THE PHYSICS AND PATHOLOGY OF WOUNDS

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Marc E. Gottlieb, MD

arimedica.com

Phoenix, Arizona

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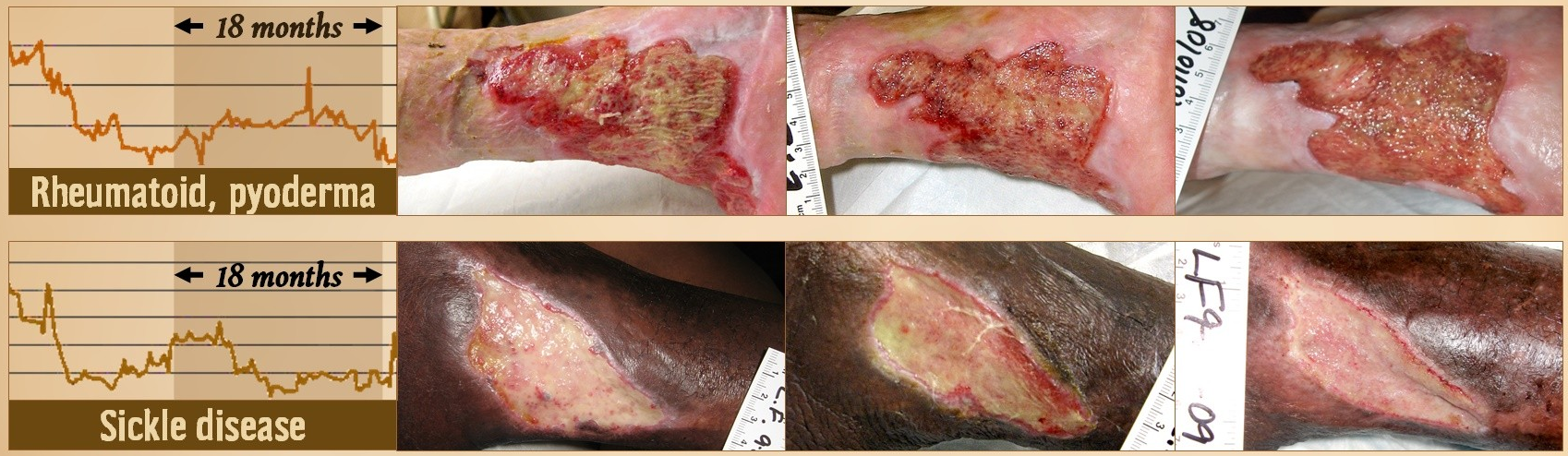
THE PHYSICS AND PATHOLOGY OF WOUNDS

SOME WOUNDS REFUSE TO HEAL,
EVEN WHEN GROSS PATHOLOGY & CAUSATIVE DISEASE ARE CONTROLLED
AND ACUTE ULCERATION AND INFLAMMATION ARE SUBSIDED.



THERE IS A REASON

these wounds go back and forth but get no better

they cannot spontaneously climb out of this attractor

multiple therapeutics are often of no benefit

this adverse behavior is independent
of the primary pathology

THESE REASONS CANNOT BE UNDERSTOOD

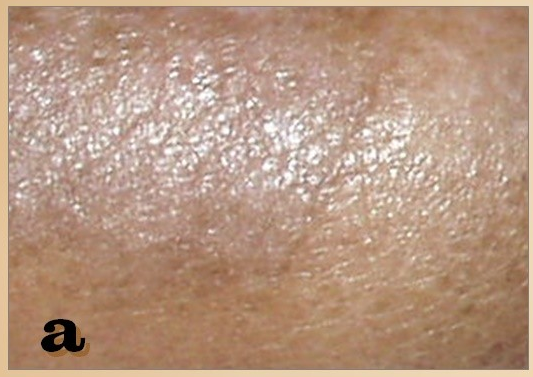
by looking at any individual cell or chemical or gene

by analysis of any dependent-vs-independent experiment

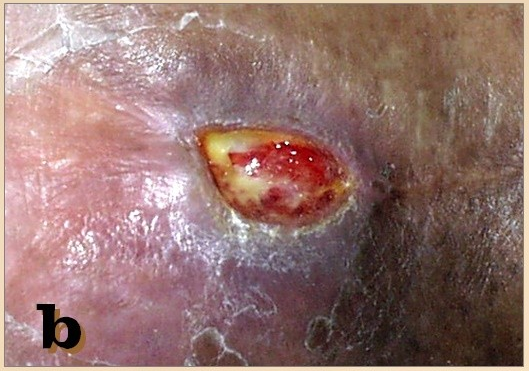
by any "conventional bioscience" type of experiment

by any type of randomized controlled trial

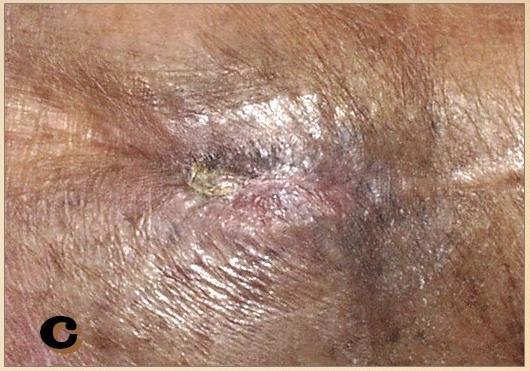
WOUNDS ARE A CLOSED LOOP CONTROL SYSTEM



Normal healthy skin. It will not change nor start healing.



Wound healing is a reserve system. It needs a trigger to start (injury).



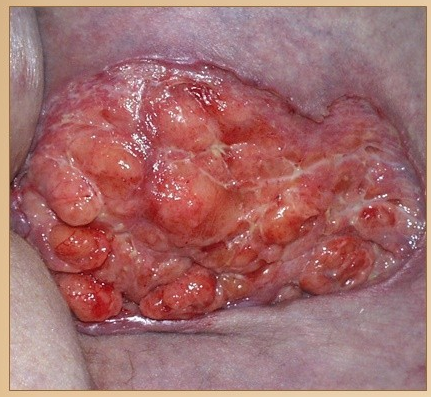
Once closed, wound healing ceases. How does it know to stop?

Wound healing is purely reactive and highly controlled.

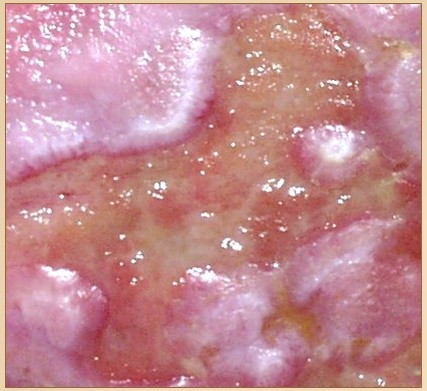
Wound healing responds if perturbed, turning itself on only when needed.
It senses its own evolving status, comparing itself to normal tissue.
It restores system to a defined reference, then ceases when complete.

Reactivity, feedback, reference, control.
The wound is a non-linear closed-loop feedback control system.

Examples where the machine is unregulated, broken, or on an atypical attractor.



No healing. Advanced active rheumatoid, on cyclophosphamide.

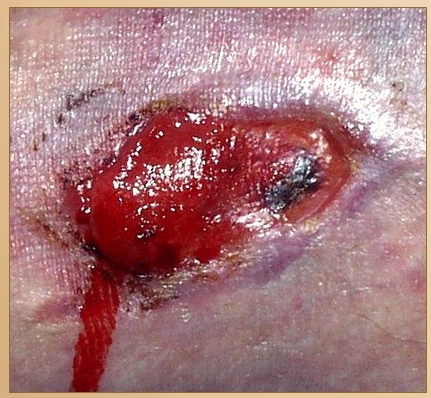


No healing. Embryonic histogenesis in a regenerative matrix, an alternate "attractor".

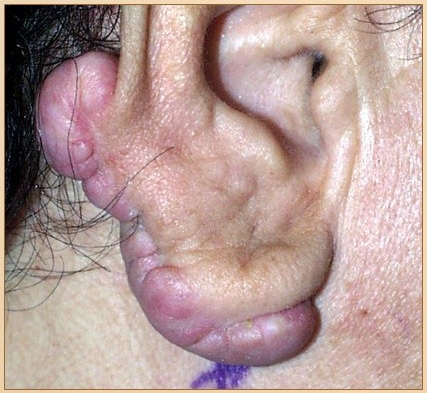
These behaviors are clinically undesirable,

– BUT –

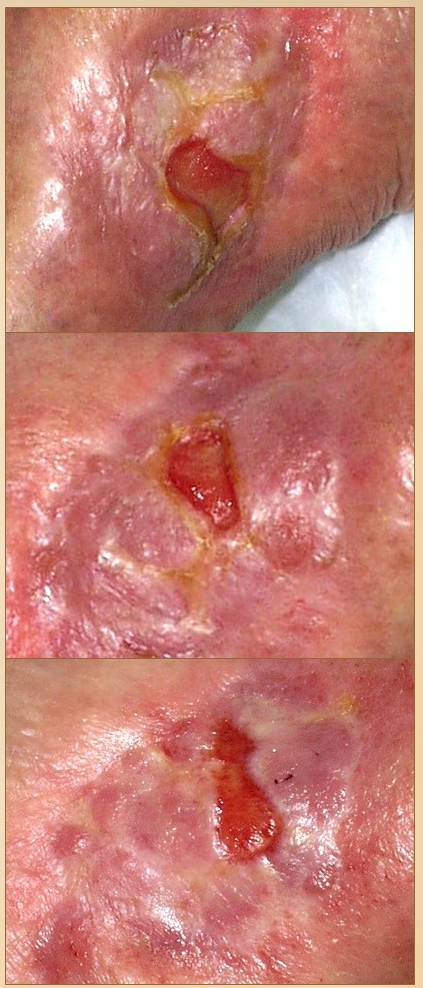
they are standard permissible behaviors (dynamics) of controlled and complex non-linear systems, such as The Wound.



Improper healing. "Pyogenic granuloma", normal controls awry, unregulated proliferation.



Excess healing. Keloid, unregulated fibroplasia: unresponsive to controls vs abnormal stimuli.



Chaotic. 1 month, then 4 month interval. No net change exam to exam. It is in a chaotic "orbit".

THE CENTURY OF THE SYSTEM

THE WOUND IS A COMPLEX MACHINE.
It must be analyzed as such.
WELCOME TO THE CENTURY OF THE SYSTEM.

Bioengineering and Systems Biology

TREY IDEKER,[1] L. RAIMOND WINSLOW,[2] and A. DOUGLAS LAUFFENBURGER[3]

[1]Department of Bioengineering, University of California at San Diego; [2]Department of Biomedical Engineering, The Johns Hopkins University; and [3]Biological Engineering Division, Massachusetts Institute of Technology

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A field known as Systems Biology is emerging, from roots in the molecular biology and genomic biology revolutions—the succession of which has led biomedical scientists to recognize that living systems can be studied not only in terms of their mechanistic, molecular-level components but also in terms of many of them simultaneously. This

computational algorithms for Mining the data to generate hypotheses concerning the potential interpretation of these data sets is necessary. In order to consequently develop new predictions for experimental test (or design), computational Modeling is required for similar reason: unaided human intuition likely cannot produce effective predictions concern-

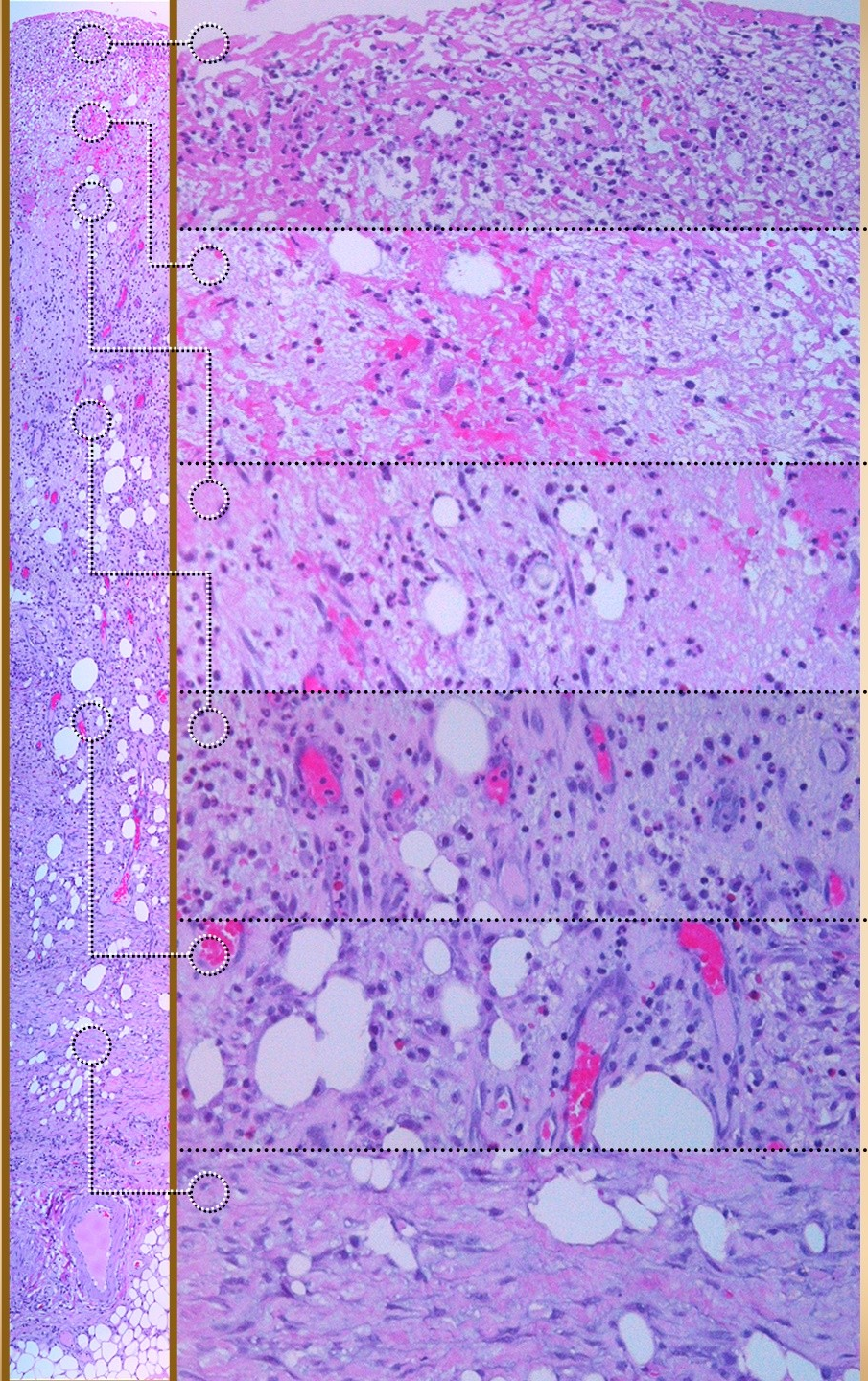
THE WOUND MODULE OF NORMAL WOUND HEALING

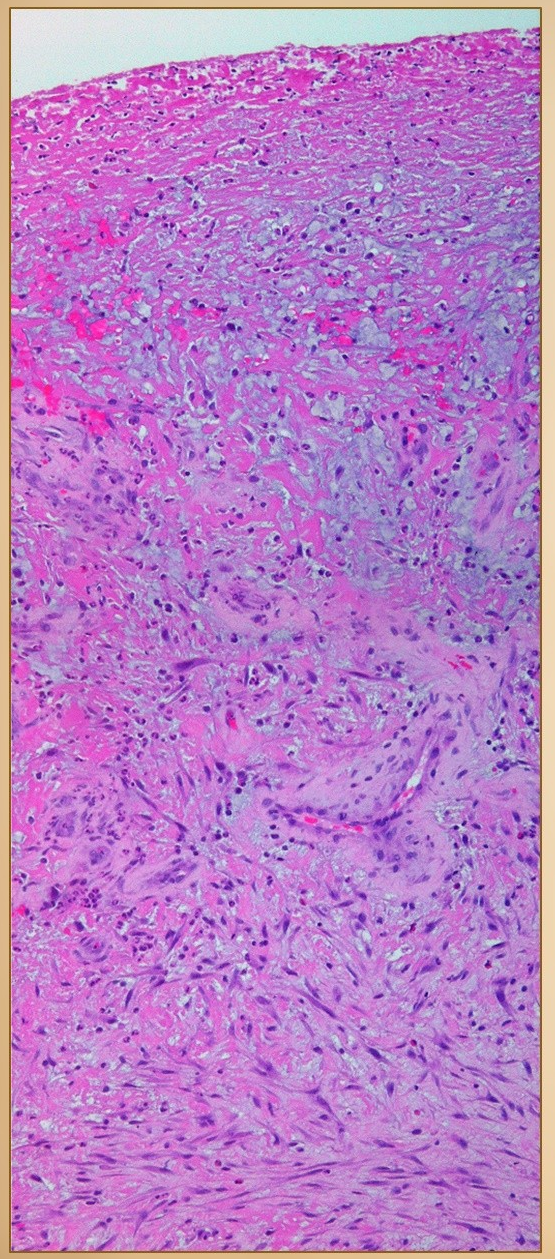
The integrated set of cells, chemicals, events, and interactions which respond to injury and heal a wound.

