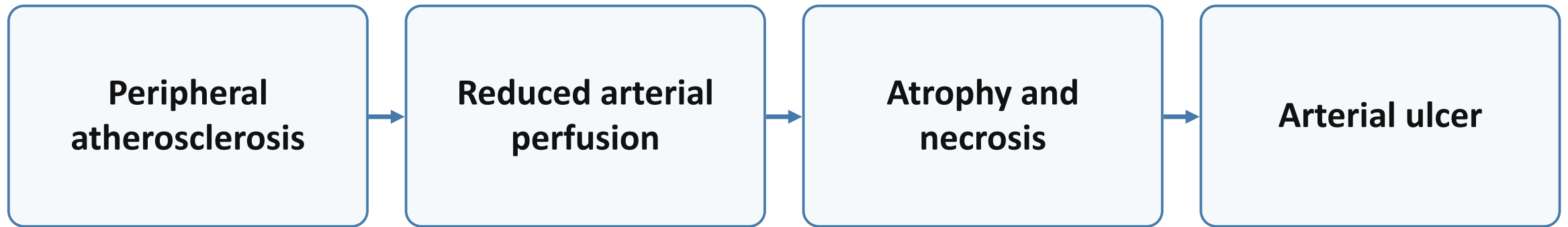
Chronic nonhealing leg ulcer

Why hemosiderin may accompany venous ulcers



Hemosiderin and chronic inflammation are described accompanying findings, not diagnostic requirements.

Arterial ulcers develop from tissue ischemia



That these lesions can be quite painful.

Diabetic ulcers are multifactorial

Perfusion

Vascular disease causes ischemia

Neural contribution

Neuropathy contributes to ulceration

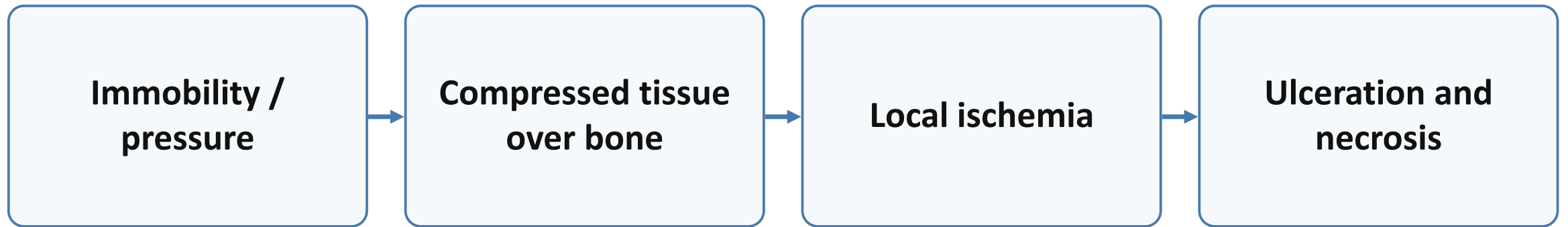
Microbiology

Secondary infections aggravate the lesion

Morphology

Epithelial ulcer and underlying granulation tissue

Pressure sores begin with sustained compression



This example links mechanical stress to an insufficiency of tissue perfusion.

Four common chronic ulcers: Causal comparison

Type	Dominant mechanism	Distinctive accompanying feature
Venous	Chronic venous hypertension	Hemosiderin / chronic inflammation
Arterial	Atherosclerotic ischemia	Atrophy, necrosis; often painful
Diabetic	Ischemia + neuropathy + infection	Ulcer with granulation tissue
Pressure	Prolonged compression	Necrosis over bony prominence

Wound dehiscence is reopening of an incision

Insufficient wound strength and/or stress across incision



Failure of mechanical integrity



Internal or external surgical wound reopening

Factors increasing dehiscence risk

Nutrition

Malnutrition

Local biology

Infection and vascular insufficiency

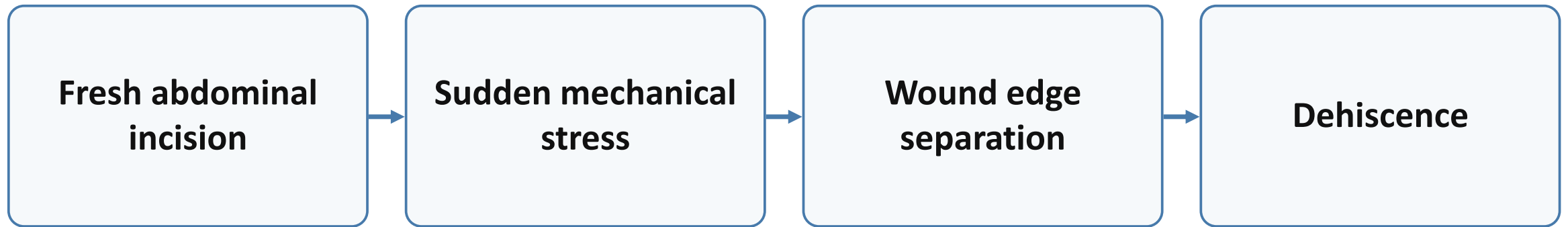
Body factors

Obesity

Mechanical loading

Excessive strain or poor apposition

Coughing and vomiting can trigger abdominal dehiscence



Robbins specifically names coughing and vomiting as possible precipitating events.

Healing defects and excessive scarring are opposites

Deficient repair

- Chronic ulcers
- Weak scar
- Dehiscence

Excessive repair

- Hypertrophic scar or keloid
- Exuberant granulation
- Contracture

Excessive scarring is treated briefly here because it is a separate adjacent Robbins teaching topic.

