SESSION 1

Anatomy
- Embryology
- Vasculature
- Segmental anatomy
- Wolff's Law

Diseases
- Auto-immunopathies
- CVD-CTD
- Hypercoagulable disorders

Math & Engineering
- Materials & mechanics
- Bioplasticity
- Soft tissue & scar mechanics
- LaPlace's law
- Flapology – free bodies
- Flapology – brownout-blackout
- Surface-volume-compliance
- Pressure
- Quickies

SESSION 2

Wounds
- Wound healing biology
- Chronic & pathological wounds
- Wound management
- Pressure

ARIMEDICA

THESE MATERIALS ARE ALL ON THE WEBSITE -- SO JUST ENJOY THE PRESENTATION

www.arimedica.com

Anatomy

Embryology

Segmental

Vasculature

Wolff's Law

ANATOMY : **Embryology**

BODY PLAN

Topology ::

total body homeomorphism to a torus
organs & tissues – homeomorphism to a plane

trilaminar

ectoderm	epithelia & derived
mesoderm	mesenchyme & derived
endoderm	epithelia & derived

fusion

Anatomy ::

stroma vs. parenchyma

mesenchyme :

(mesoderm)

stroma

* anatomical binding
  (fibroblasts :: ground-connective matrix)
* vascular distribution
  (angiocytes :: vessels)

other common services

defense
energy storage

force & motion

fascias
musculoskeletal
serosas & coeloms

parenchyma :

(ectoderm, endoderm)