ANATOMY
Strata

PHYSIOLOGY
Sequential events

CLINICAL
Correlated physical findings





THE WOUND MODULE

OF PROLIFERATIVE REPAIR

and the

PHYSIOLOGIC EVENTS - CLINICAL SIGNS

0
injury
inflammation

1
inflammation
subsides

2
macrophages,
eschar separation,
cytokines

3
ground substance,
mucus

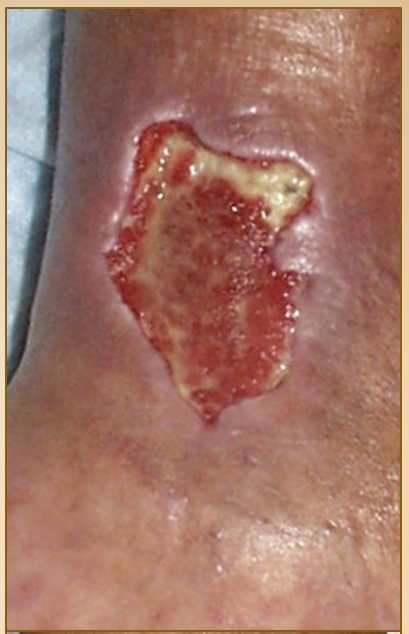
4
"granulation"
angiogenesis

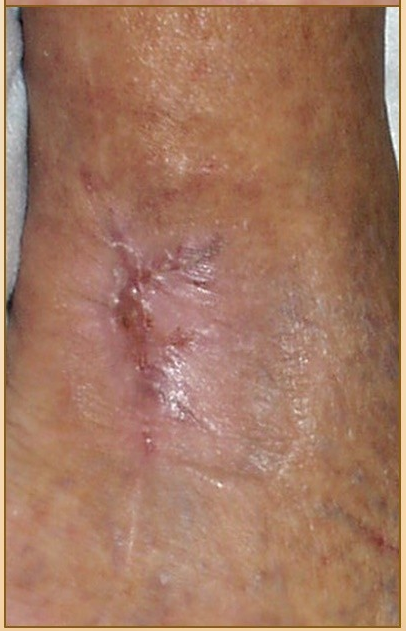
5
histioblasts, fibroblasts,
fibroplasia

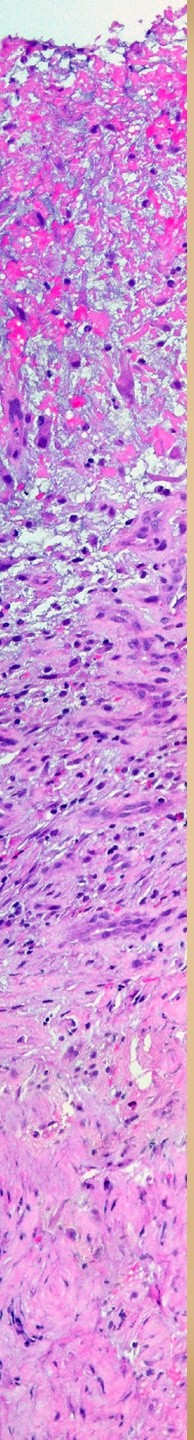
6
myofibroblasts
contraction

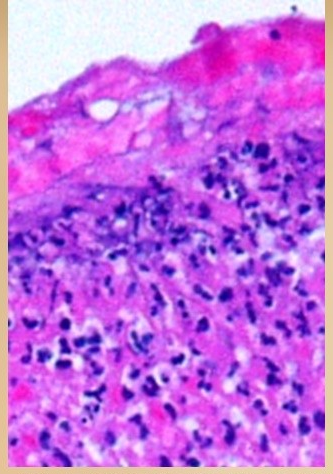
7
epithelialization

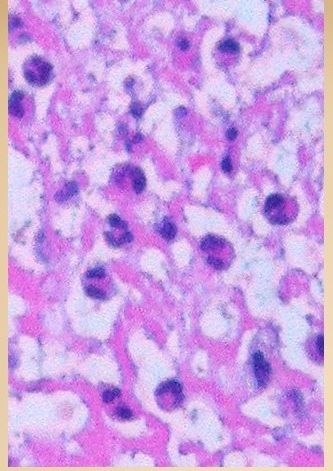
8
maturation

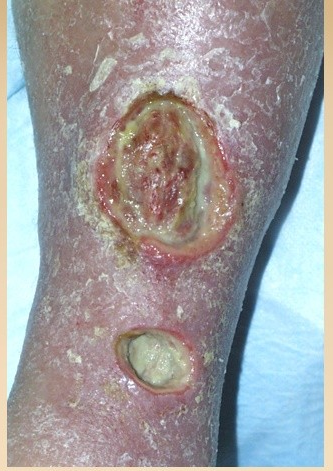










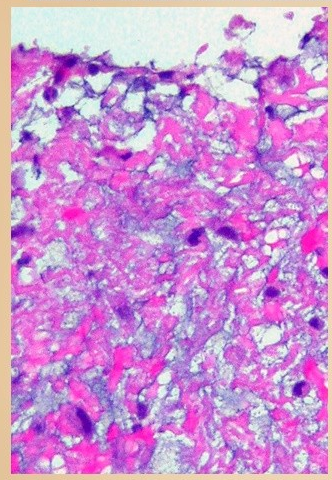


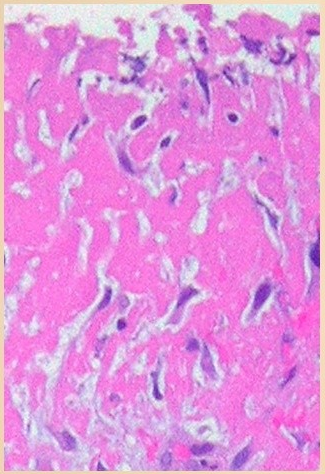
0 - Active injury & inflammation

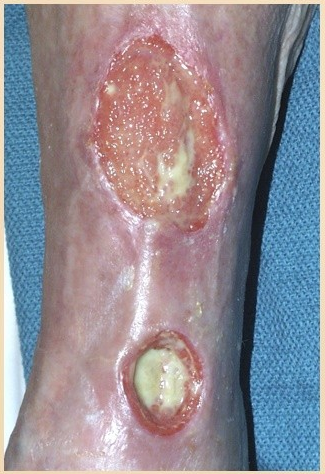
The response to injury, the trigger for repair. Inflammation and repair are integrated sequential processes.

a, b – Wound surface with neutrophils and plasma exudates.

c – An injured leg, inflamed, not healing.





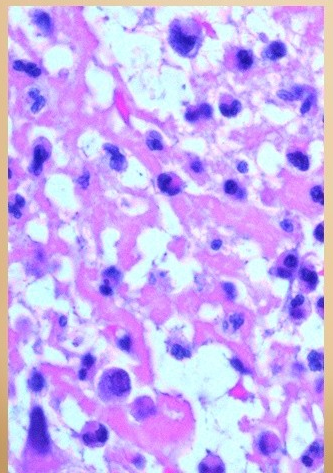


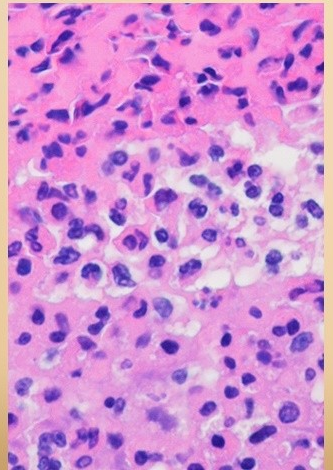
1 - Inflammation subsides

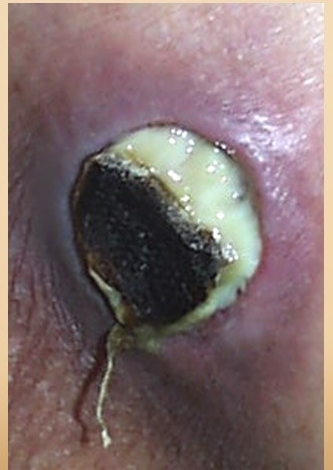
Sustained inflammation suppresses repair. It must subside for repair to proceed.

a, b – Wound surfaces well cared for, free of neutrophils and excess plasma exudates.

c – The same clinical case after 2 weeks of care, now healing.







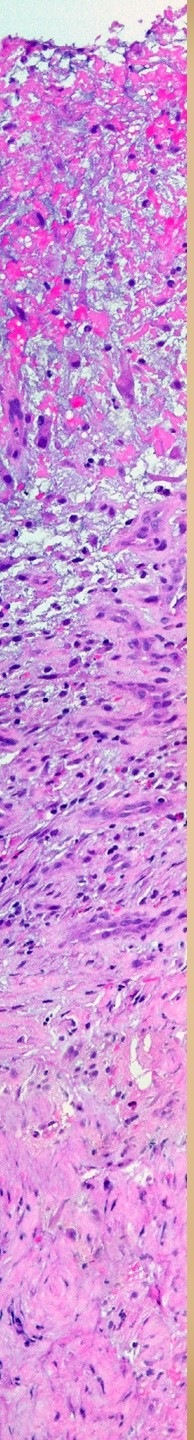
2 - Macrophages, eschar separation

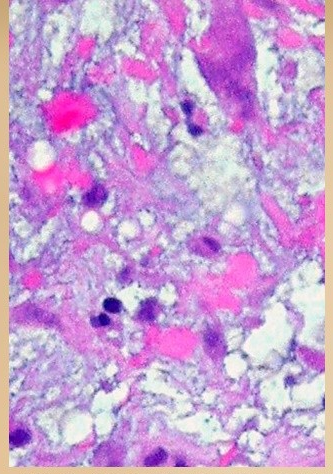
Macrophages are monocytes transformed by inflammation; have multiple functions.

a – Enlarging mononuclear cells in the inflammatory layer.

b – Afferent function is eschar separation, the cleavage line.

c – Eschar separation seen clinically.





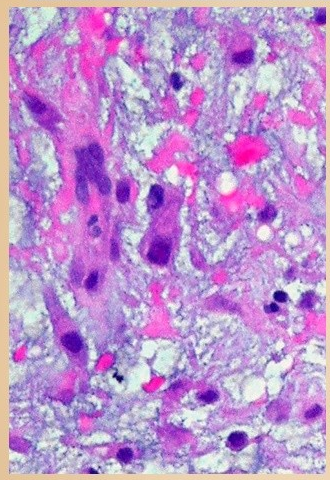
3 - Aminoglycan ground substance

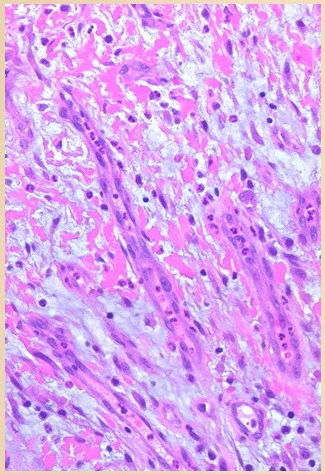
Under the plasma layer, required as an "ether" for early repair cells to migrate.

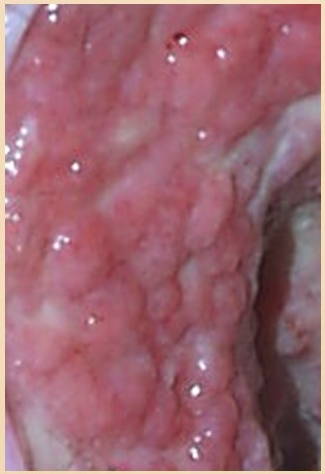
a – The ground substance, free of collagen.

b – Alcian blue. New vertical vessels migrate from below.

c – Normal wound mucus.







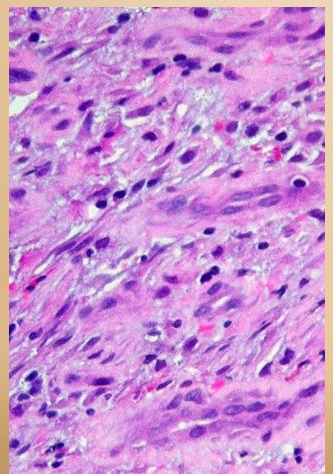
4 - Angiogenesis

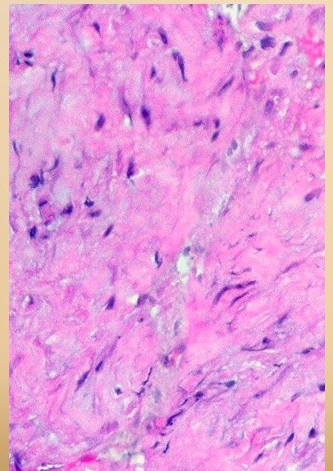
Macrophage efferent function makes growth factors to initiate and attract repair cells. First is the attraction of new vessels.

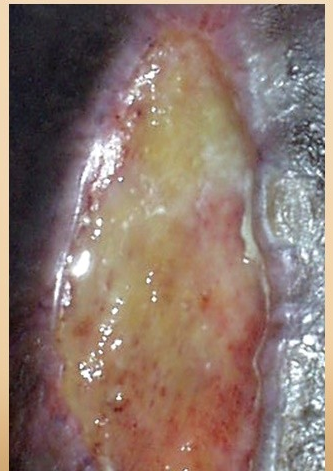
a – Dis-associated angiocytes migrating and reassembling in the aminoglycan layer.

b – New vessels fully organized in mid layers.

c – "Granulation tissue".







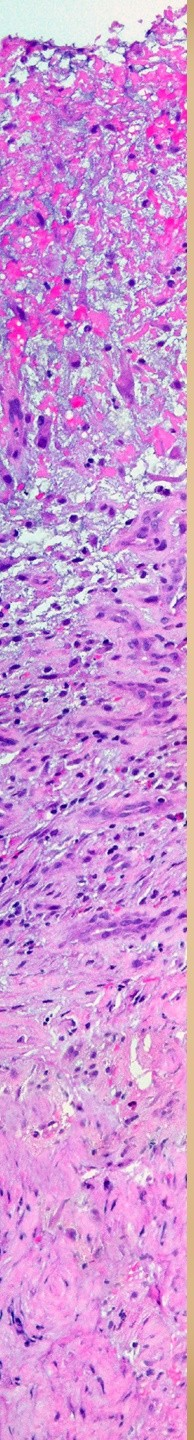
5 - Fibroplasia

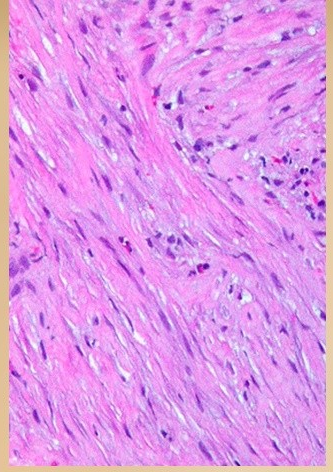
Once new vessels restore a good environment, fibrous cells create fibrous structural matrix.

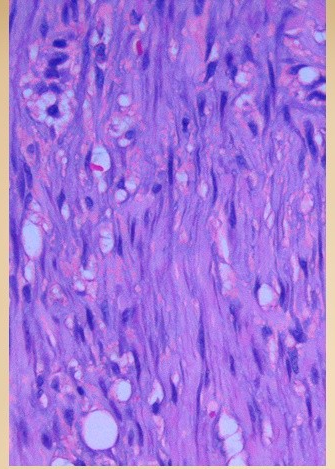
a – Youngest new fibrous cells among new vessels, just starting to make faint collagen.

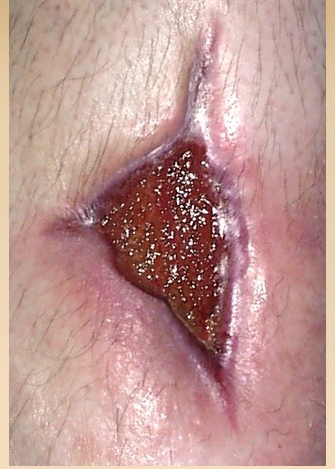
b – Advanced collagen production.

c – In a wound with atrophic upper layers, older, deeper fibrosis is easily seen.









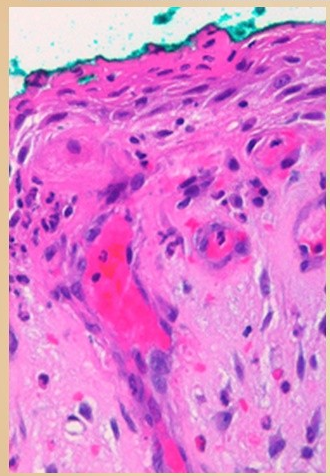
6 - Contraction

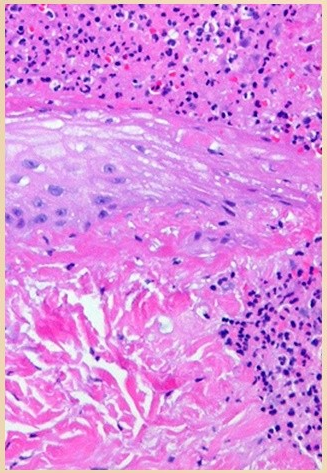
Progressive fibroplasia creates dense scar. Some of it contracts, due to myofibroblasts.

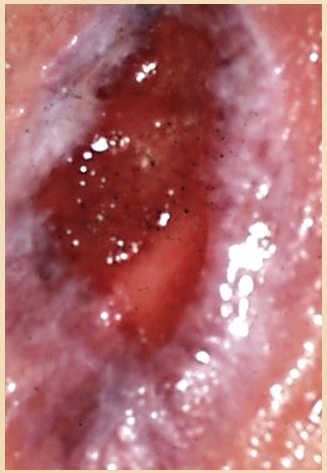
a – Dense new scar, with typical features responsible for its mechanical properties.

b – Dense, highly cellular scar from a "genu" of contraction at a wound margin.

c – A wound actively closing by contraction.







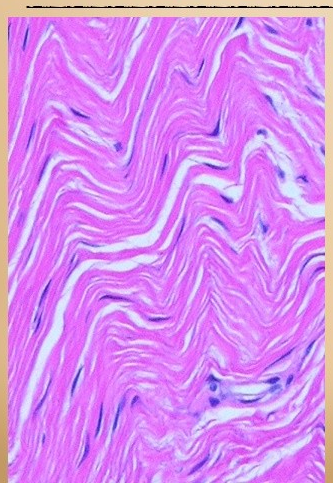
7 - Epithelialization

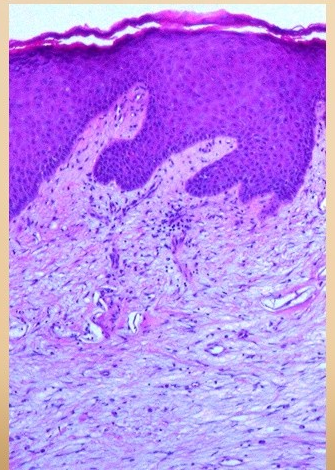
A wound is nominally closed when epithelium is continuous, mesenchyme fully sequestered from ambient world. Epithelium migrates only over other healthy wound module components.

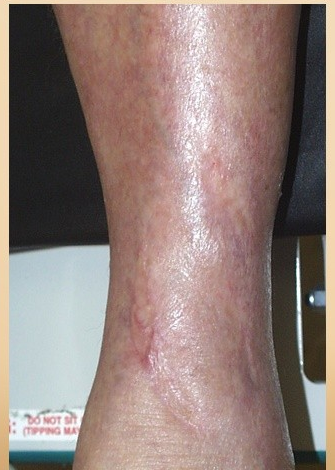
a – Epidermis at edge of a healthy wound.

b – Advancing epithelium cleaving eschar.

c – Clinical view of epithelial ingrowth.