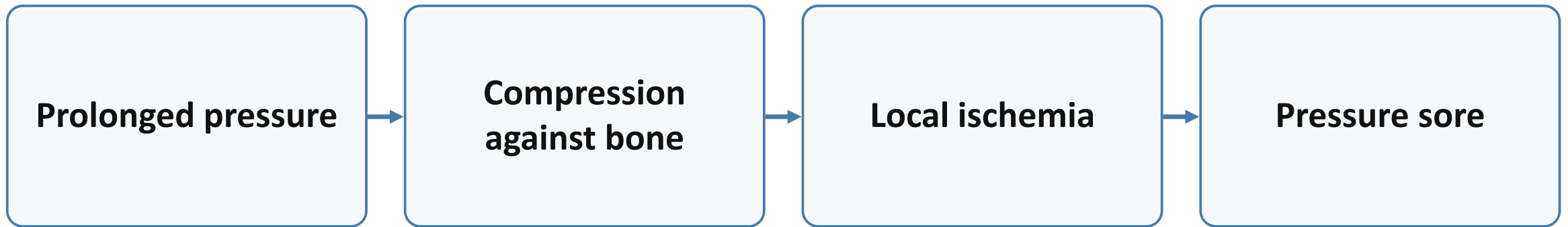
Case 1 — A pressure-related ulcer

An older immobile patient develops ulceration and necrosis of skin over a bony prominence.

Reason through the mechanisms

- What immediate physical factor caused the injury?
- What is the key vascular consequence?
- Which injury pattern best fits the description?

Case 1 — Mechanism and answer



Pressure is a mechanical factor; Tissue necrosis is mediated through insufficient local blood flow.

Case 2 — A persistent diabetic foot ulcer

A patient with diabetes has a chronic foot ulcer with tissue necrosis and signs of secondary infection.

Reason through the mechanisms

- List the three major mechanisms emphasized.
- Which factor directly reduces oxygen delivery?
- Why can inflammation remain prolonged?

Case 2 — Converging reasons for poor healing

Vascular disease	Neuropathy	Secondary infection
Ischemia → tissue injury	Contributes to foot ulceration	Sustains inflammation and injury

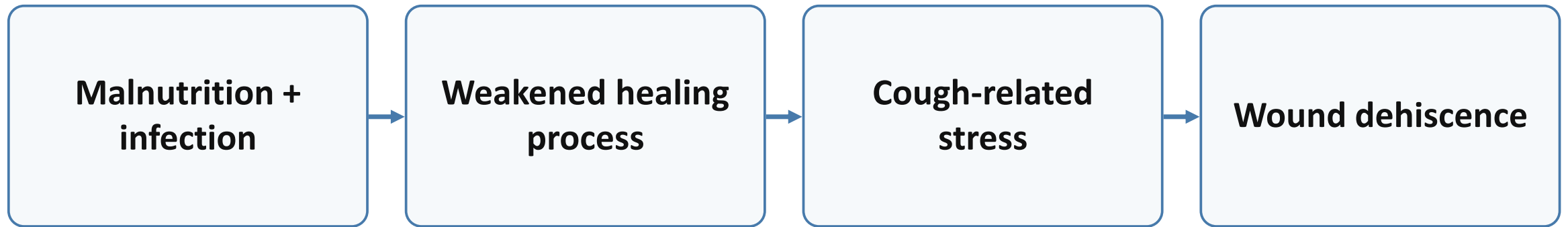
Case 3 — An incision reopens

After abdominal surgery, a malnourished patient with wound infection develops incision separation after repeated coughing.

Reason through the mechanisms

- Name this complication.
- Identify the systemic, local, and mechanical risk factors.
- Which factors can compromise collagen formation or scar strength?

Case 3 — Dehiscence has combined causes



The clinical outcome depends on both repair biology and mechanical load.

Case 4 — An inflammatory cavity exudate

Two pleural inflammatory exudates evolve differently: One disappears without residual architectural damage; The other is replaced by fibrous connective tissue.

Reason through the mechanisms

- What is the first outcome called?
- What is the second outcome called?
- What role does the size/persistence of the exudate play?

Case 4 — Resolution versus organization

Exudate cleared

- Proteolytic digestion and resorption
- Resolution
- Architecture generally restored if no necrosis

Exudate retained

- Granulation tissue grows into material
- Organization
- Fibrous scar forms

Pattern recognition: Connect factor to mechanism

Finding / exposure	Immediate concern	Repair consequence
Infected wound	Persistent inflammation	Delayed healing
Reduced arterial flow	Ischemic tissue injury	Nonhealing ulcer
Protein / vitamin C deficiency	Reduced collagen synthesis	Delayed repair
Steroid exposure	Reduced TGF- β / fibrosis	Weak scar
Excessive motion	Loss of edge apposition	Separation / dehiscence

Synthesis: Successful healing needs several conditions

Offending agent controlled

The inflammatory stimulus must abate

Functional perfusion

Tissue must receive adequate blood flow

Capacity to lay down matrix

Nutrition and fibroblast signaling are sufficient

Stable wound geometry

Margins stay apposed without excessive pressure

Clinical interpretation begins with mechanisms

- A chronic wound may reflect more than one modifying factor.
- Identify whether the principal problem is inflammation, perfusion, matrix synthesis, or mechanics.
- Consider the injury depth, intrinsic regenerative potential, and anatomic site.
- Different causal combinations can produce the same outcome: Delayed healing.

References and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 3: Inflammation and Repair; pp. 94–99.
- Primary topic: Factors That Influence Tissue Repair (pp. 97–98).
- Context used: Repair by Scarring, Healing of Skin Wounds, and Defects in Healing: Chronic Wounds (pp. 94–99).
- All illustrations in this lecture are editable conceptual schematics, not actual histologic or clinical specimens.