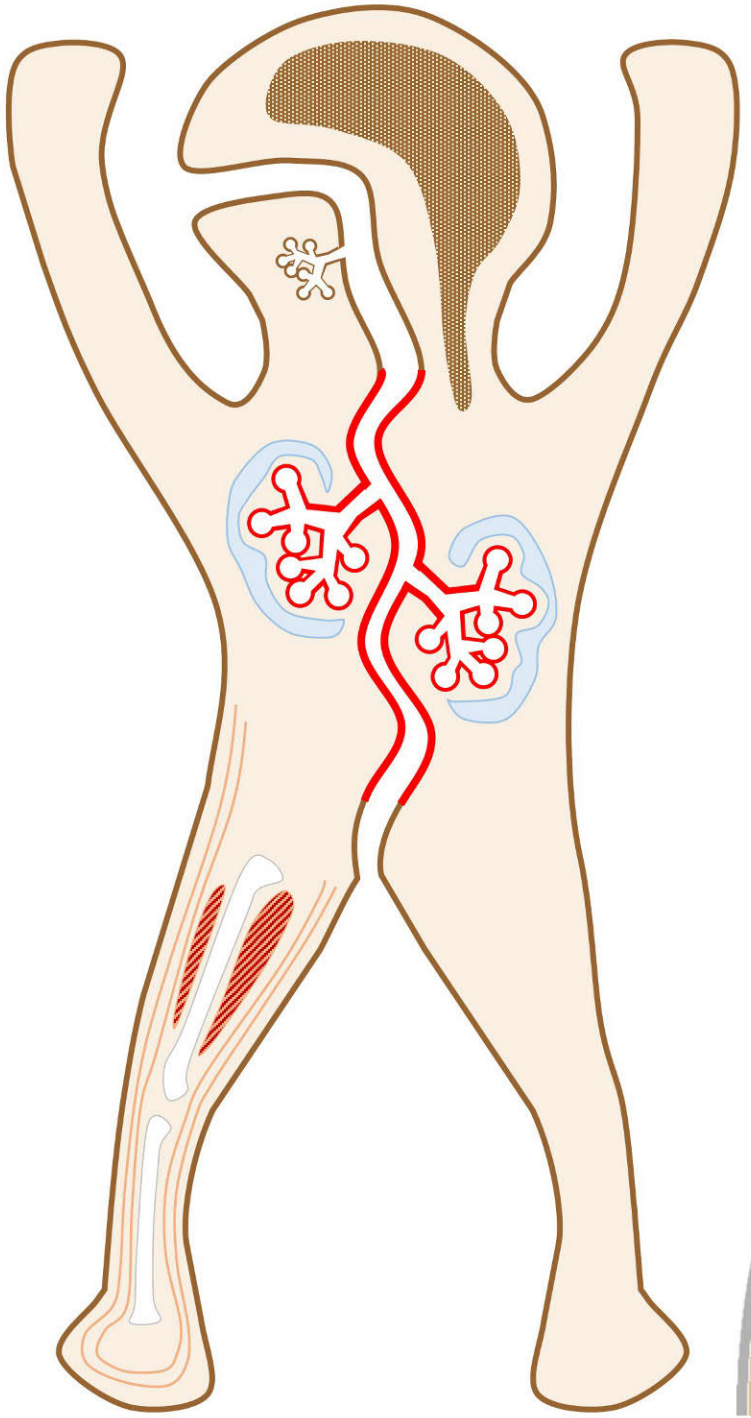
epithelia

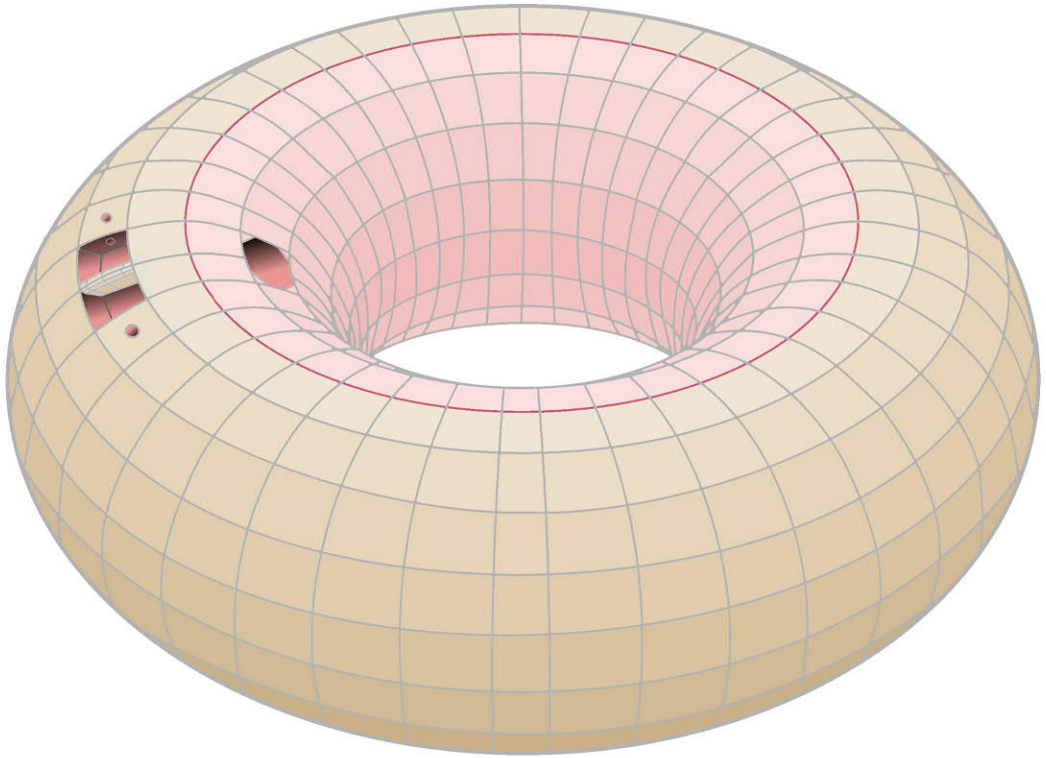
ambient interface

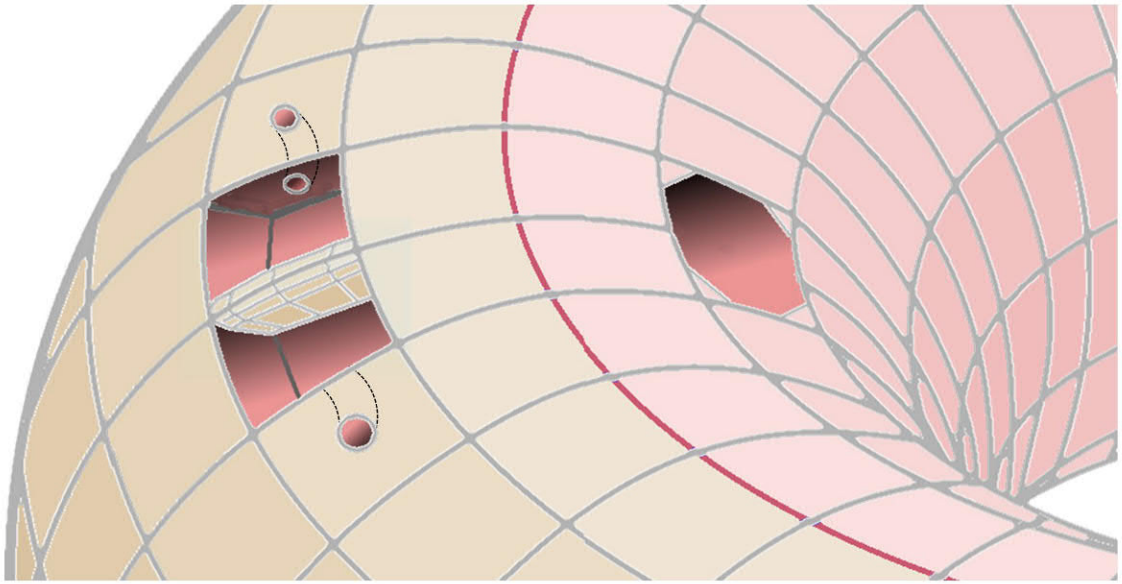
adeno-exocrine, endocrine

metabolism, nutrition, control

cns (sequestered)







ANATOMY : **Embryology**

BODY PLAN

Topology ::

total body homeomorphism to a torus
organs & tissues – homeomorphism to a plane

trilaminar
- ectoderm — epithelia & derived
- mesoderm — mesenchyme & derived
- endoderm — epithelia & derived