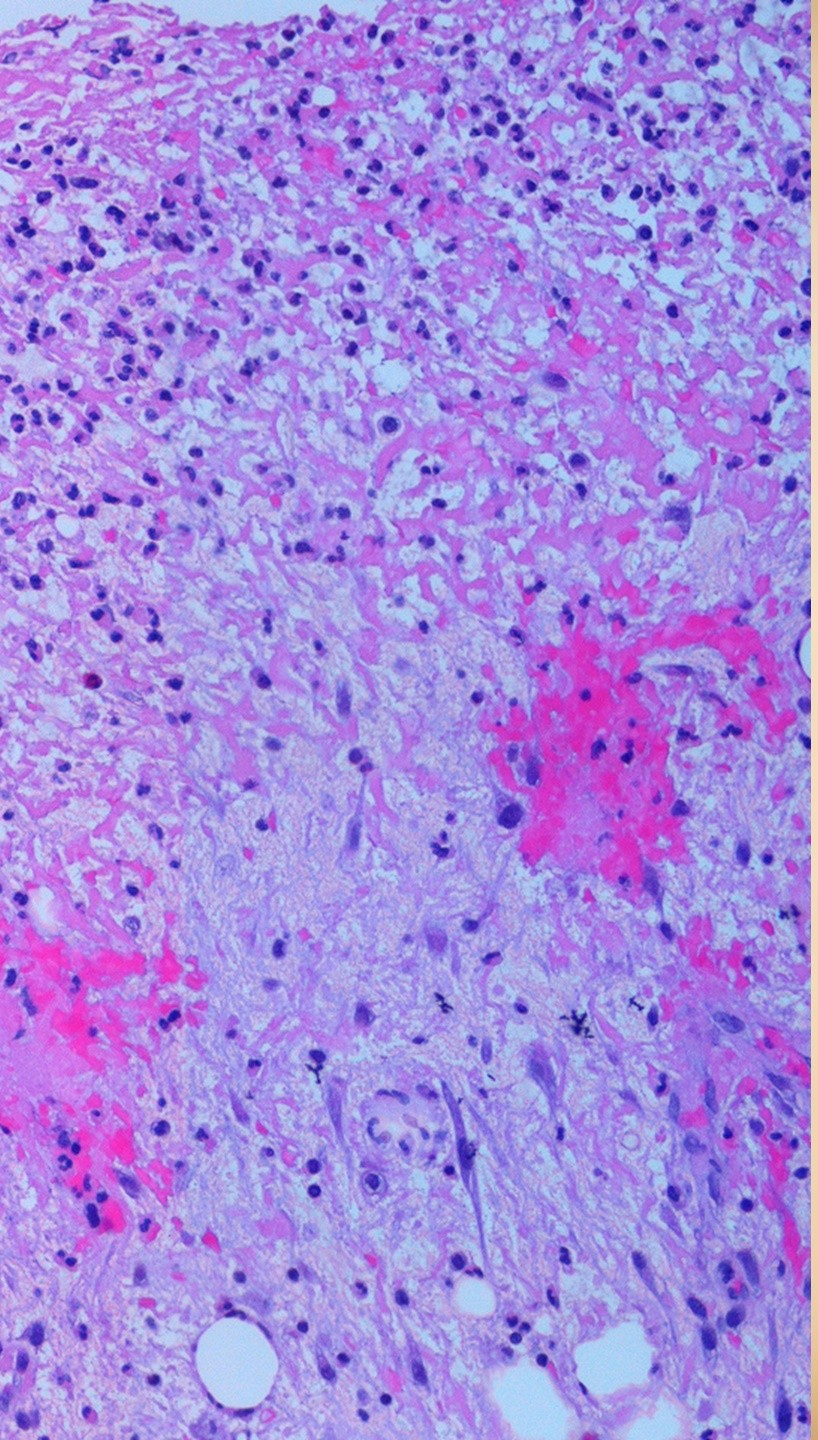
8 - Maturation

Once epithelialized, wounds mature, a slow remodeling of young scar back toward native stromal histology.

a – Mature scar returning to dermis or fascia.

b – Epidermis maturing, and forming a lamina propria (papillary dermis).

c – The same leg as 0 & 1, healed and mature.



THE WOUND MODULE - NORMAL WOUND HEALING

MAIN EVENTS AND CELLS:

INFLAMMATION
(BLOOD BORNE CELLS)
Platelets
PMN leukocytes
(Granular leukocytes) *(No lymphoid cells)*

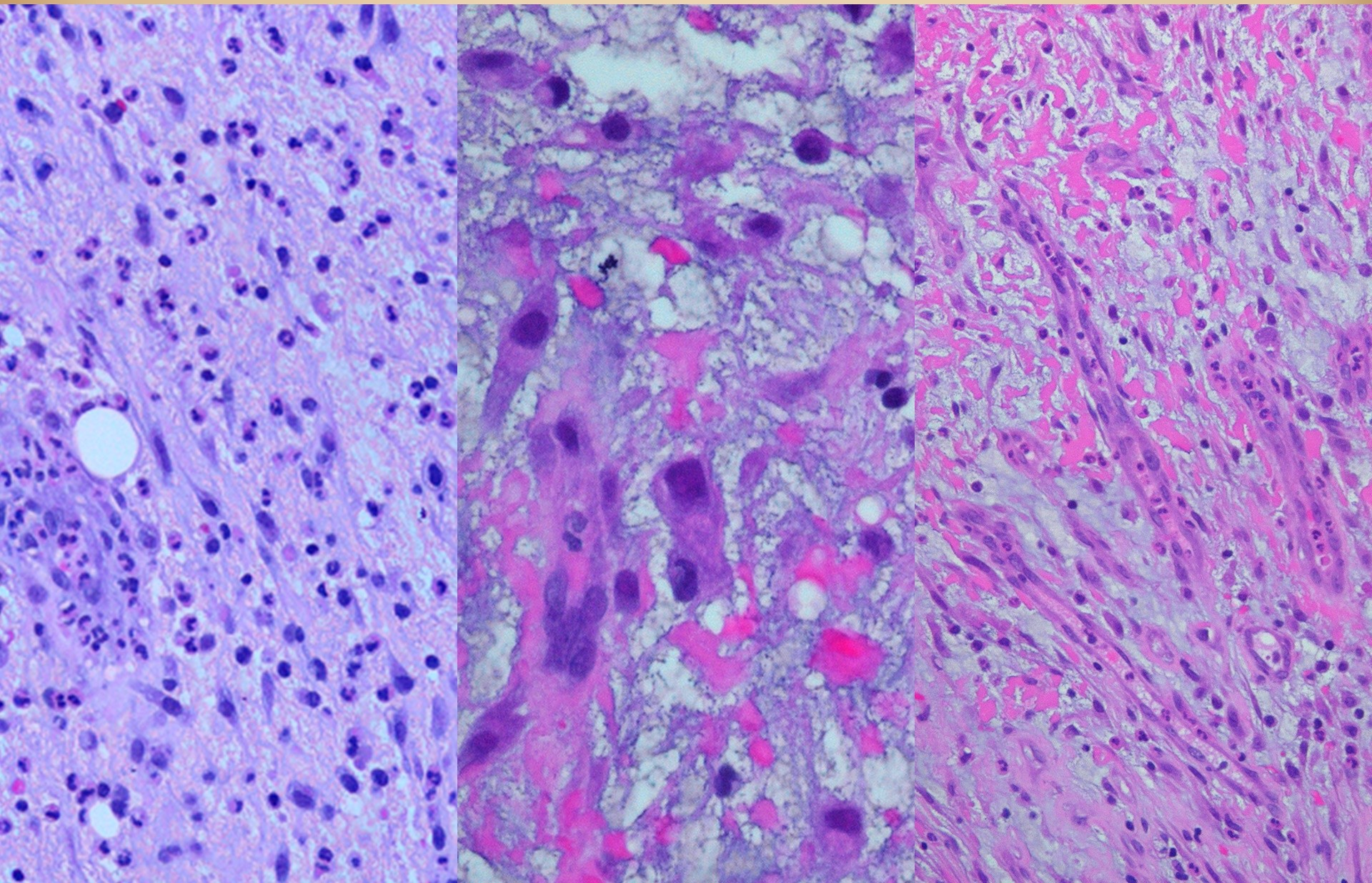
AFFERENT WOUND EVENTS
(TRANSFORMED CELLS)
Macrophages

MESENCHYMAL REPAIR
(LOCAL CELLS)
2 cells:
Angiocytes & Fibroblasts

SEQUESTRATION
(LOCAL CELLS)
Epithelium

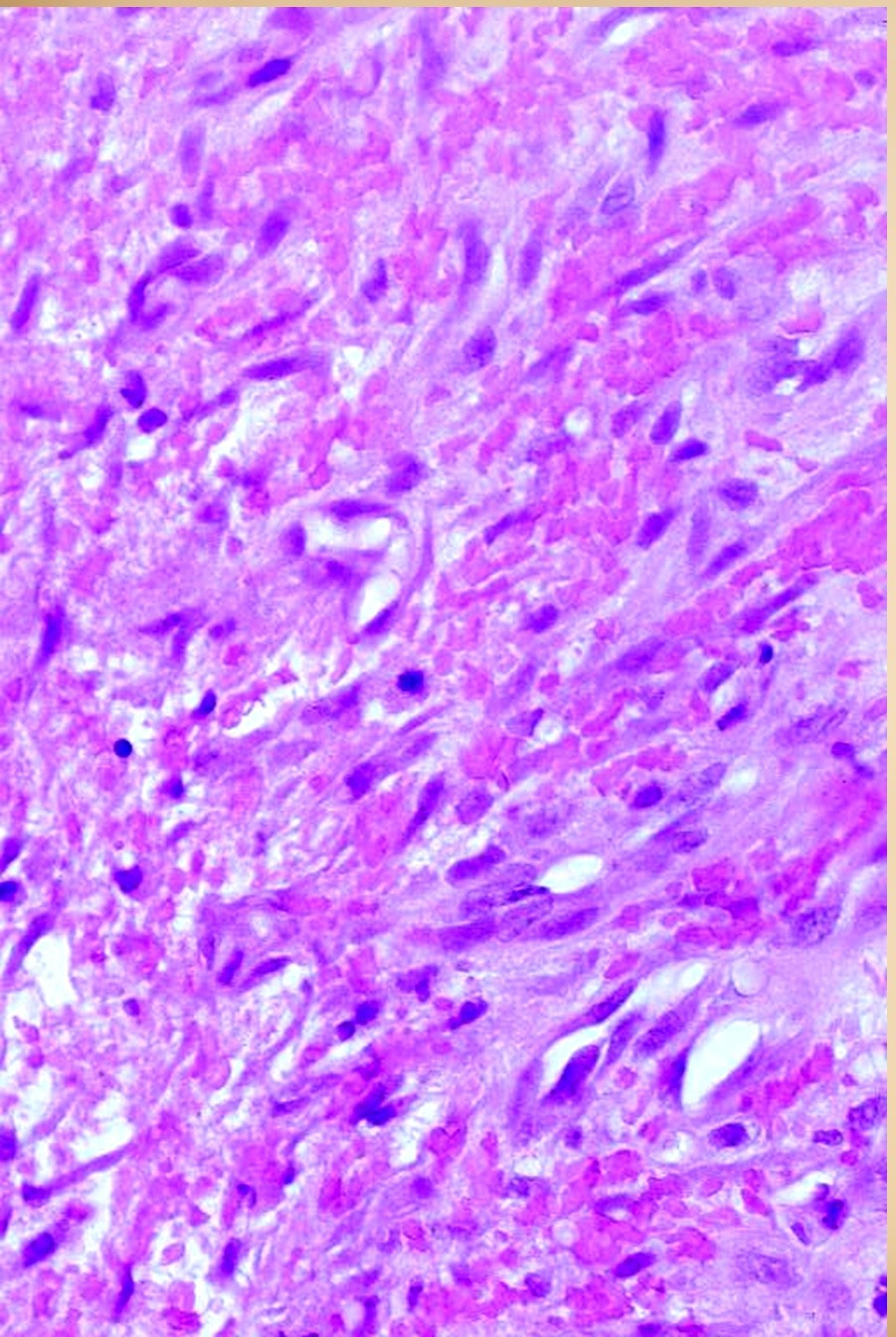
RESTORATION OF STROMA

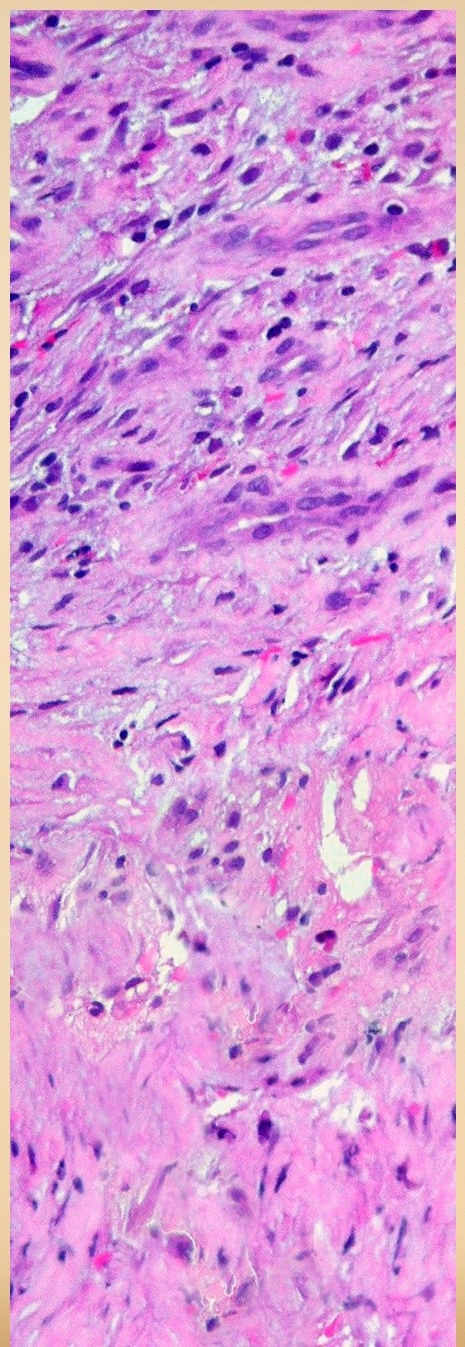
REPAIR IS BASED ON 2 CELL TYPES - ANGIOCYTES & FIBROBLASTS

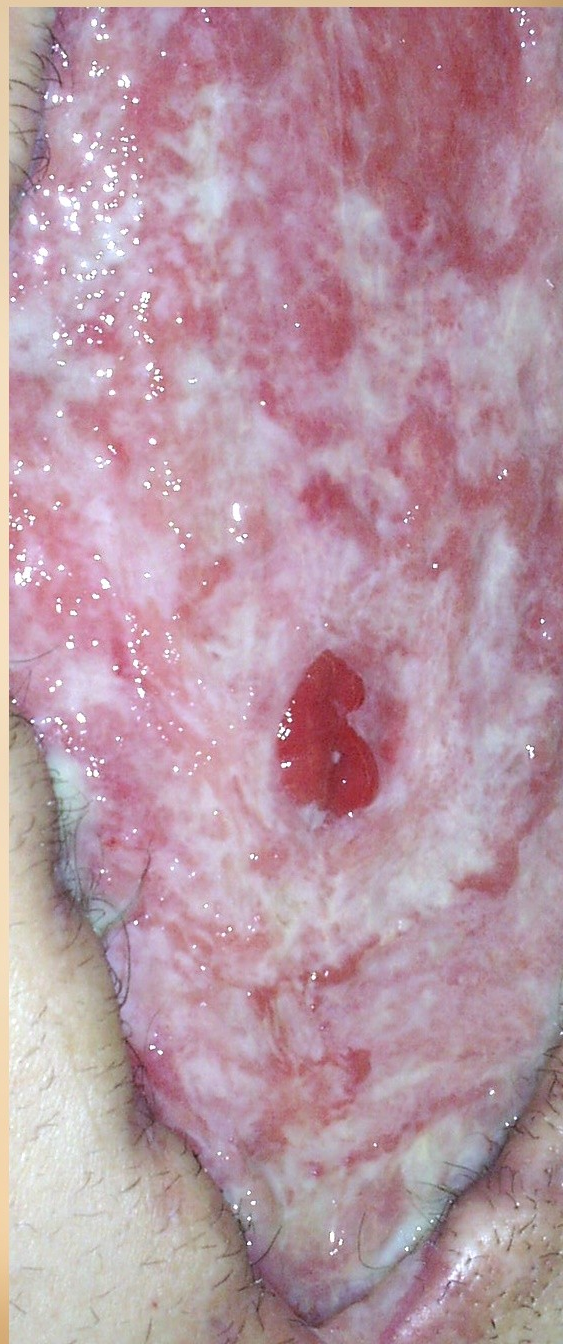


ANGIOCYTES & FIBROBLASTS

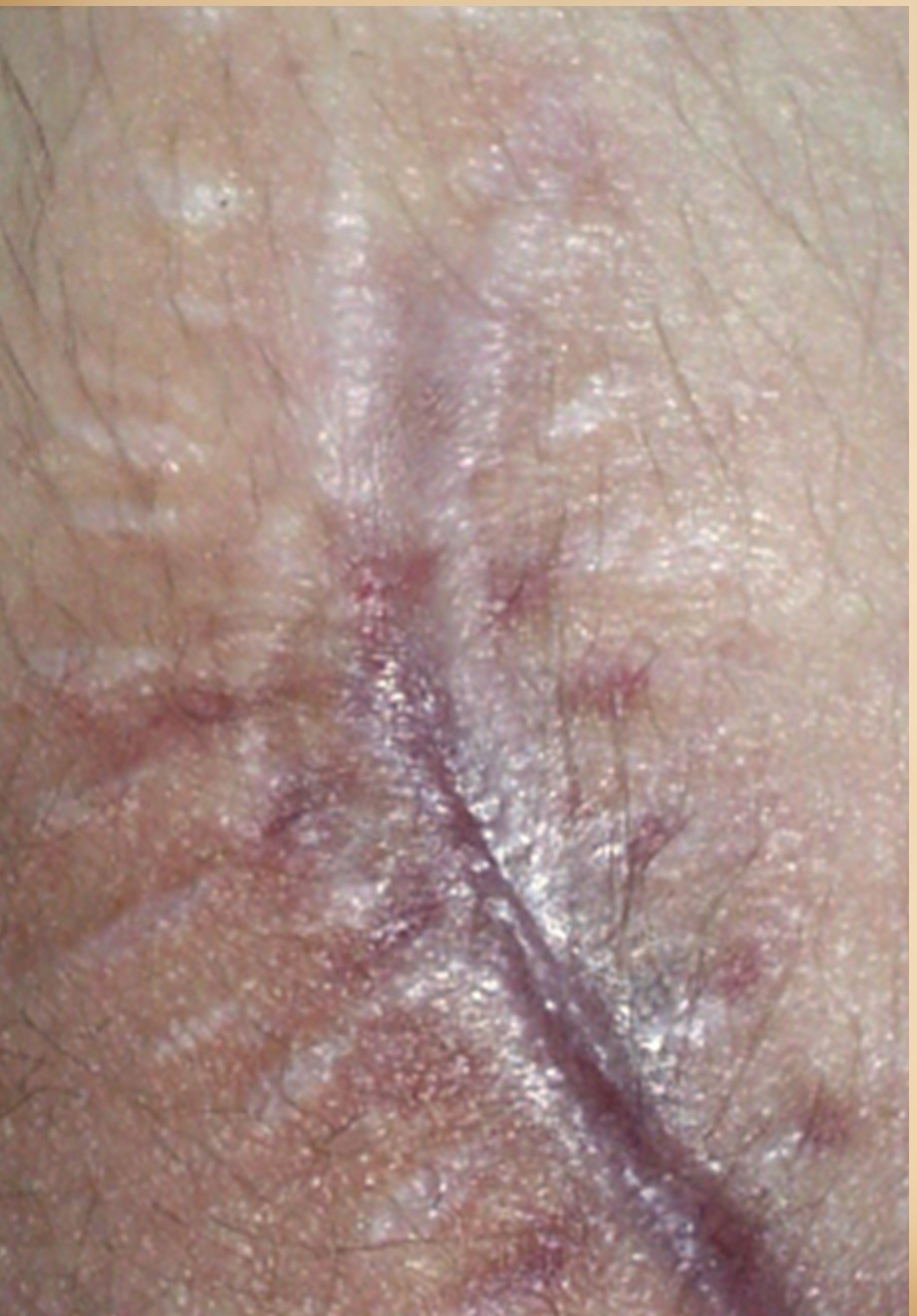
ANGIOCYTES & FIBROBLASTS - RESTORATION OF STROMA

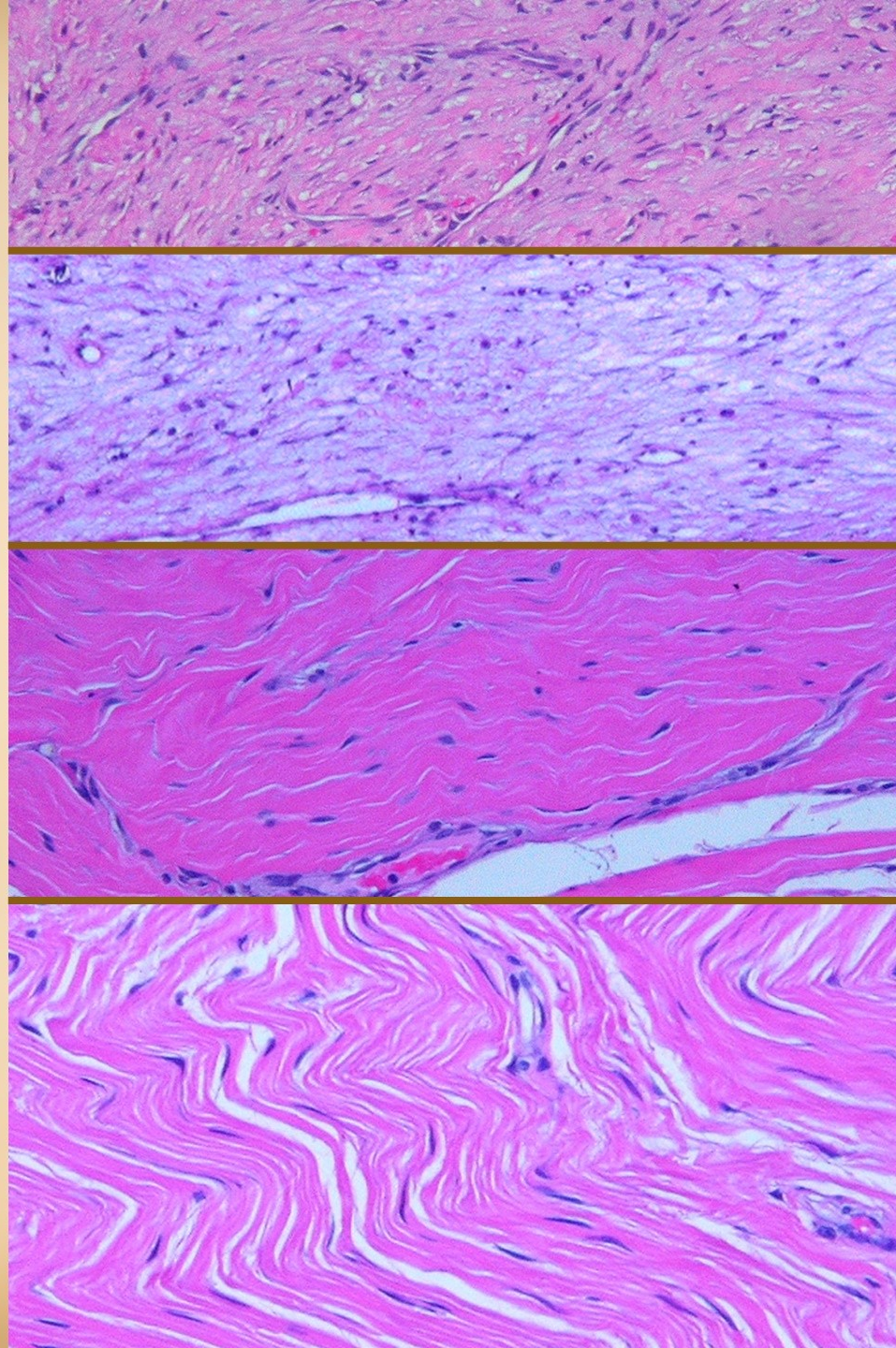




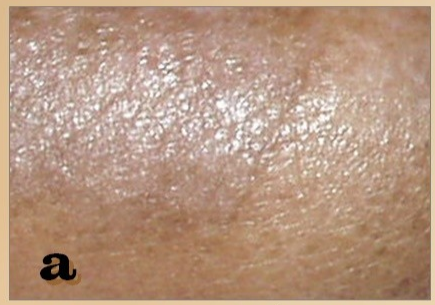


MATURATION OF STROMA

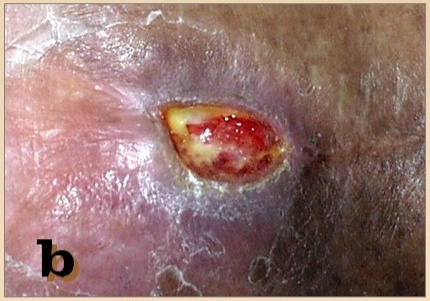




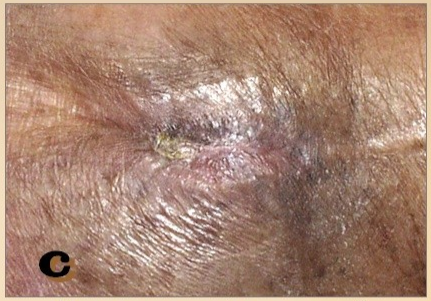
CONTROL & NON-LINEARITY - GENERAL PRINCIPLES



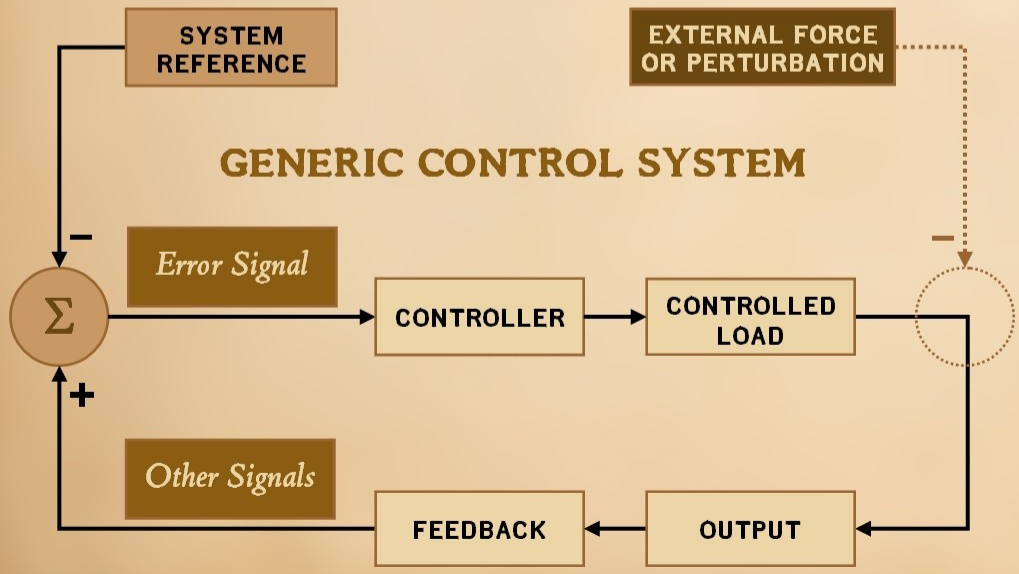
Static, no activity / reactivity without injury.



Wound healing - a reserve system, needs a trigger.



Once restored to normal, wound healing ceases.



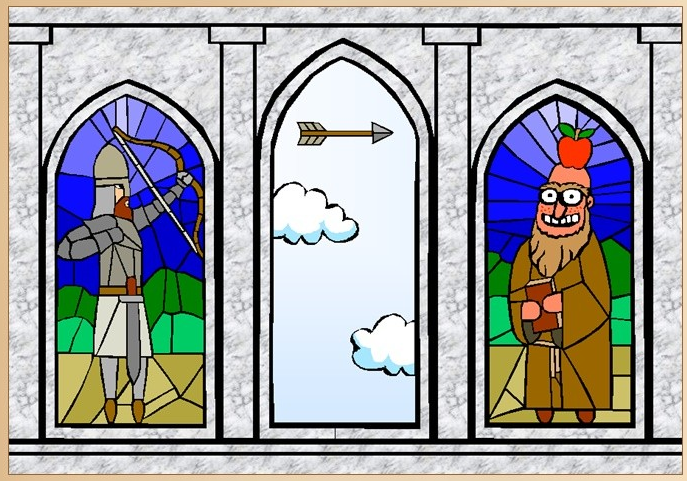
CLOSED LOOP CONTROL SYSTEMS react to correct differences between actual state and a reference value.

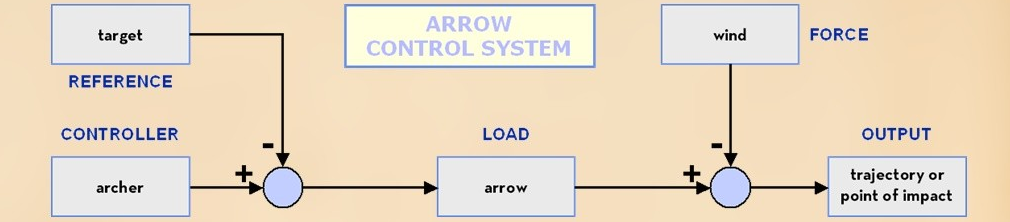
REFERENCE: The target the system works to maintain.
NODES: Combinatorial points that yield values.
SIGNALS: To convey information between blocks.
CONTROLLER: Mechanism to implement corrections.
LOAD: Element that is acted on by the controller.
OUTPUT: Product of control reaction; modified system.
FEEDBACK: Method to report current system state.

FORCES: Extrinsic perturbations which force response.

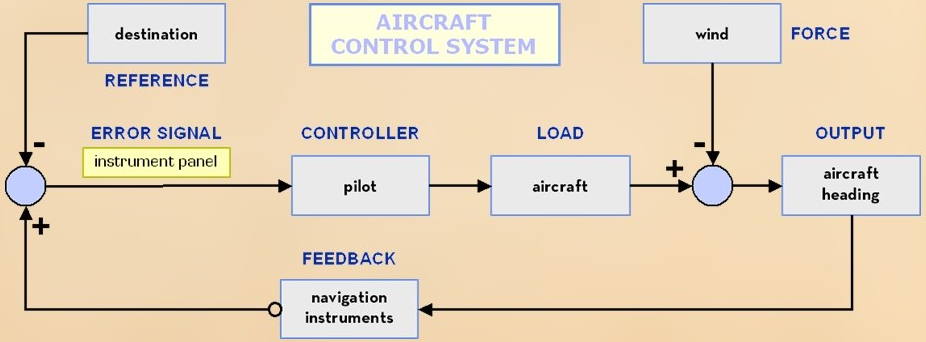
CONTROL & NON-LINEARITY - THE NEED FOR CONTROL

Control lets a system hold itself to a desired output, state, or attractor. Key to control is feedback, the ability to sense the system state or output, which then drives an error correcting mechanism.





ARROW: No feedback - open loop. Course cannot be assessed nor corrected. Must be calibrated (aimed), and if a gust of wind or anything upsets that calibration, the system misses its mark.

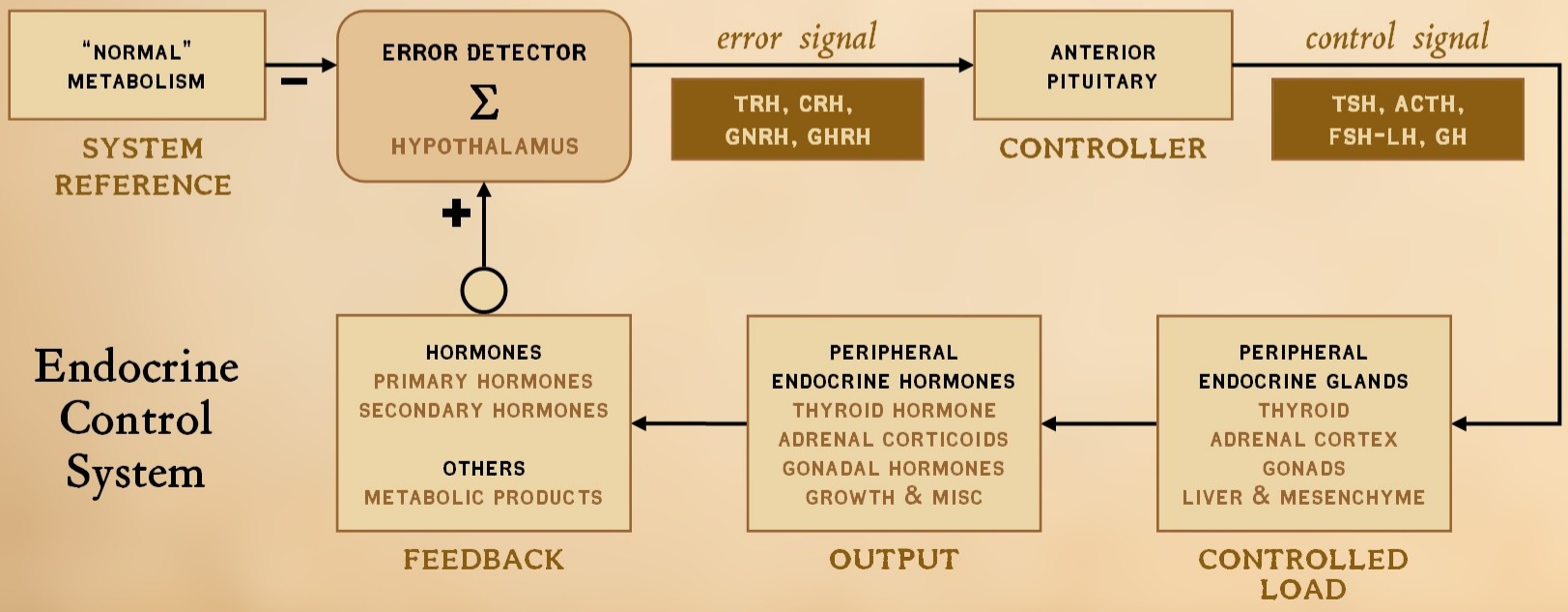


AIRPLANE: Steered, not aimed. Pilot and flight controls assess and correct the plane's heading. Feedback and closed loop control assure that system reaches target, even when perturbed.

CONTROL & NON-LINEARITY - IN BIOLOGICAL SYSTEMS

Twentieth Century biological science and systematology were colored by discoveries of the latter 19th century, with *"homeostasis"* and chemical *"reaction kinetics"* being the basis for much of physiology research and doctrine, anchored in the dependent-versus-independent method of experimental biology.

These are inherently linear concepts which cannot account for systems physiology, which was ignored because non-linear and N-body systems were deprecated as *"intractable"*. Feedback and control systems in biology were recognized, but were oddball incidentals, such as the hypothalamic-pituitary-endocrine system.



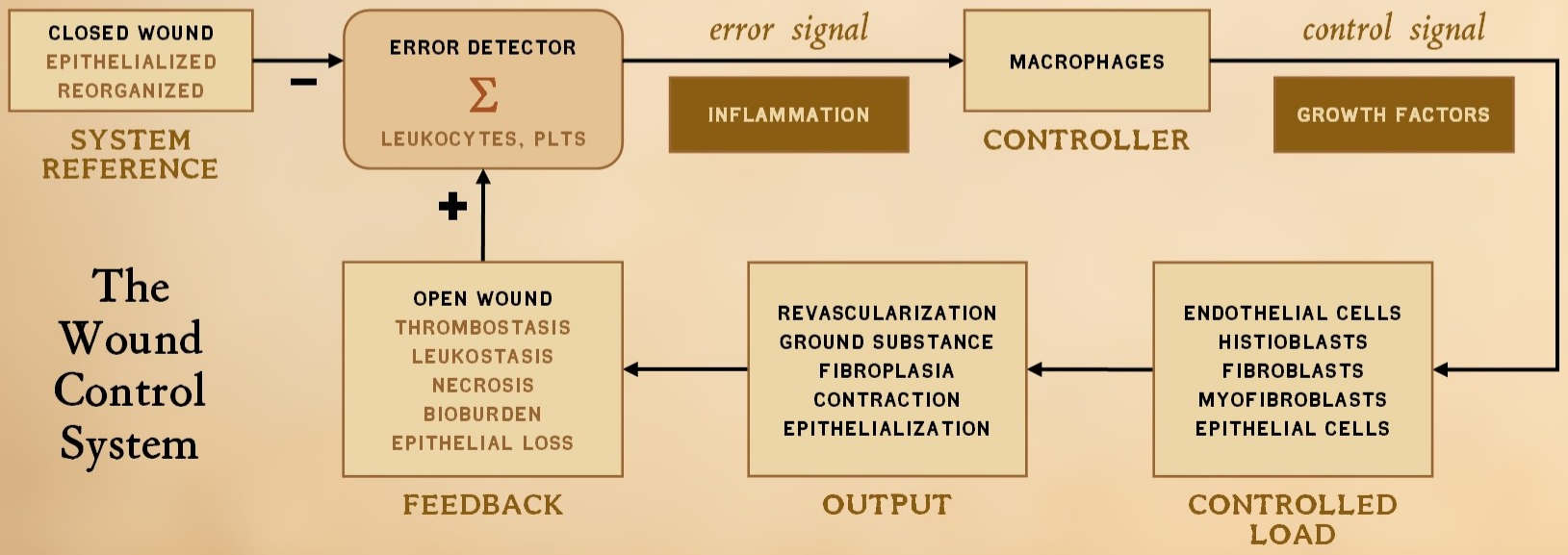
CONTROL & NON-LINEARITY - BIOLOGY, THE WOUND

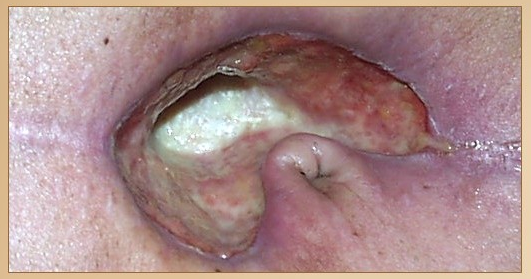
THE WOUND IS A NON-LINEAR CONTROLLED MACHINE

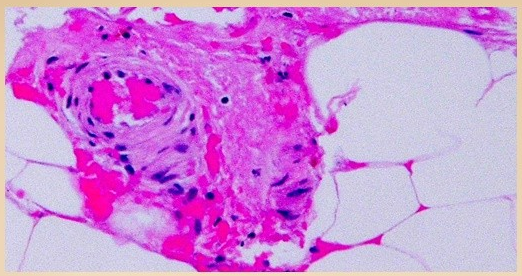
The proliferative module of normal post-inflammatory wound healing must be regulated: when to turn on, how much output to create, when to cease. This control or regulation is a non-linear process based on a closed feedback loop having all of the elements of any well-controlled machine.

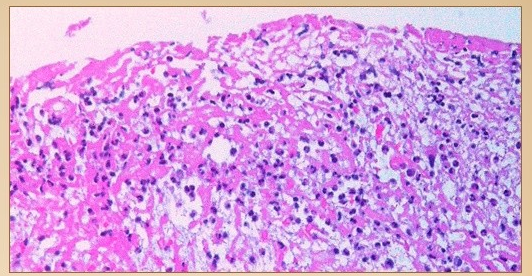
The anatomical constituents and physiological events of the wound module all correlate with elements in the wound control system.

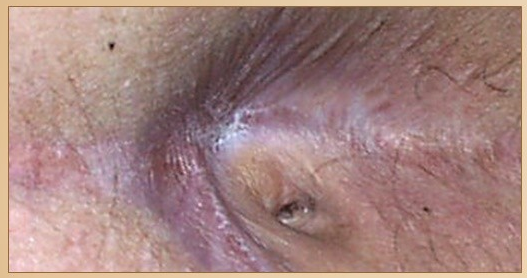
The Wound Main Control Loop

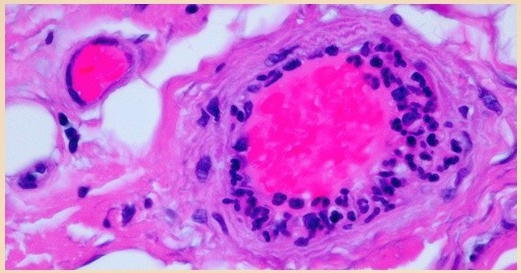


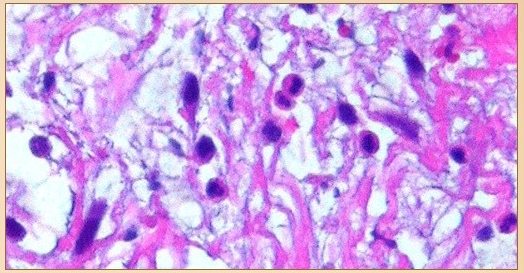












System reference = a closed wound

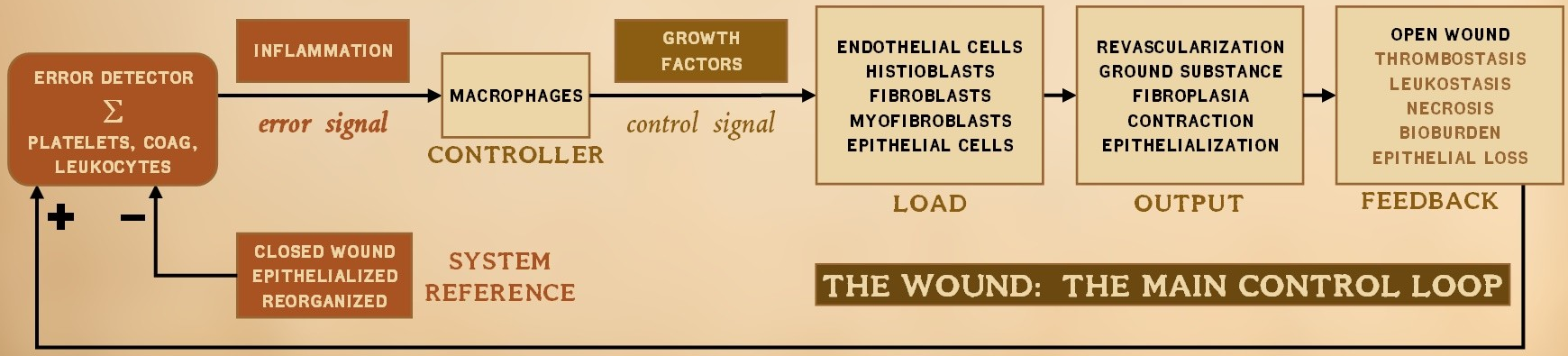
A closed wound, continuously epithelialized, mesenchyme fully sequestered. The wound control loop works to restore this when system state is disturbed, and ceases when complete.

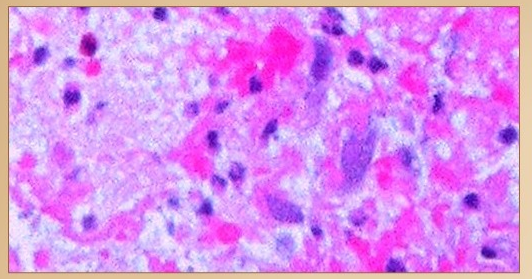
Error detector / comparator = blood

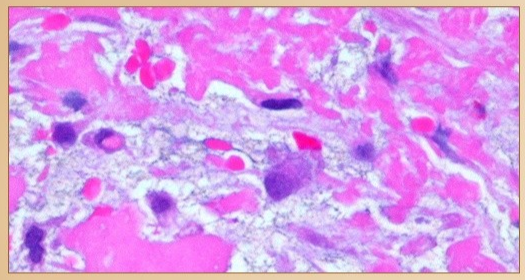
Plasma, platelets, and leukocytes recognize conditions of injury or epithelial loss. Variance from reference state generates inflammation, which ceases when variances subside.

Error signal = inflammation

Inflammation is a complex multi-control system with many purposes, including an integrator signal to transform and accumulate macrophages to turn on wound healing.

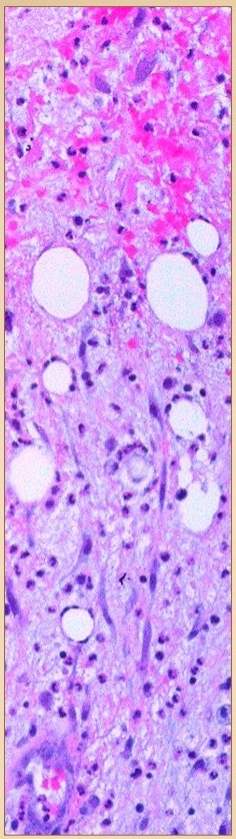






Controller = macrophages

Macrophages do not themselves heal the wound. They muster local wound healing cells. As the regulators of the repair machinery, they are the system controller.

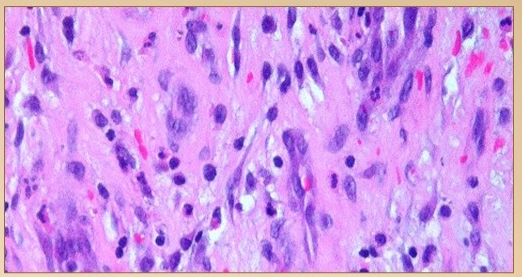


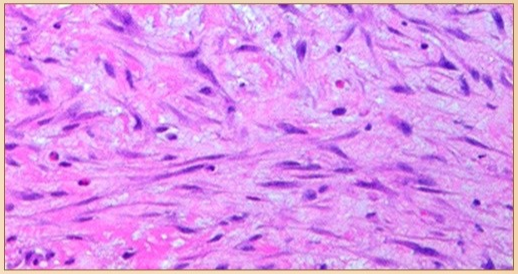
Control signal = growth factors

Macrophage controllers issue orders by making peptide growth factors: PDGF, TGF, FGF, EGF, IGF, TNF, IL, etc.

They transform and attract local progenitor cells into a state of histogenesis, including mitosis, migration, and phenotyping.

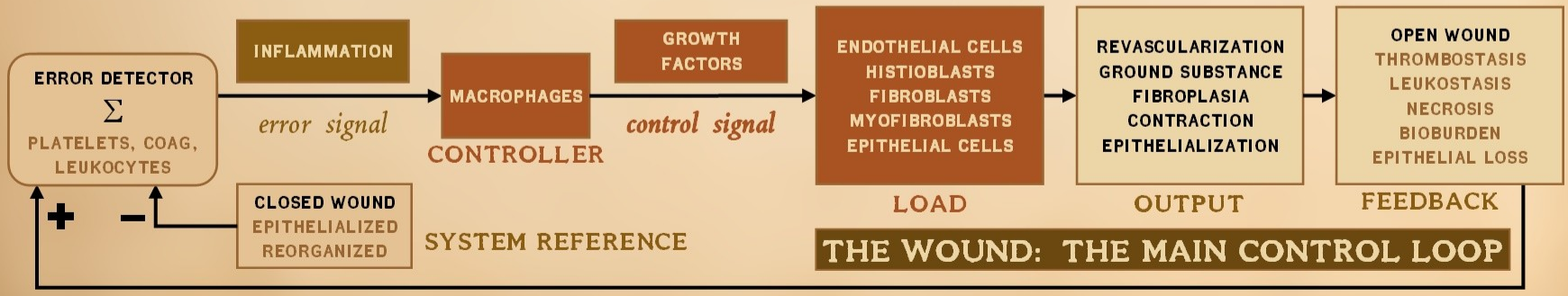
Chemotropic attraction is easily seen as angiocytes stream upward from parent vessels toward stimulus cells.

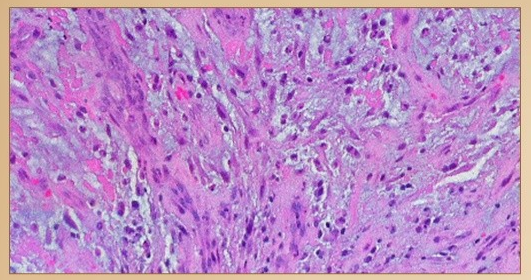


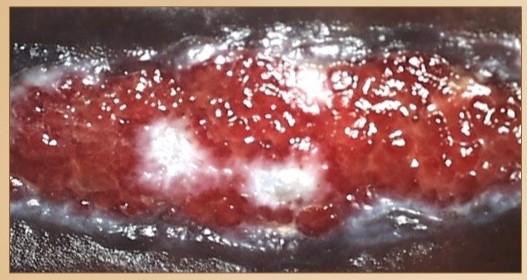


Controlled load = responder cells

System load is the cell set activated by macrophages: angiocytes first, then histioblasts which differentiate to output-producing fibroblasts and myofibroblasts.

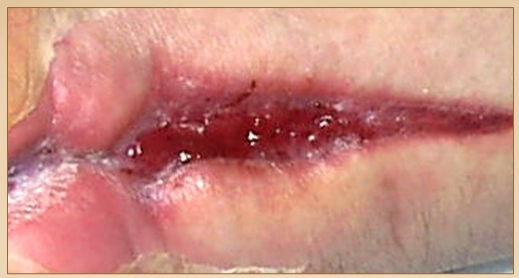


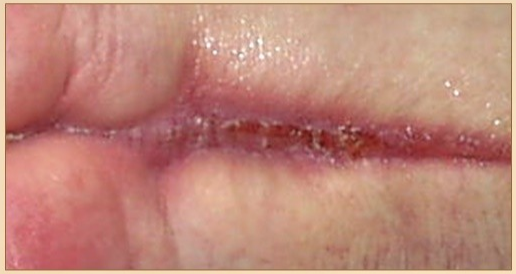




Output = proliferative wound module

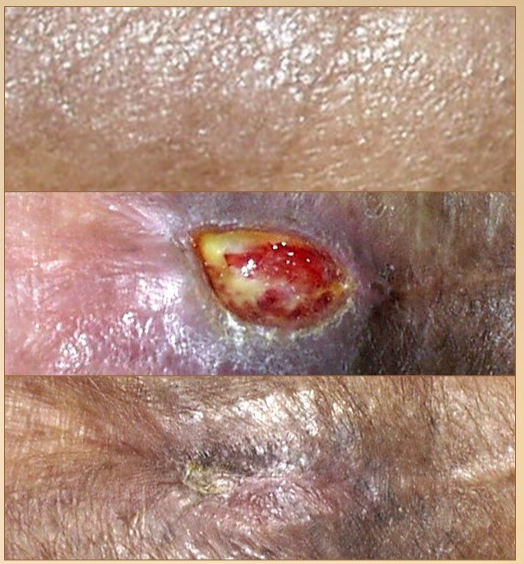
Regeneration and repair components made by load cells: gag's, then vessels & connectives, stroma and body continuity, then contraction, epithelialization, sequestration-closure.





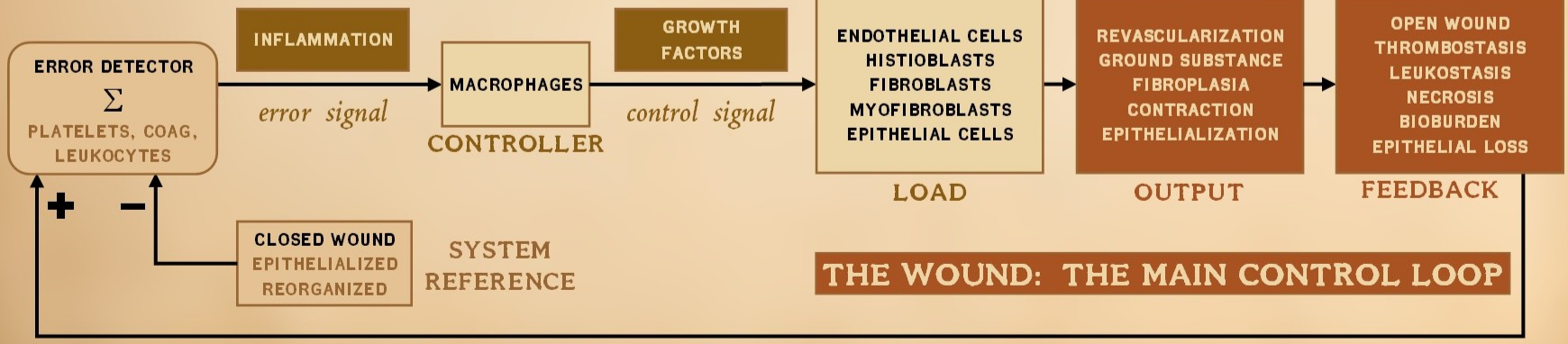
Feedback = open wound

Plasma leak, thrombo-leukostasis, necrosis, bioburden, epithelial loss are variances from normal which drive inflammation and healing until closed reorganized tissues are restored.



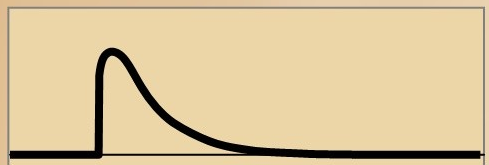
The wound main control loop

Once closed & reorganized, the control loop diverts to chronic maturation phase, and then back to standby. This self-organizing system is purely reactive and reference-error driven.



BEHAVIOR OF CONTROLLED & NON-LINEAR SYSTEMS

A control system monitors itself. If it senses variances from reference, it tries to counteract them, pulling back in the opposite direction, trying to keep as close as possible, as smoothly as possible, at reference or target level. This can work well, or there can be instabilities. Here is a sampler of possible responses.



a. one-shot

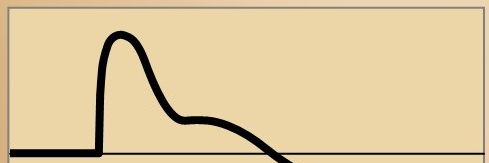
Perturbation is corrected by a smooth return to reference (linear, exponential, etc).

The response of a healthy wound to simple injury.

b. saturation-extinction

Control may fail or be over-whelmed, the system failing at its extrema.

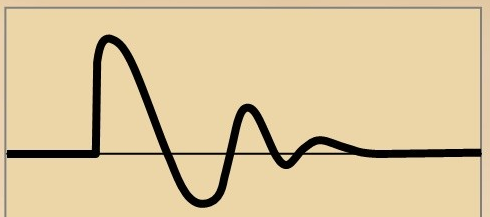
The wound response to severe inflammation or active disease.



c. amplification-attenuation

Blunted or exaggerated reactions result in over- or under-correction.

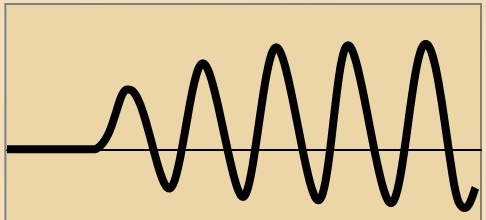
e.g. Pyogenic granuloma or keloid.



d. damped sine

Compensatory reactions over-shoot target, oscillating during the decay back to reference.

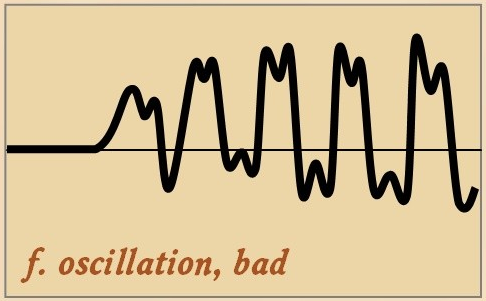
Seen in various micro-scale physiologic systems.



e. oscillation, good

Overshoot goes back-and-forth, creating oscillations. This can be intentional or desirable, as in clocks or radio wave circuits.

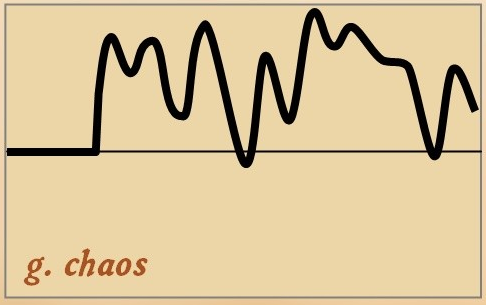
e.g. A bee's wingbeat, or a heartbeat.



f. oscillation, bad

Unintended, exaggerated, and multi-harmonic oscillations are the bane of good control.

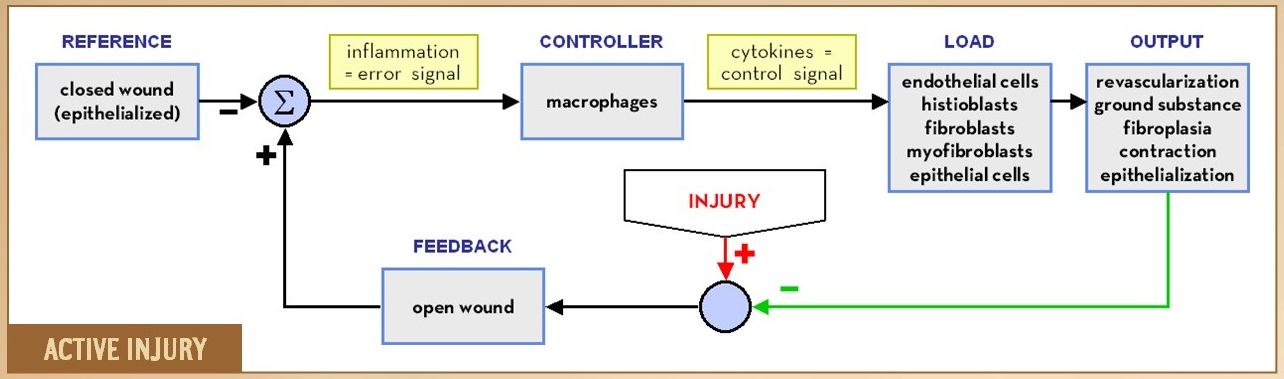
e.g., Parkinson or cerebellar tremor.

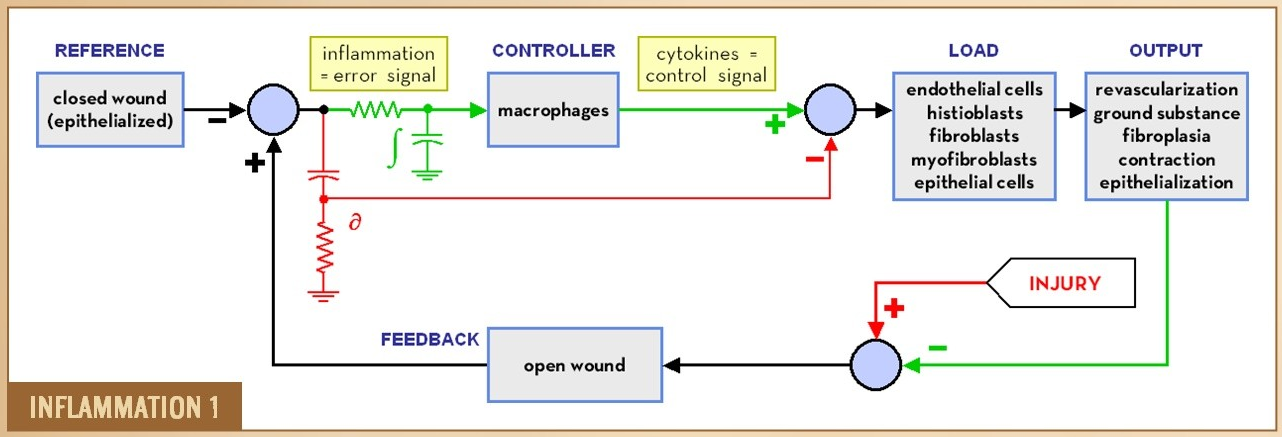


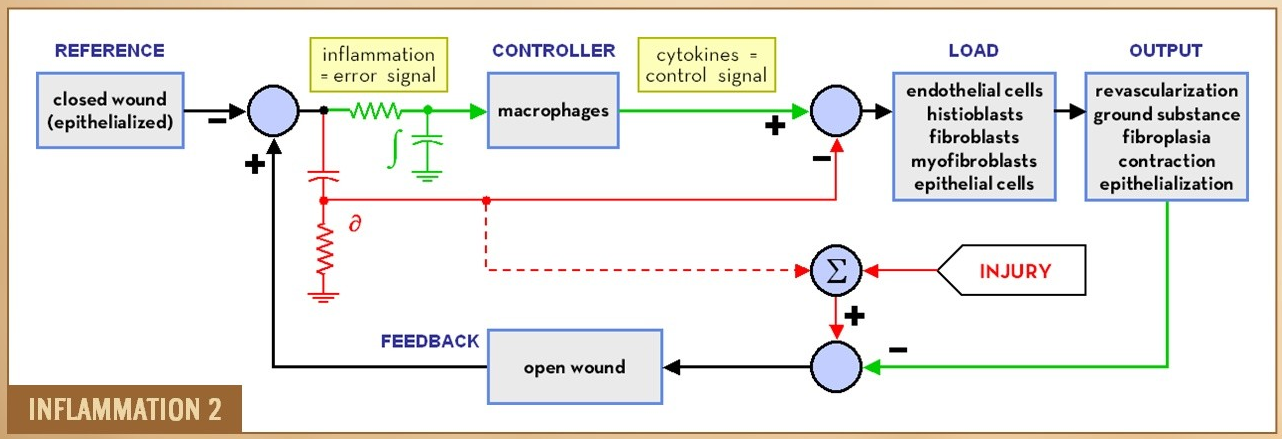
g. chaos

Instability in multi-control systems can be erratic, non-harmonic, non-analytical – aka chaotic.

Most chronic wounds and re-ulceration.







MODELING REAL WOUNDS

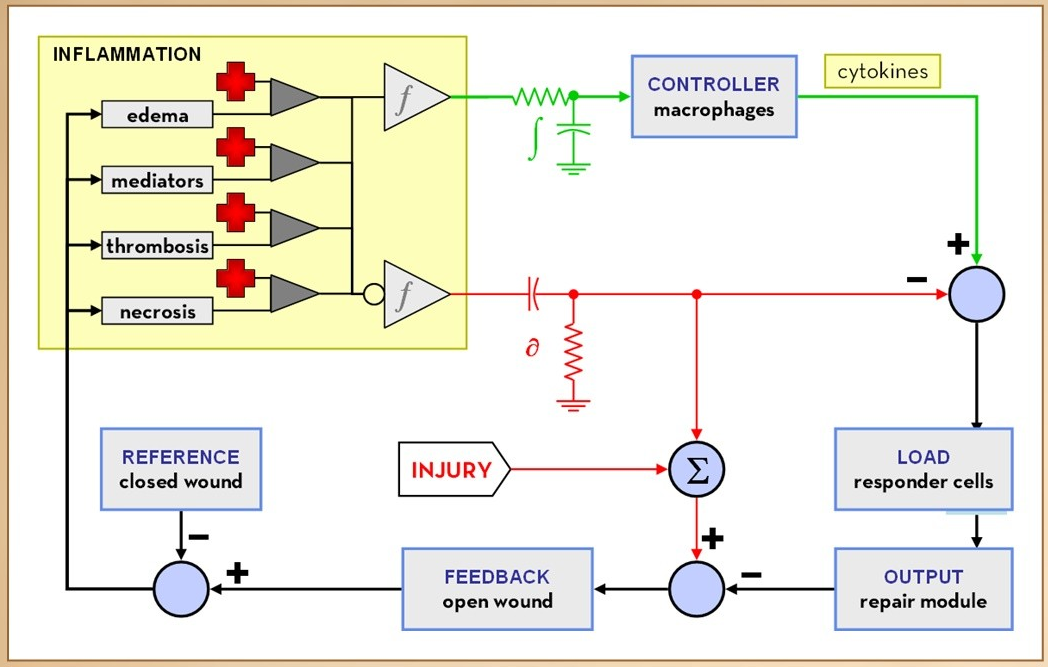
Healthy healing due to one-time injury is a one-shot. What if the wound is sustained by disease or repetitive injury? The **Wound Control Main Loop** is an **open kernel** that can be amended and appended to represent and analyze all physiological, pathological, and clinical variances of a wound.

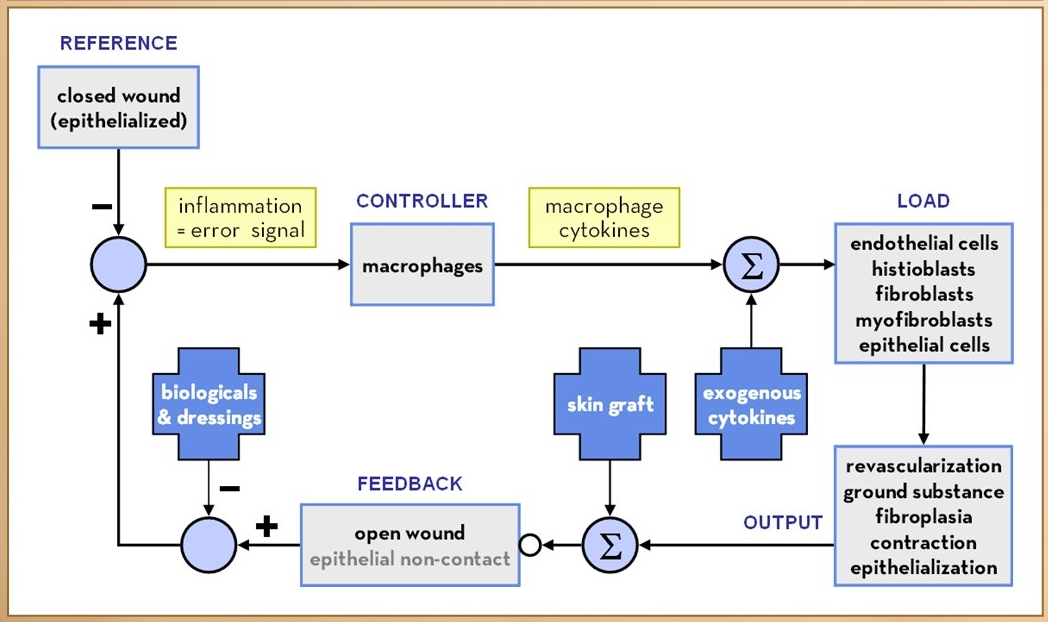
THE CHRONIC ACTIVE WOUND

Active injury: Loop output lessens "open wound". Active injury creates more open wound, which can be summed in at the node shown.

Inflammation 1: Inflammation induces wound module, but acute inflammation also inhibits healing (why it must abate for active repair to occur). To model this, split inflammation: an integrator gradually builds macrophage mass, for robust healing at the right time; a differentiator transiently suppresses active healing during "flare-ups".

Inflammation 2: Intense inflammation is itself injurious and ulcerative, modeled by summing part of inflammation into the injury node.





MODELING REAL WOUNDS

WOUND TREATMENT

BASIC WOUND THERAPIES

Mediators within the inflammation "black box" are counteracted by basic "red cross" therapies (inverting inputs) which correct injury, maintain hygiene, and control debris, inflammation, & edema. Inflammation outputs through filters *f* which sum these elements, to have them drive the two main functions of protect-the-host-but-suppress-healing versus active-healing.

WOUND HEALING THERAPIES

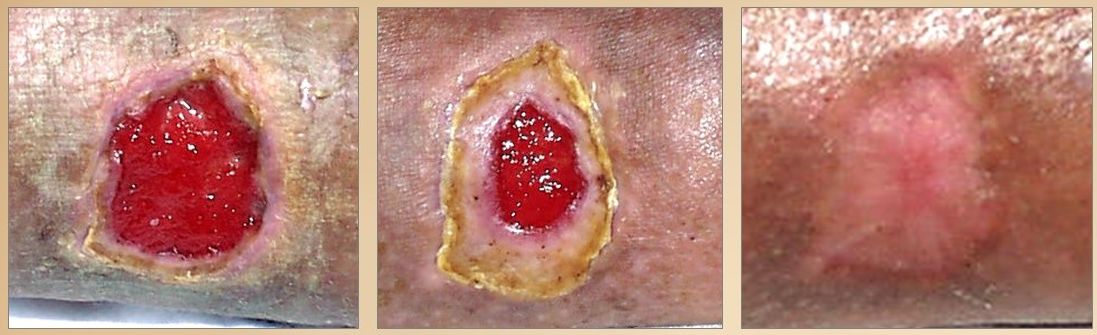
Technological modalities used to stimulate repair after initial "red cross" therapies have controlled injury and inflammation. These treatments directly effect the intrinsic engine of repair: the efferent elements of the wound module and the wound healing control loop.

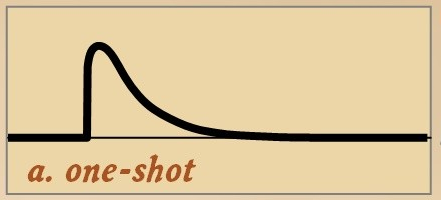
Exogenous cytokines: Pharmaceuticals, such as PDGF and neonatal cell therapies, which mimic macrophage activity and sum into their node.

Skin grafts: These and other operations, which directly restore epithelium, sum into the output node.

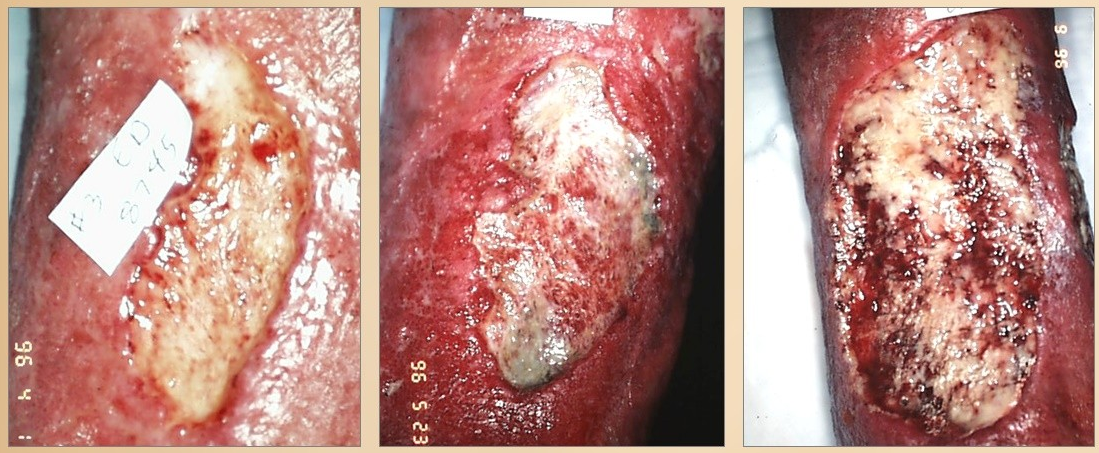
Biologicals: These and special dressings, which do not restore epithelium but have a comparable biological effect, sum into the feedback node, reporting to the system that the wound is acting as though it is closed.

MODELING REAL WOUNDS - WOUND PATHOLOGY

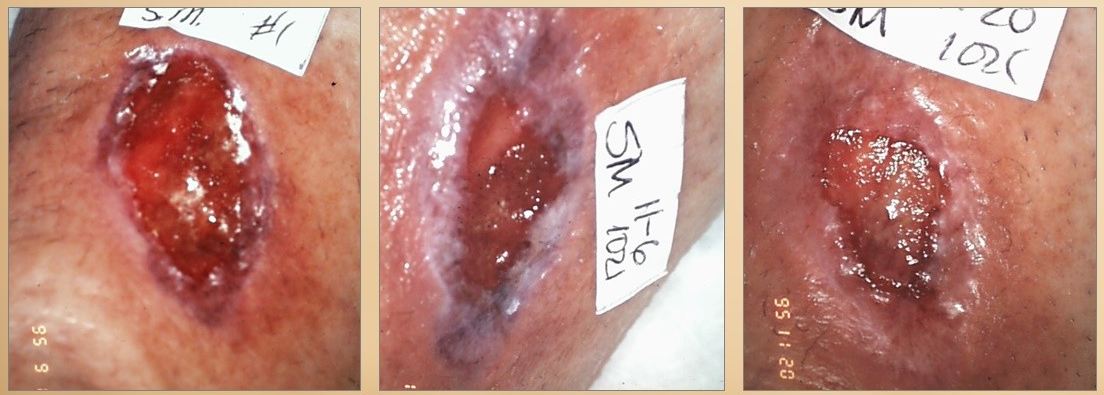


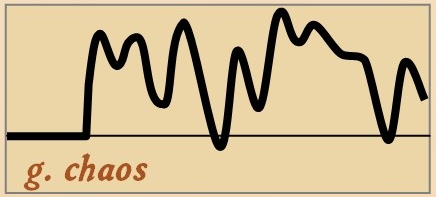


The healthy wound - convergent: One-shot recovery from injury, a simple "decay" and smooth return from open and disrupted back to closed and reorganized.



The sick wound - divergent: The acutely pathological wound, inflamed and actively ulcerating by lysis and necrosis. The control loop is overwhelmed as the system saturates in the undesirable state. Bringing the wound back into the operating range of the control loop requires deliberate active therapy.





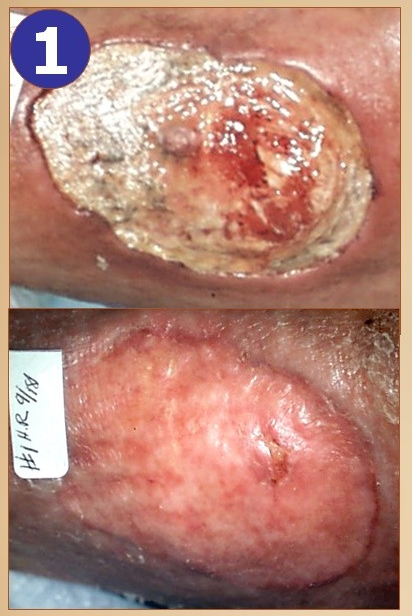
The impaired wound - chaotic: Exam-to-exam, for many months, no net change. The control loop "orbits" on an attractor from which it can escape only with therapies that strongly regulate or drive control nodes.

MODELING REAL WOUNDS

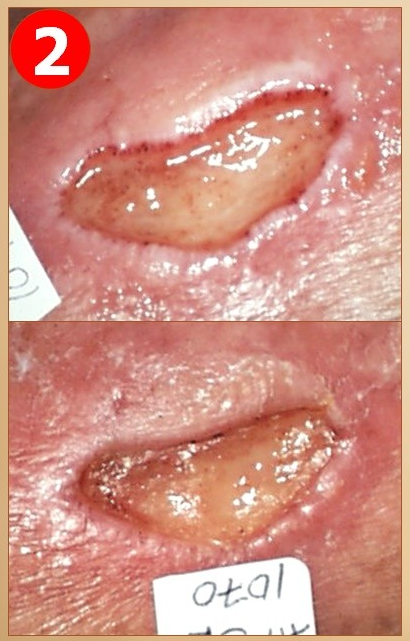
WOUND PATHOLOGY

OPEN CIRCUIT WOUNDS

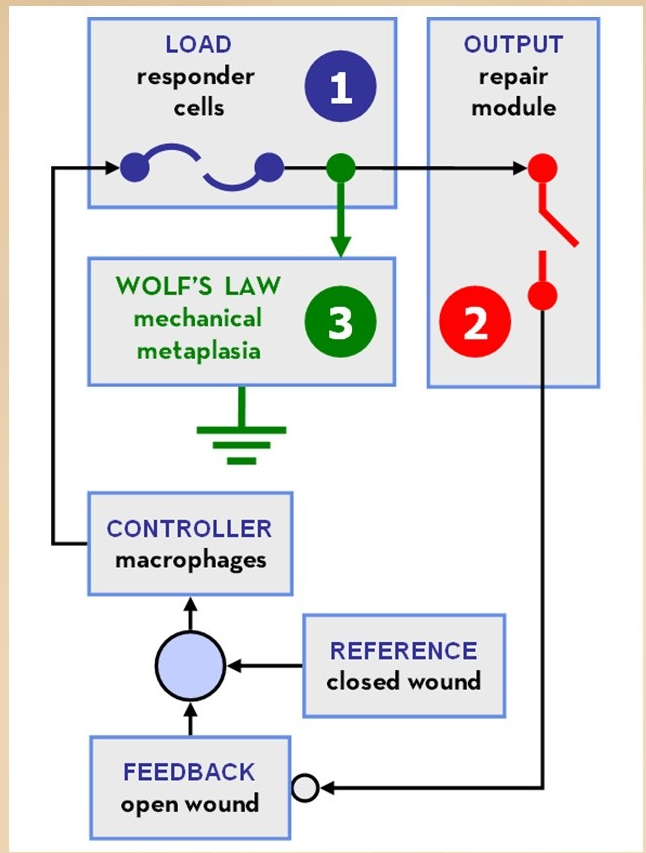
Some pathologies do not alter loop dynamics, but rather arrest the loop, stopping wound healing until the open circuit is reclosed or restarted.

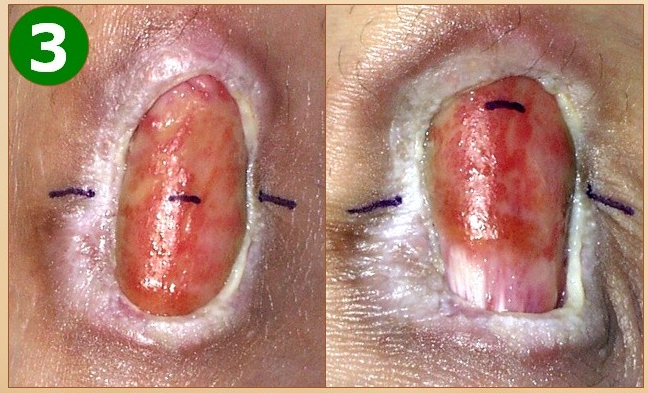


1 - Radiation wound = blown fuse: High dose radiation damages local progenitor cells, abolishing proliferation. Responder cells are gone, and the loop cannot restart without replacing the damaged components. *(Ankle ulcer after 6500cGy, prolonged non-healing until injected with a cell suspension prepared from a donor wound.)*



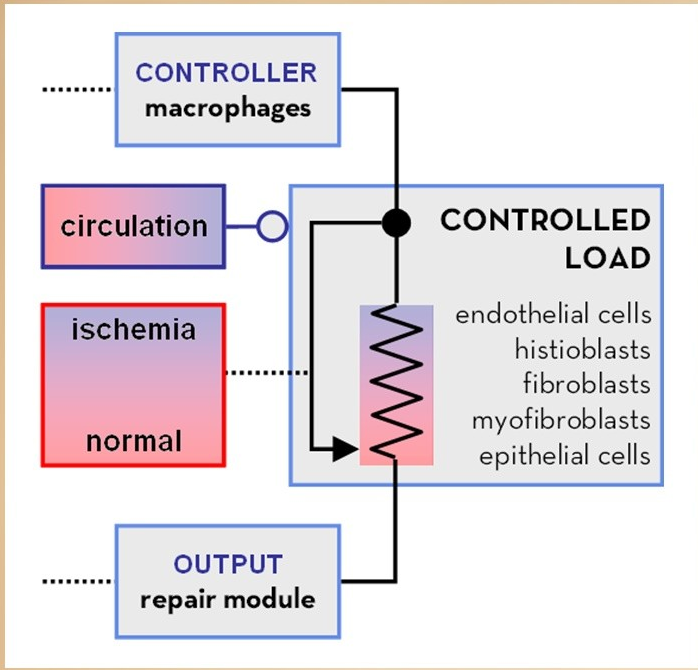
2 - Chemotherapy = open switch: Antimetabolite drugs transiently diminish responder cell output, an on-off switch in the output of the control loop. *(With cycles of hydroxyurea, this ankle ulcer cyclically stopped then restarted healing, progress shown during an "on" period.)*

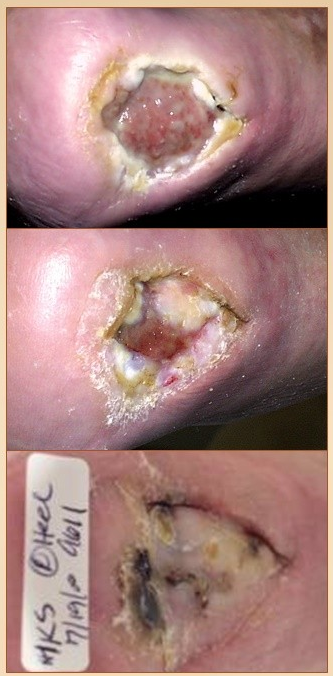




3 - Shear = ground out: Mesenchyme responds to applied force, differentiating to resist the load (Wolf's Law; compression begets bone, tension begets tendon, etc). Shear induces synovial or serosal metaplasia, a response that assumes that motion is anatomical (tendons, joints, bursas). Wound healing is simply shut down as the system is shunted off to a physiological "program" of synovial metaplasia. *(EDC tendon across ankle. Marks show motion. Surfaces have either normal tenosynovium or else only marginal signs of wound healing.)*

MODELING REAL WOUNDS - WOUND PATHOLOGY

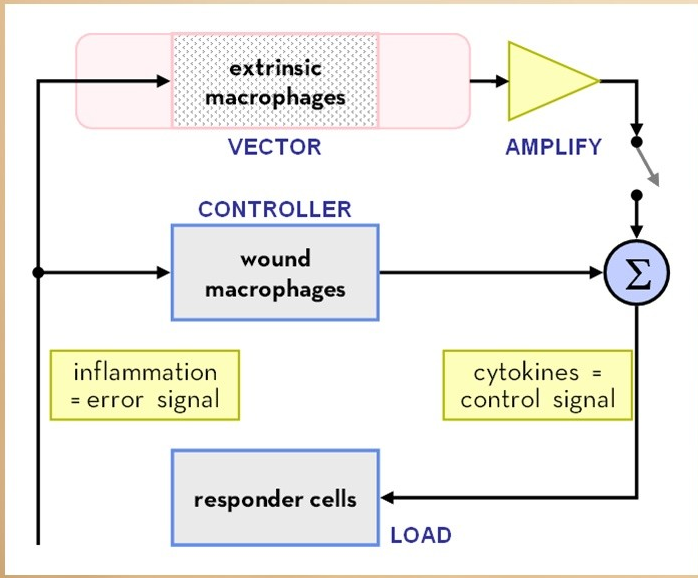


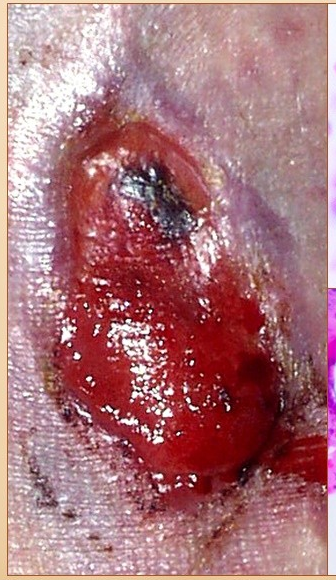


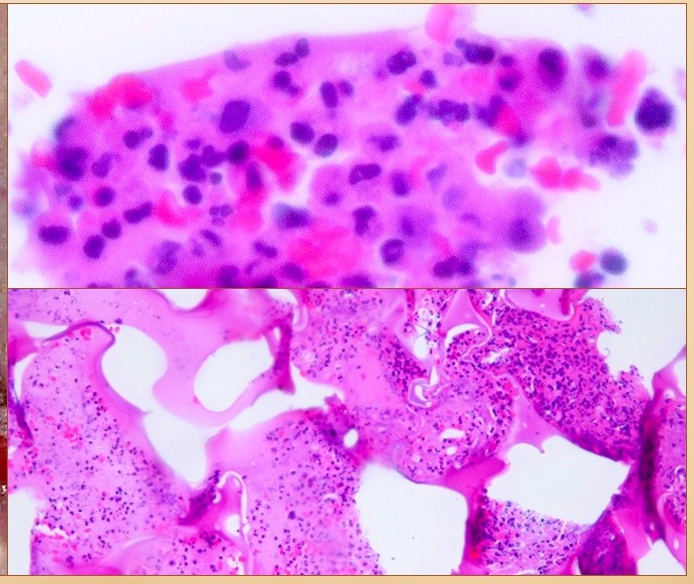
A PLACE FOR EVERY OPTION & EVENT

Top: Heel ulcer, with severe arteriosclerosis, healed after a year of topical care. Ischemia suppresses responder cells. It could be added as a simple inversion or negative latch, but since the wound healing effects of arterial disease are "dose" dependent, ischemia can be modeled as a variable impedance, retard, or attenuation.

Bottom: Pyogenic granulomas all have a story of prolonged unchanged bandages. The gauze is a haven for inflammatory leukocytes, harboring large mononuclear cells (the microscope specimen is of the bandage). Growth factors they issue are a spatial vector which attracts the repair module out of the defect, toward the dressing. They can be added to the loop as an amplified or unregulated element parallel to normal macrophages.







THE PHYSICS AND PATHOLOGY OF WOUNDS

DISORDERS AND DISEASES OF THE WOUND HEALING PROCESS

The Wound is a System.

The Wound Main Control Loop describes the behavior of this System as a controlled reactive Machine.

It explains how the body responds to perturbations of the tissues.

However, to understand the specific dynamics of specific wounds, it is necessary
to understand the nature of the perturbations or aberrant inputs that challenge the System.

WHAT IS THE DIFFERENCE BETWEEN HEALTHY WOUNDS THAT HEAL EASILY,
AND CHRONIC AND PATHOLOGICAL WOUNDS THAT DO NOT HEAL EASILY?

CAF WOUNDS

Chronic and Pathological

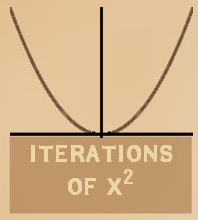
1 - Wounds caused by chronic illness or pathology.

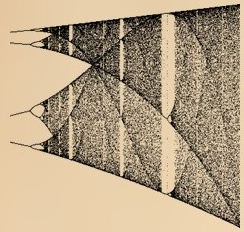
2 - Wounds that fail due to diseases of the healing process.

THE PHYSICS AND PATHOLOGY OF WOUNDS

WHAT DO CONTROL and NON-LINEARITY MEAN to the SICK / CAP WOUND ?

NON-LINEARITY



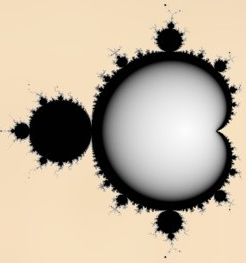


$x \leftarrow Ax(1-x)$

Logistical plot (real)

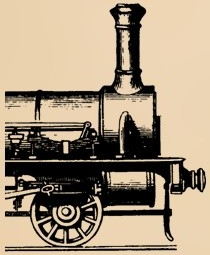
$x \leftarrow Ax^2 + C$

Mandlebrot set (complex)



N-BODY SYSTEMS & MULTI-CONTROL

OUTPUT (φ) = RATE (R) X VOLUME (V)



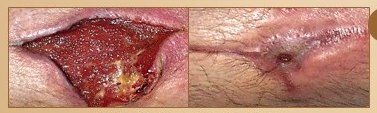
$d\varphi = v\partial r + r\partial v$
$\partial\varphi = v\partial r$
$\partial\varphi = r\partial v$

Linear pump (sum of partials)

$d\varphi = v\partial r + r\partial v$
$v = f(\varphi, r)$
$r = f(\varphi, v)$

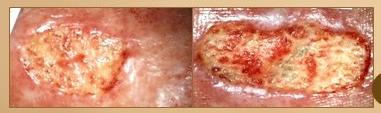
Non-linear pump (non-analytical)

CHAOS



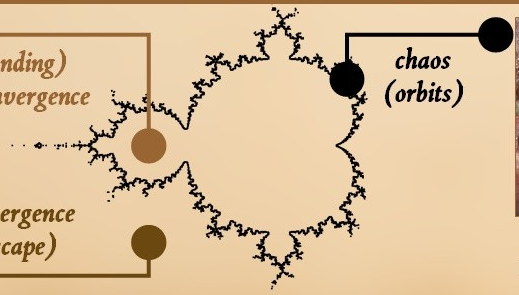
ACTIVE HEALING

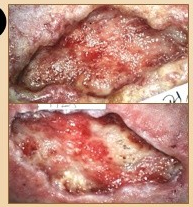
ACTIVE ULCERATION



(landing) convergence

divergence (escape)





CHRONIC NON-HEALING

CAP wounds are often hard to heal and refractory to care: divergent, chaotic, non-convergent. The reasons why are found in the study of complex systems.

Wound healing is a dynamical process operating as a closed loop feedback circuit. Feedback means non-linearity. Non-linearity implies complexity.

When pathological stressors are present in a wound, the Main Control Loop gets locked into complex states that prevent resolution of the wound.

RELEVANT CONCEPTS
that explain why this happens include:

non-linear dynamics
control & multi-control
N-body dynamics & chaos

population logistics
cellular automata & self-organization

how these interact with anatomical and pathological alterations in a CAP wound (parts 2 & 3)

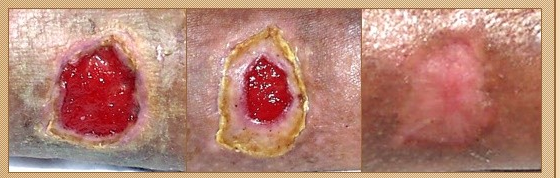
THE PHYSICS AND PATHOLOGY OF WOUNDS

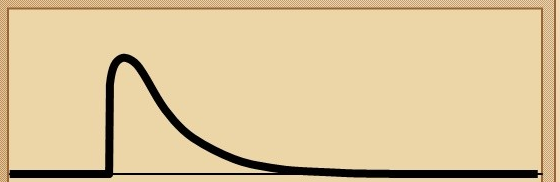
DISORDERS AND DISEASES OF THE WOUND HEALING PROCESS

Compare: The hypothalamic-pituitary-endocrine control system
is a free-running, continuously monitored loop.

The Wound Main Control Loop is an ad hoc reserve system on quiet standby,
responding if and only when needed to incidental triggers.

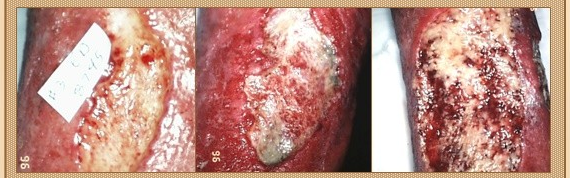
The wound control system has three major dynamical attractors.

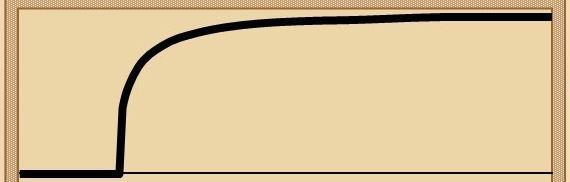




a. one-shot

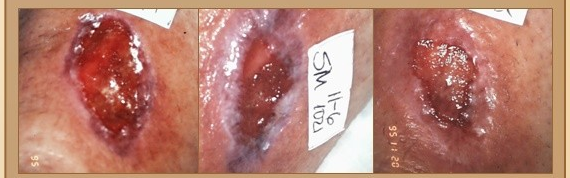
the healthy wound
healing - closing
convergent





b. saturation-extinction

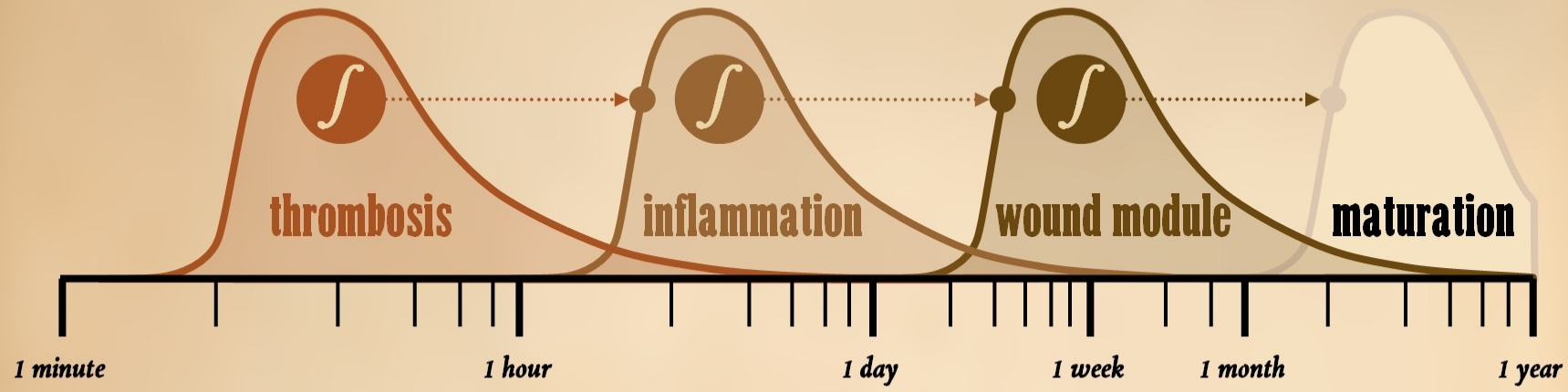
the sick wound
ulcerating - enlarging
divergent



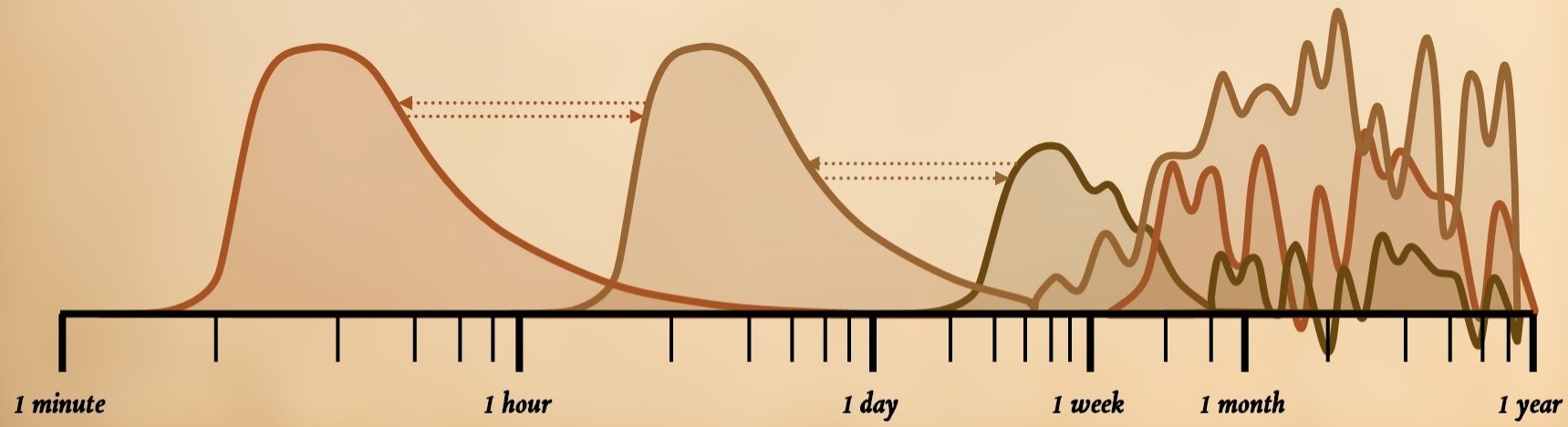
g. chaos

the impaired wound
stagnant - orbiting
chaotic

NORMAL HEALTHY RESPONSES = SEQUENTIAL LINEAR ONE-SHOTS



CHRONIC PATHOLOGICAL RESPONSES = NON-LINEAR CHAOS



THE PHYSICS AND PATHOLOGY OF WOUNDS

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Marc E. Gottlieb, MD, FACS

Phoenix, AZ

1

The Wound as a System and a Controlled Machine

The wound module, the wound control loop, wound pathology, and the basic dynamics of healthy and impaired wounds.

2

Auto-Immunopathy and the Intrinsic Disease of Wound Healing

The cellular and histopathological basis of intrinsic wound failure & wound chronicity: chronic inflammation, wound autoimmunopathy, and the 3-population wound.

3

Chronicity and the Physics of Wound Failure

The physics of wound failure and chronicity: N-body dynamics and chaos, population logistics, cellular automata and self-organization.

THE PHYSICS AND PATHOLOGY OF WOUNDS

SUMMARY - THE WOUND AS A SYSTEM AND A CONTROLLED MACHINE

THE WOUND IS A COMPLEX NON-LINEAR MACHINE.
IT MUST BE STUDIED THAT WAY TO UNDERSTAND ITS DYNAMICS.
THE MAIN CONTROL LOOP OF THE WOUND MODULE IS THE FOUNDATION SYSTEM.

The wound is a control system: It is a reactive reference-driven feedback system that ensures that wounds start and stop healing at the correct time, and with the correct result, the restoration of sequestered stroma.

The wound module & control loop: The wound healing system is a small set of key cells and interactions. The Main Wound Control Loop simply explains how these kernel elements interact to correct the effects of injury.

Wound dynamics: Healthy acute wounds heal as a one-shot transition back to reference (reorganized & closed). Chronic and pathological CAP wounds are chaotic, orbiting on attractors that are dynamically hard to change.

Modeling wounds: The wound control loop is an open kernel. Physiologic, pathologic, & therapeutic elements, interactions, states, & events can all be added to show where errors occur, and where therapy can be introduced.

Complex biological systems must be studied as any complex system, as non-linear controlled machines, not just collections of isolated one-on-one elements. This understanding is mandatory for the self-organizing wound, if timewise dynamical behavior and the response to injury and therapy are to be understood, especially in the impaired wound and the chronic and pathological CAP wound where the road to the desired result is not so easily traveled.

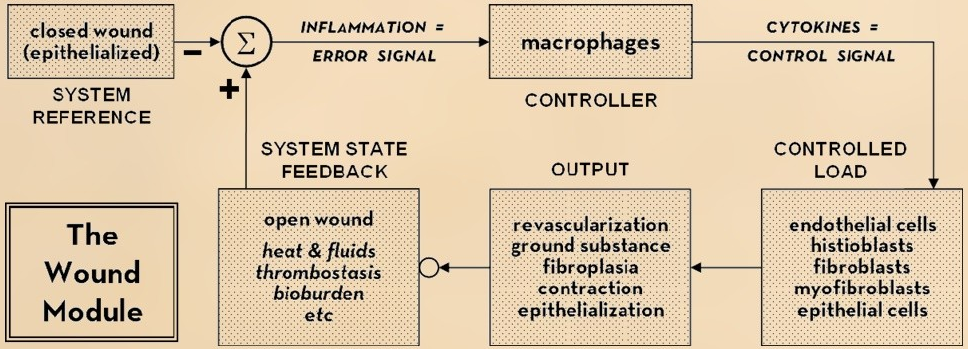

END

The Physics and Pathology of Wounds. Part 1.
The Wound as a System and a Controlled Machine.

Marc E. Gottlieb, MD, FACS Phoenix, AZ

The wound is a transient organ of inter-operating cells, triggered into being by injury and inflammation, then extinguishing as it completes its repair of injured stroma. It is a system. Conventional bioscience tends to characterize properties and interactions of individual or one-versus-another elements within a system, but physics is required to understand the integrated timewise behavior of whole systems. Intrinsic wound pathology and chronicity, and wound failure and therapeutics are easily explained when wounds are seen as a ***non-linear System*** (rather than as a collection of dual-element linear interactions). For normal wound physiology and for the pathophys-iology of altered and failing wounds, the governing principles are the physics of complex systems: non-linear N-element dynamics, control science, population logistics, and self-organizing automata.

Understanding wound physics begins by characterizing normal wound physiology. The wound is a closed-loop reference-driven non-linear multicontrol system. Sick and altered wounds have layers of added complexity, but the quintessential intrinsic machinery of wound healing – the ***Wound Module*** of post-inflammatory wound repair – functions as just a single control loop. When tissues are injured, the ***Main Control Loop*** of physiological wound repair will drive cells to reorganize back to a repaired stroma.



The wound control system is composed of these elements: The ***system state*** is the open wound and its conditions. It is compared (Σ) to a ***reference***, normal epithelialized tissue. Variances generate an ***error signal*** in the form of inflammation. This activates macrophages which are the ***system controller***. They in turn generate a ***control signal*** in the form of cytokines. The ***controlled load*** is the group of local responder cells. Their ***output*** are the elements of histogenesis, which modify the state of the system, which then feeds back to the loop at the summing point. Any discussion or research of the collective behavior of a wound must acknowledge this basic control system.

Marc E. Gottlieb, MD, FACS
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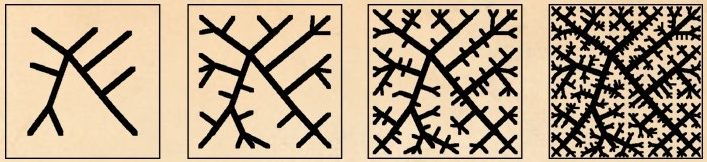

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Marc E. Gottlieb, MD, FACS

P.O. Box 86040
Phoenix, AZ 85080

Phone 602-252-3354
Fax 602-254-7891

meg99az@cox.net

The Physics and Pathology of Wounds. Part 1. The Wound as a System and a Controlled Machine.

Original presentation February 22-26, 2010, Maui, Hawaii
at the
John A. Boswick, M.D. Burn and Wound Care Symposium

The presentation and related materials can be viewed and used at:
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The Physics and Pathology of Wounds. Part 1.
The Wound as a System and a Controlled Machine.

Marc E. Gottlieb, MD, FACS Phoenix, AZ

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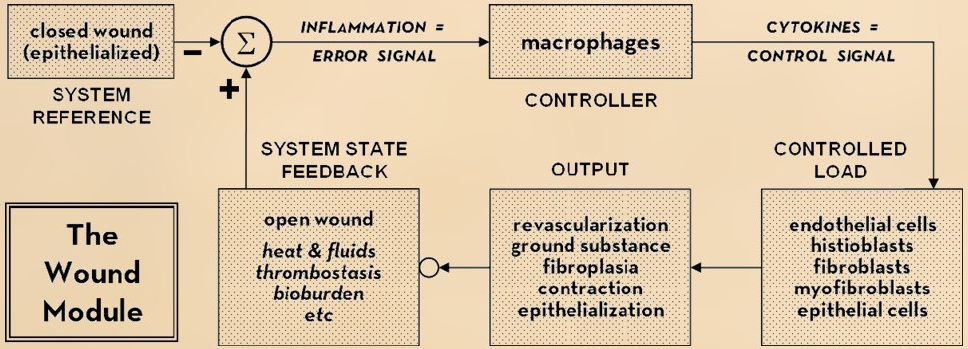

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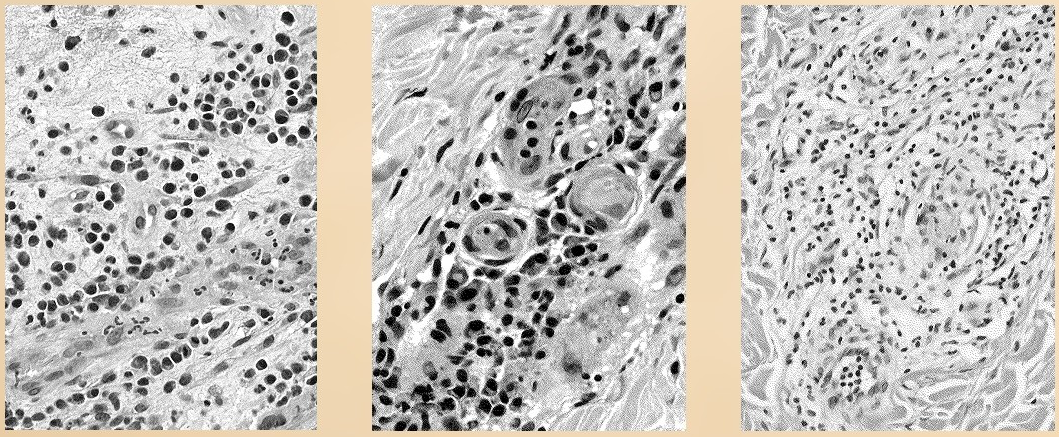
The Physics and Pathology of Wounds. Part 2.
Auto-Immunopathy and the Intrinsic Disease of Wound Healing.

Marc E. Gottlieb, MD, FACS Phoenix, AZ

Many chronic wounds result from disorders extrinsic to the healing process, e.g. pressure or arterial disease. What then are the intrinsic diseases of wound healing? Compare the wound to other organs. The quintessence of heart failure is that it is an inadequate pump, for lung failure it cannot exchange gases. But the wound is neither pump and pipes, nor bellows and diffusion membrane, nor is it like any organ with macro-anatomical structure. It is a transient collection of mutually interacting self-organizing cells. Stromal angiocytes and fibroblasts (wound cells) have remarkably few inherent metabolic or genetic faults. Dysfunction of the aggregate population is almost always the result of deprivation or predation. Adverse states can be caused by (1) non-targeted exogenous conditions such as arterial ischemia or repetitive trauma, and (2) targeted damage directed against these cells and their structures. As will be presented here, predation against the wound module is due to a state of auto-immunopathy in which lymphoid cells are sensitized to wound components. Not only does this occur with classic connective tissue disorders and other well-recognized auto-immunopathies, but it happens when a wound becomes intrinsically chronic and pathological. Hypercoagulability and other conditions of persistent thrombosis and acute inflammation are the underlying states that induce the auto-immunization. Simply put, intrinsic wound pathology and chronicity is a dynamical disorder of complex populations caused by auto-immunopathic disruption of the wound module.



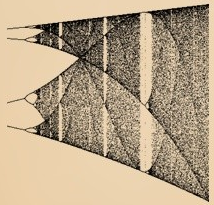
*In these chronic non-healing wound samples, the vascular locus is infiltrated with immune cells (**left**, plasma cells; **middle**, plasma cells and eosinophils; **right**, lymphocytes.) On the left, plasma cells are mixed with the migratory angiocytes (spindles) that are trying to assemble the wound. At middle and right, chronic thrombosis due to a primary hypercoagulable disorder is not only present, it is the root cause of this entire state.*

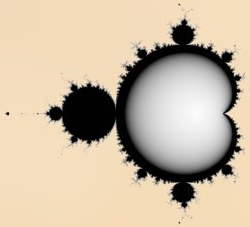
The Physics and Pathology of Wounds. Part 3.
Chronicity and the Physics of Wound Failure.

Marc E. Gottlieb, MD, FACS Phoenix, AZ

The wound module is a transient set of interacting cells which collectively restore in-jured tissue to normality, a fibrous stroma of angiocytes and fibroblasts. Its healthy aggregate behavior is a well behaved machine, governed by the physics of control systems. A sick system can result from various extrinsic perturbations, but the core mechanism of self-sustaining persistent dysfunction, the true intrinsic disease of wound healing is chronicity itself, the paramount cause being wound module autoimmunization. This state is disruptive but not fully toxic or lethal, thus immunopathic wounds have complex behaviors, at times better-worse-stable-variable, often looking healthy, but always frustrating as they refuse to cross the finish line. How does one explain such variable behavior and the differences between normal and chronic-and-pathological (cap) wounds?

Simply stated, intrinsic wound pathology and chronicity is a dynamical disorder of complex populations. The physics governing complex behaviors in complex systems is ***non-linear dynamics*** (nld). In addition to ***control***, three aspects of NLD are especially important to wound pathology. (1) ***Population logistics***. Healthy healing is a sequence of one-shot self-completing linear events: primary injury & thrombosis –*then*– acute inflammation –*then*– wound module. Pathology creates abnormal population dependencies (nutrition, starvation, predation, cultivation) and a new population, chronic inflammation. Non-linear perpetual complexity arises in the logistics of injury & thrombosis –*vs*– acute inflammation –*vs*– wound module –*vs*– chronic inflammation –*vs*– injury & thrombosis. (2) ***Cellular automata & self-organization***. The "cellular" agents of the wound module (real biological cells in this case) have a small set of deterministic rules of interaction with each other. When allowed to function properly, stromal rebuilding is automatic and correct. Under pathological conditions, self-organization, i.e. wound healing is disrupted. (3) ***Chaos & N-body dynamic***s. The net effect is that the wound, a set of several interacting cell populations, has 3 attractors (basins, dynamically stable states or behaviors): convergence (healing), divergence (ulcerating), and self-sustained chaotic orbits (chronicity).





*Basic methods to demonstrate non-linear dynamics: l**eft**, the logistical map of competing populations; **middle**, diffusion-limited-aggregation, an example of self-organizing automata; **right**, attractors and chaos in the Mandelbrot set of complex-plane iteration. While seemingly abstract, these structures are directly correlated with wound events.*