fusion

Anatomy ::

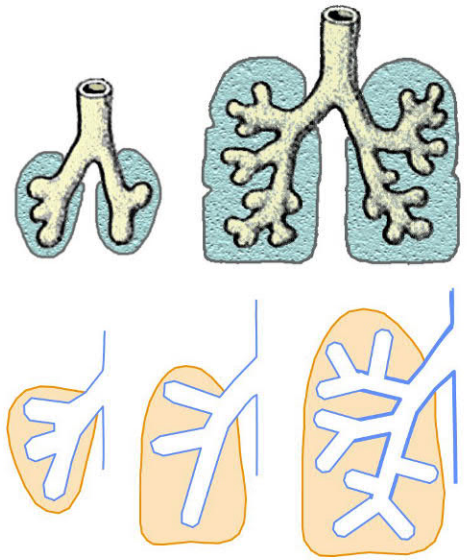
stroma vs. parenchyma

mesenchyme :
- (mesoderm)
- stroma
  - * anatomical binding
    - (fibroblasts :: ground-connective matrix)
  - * vascular distribution
    - (angiocytes :: vessels)
- other common services
  - defense
  - energy storage
- force & motion
  - fascias
  - musculoskeletal
  - serosas & coeloms

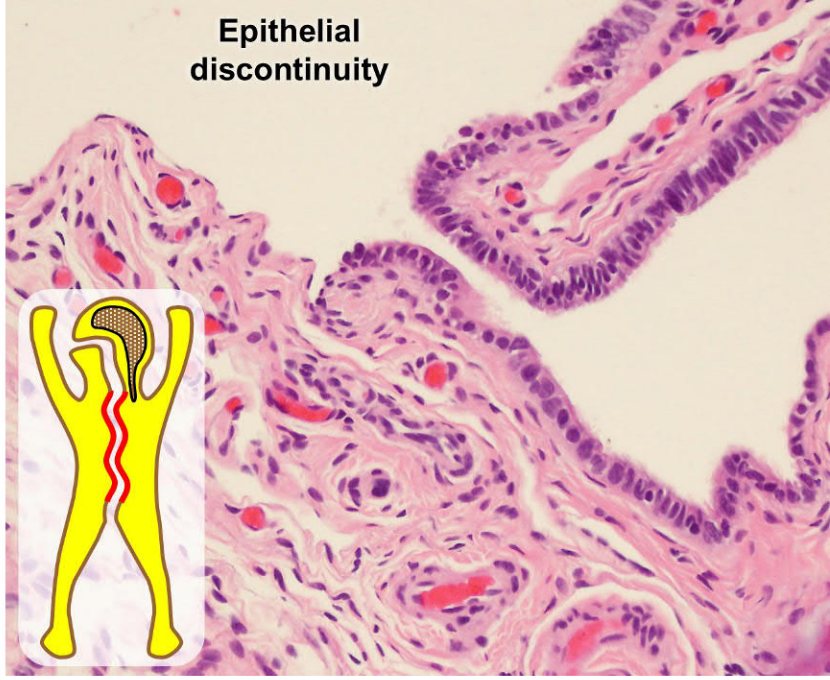
parenchyma :
- (ectoderm, endoderm)
- epithelia
  - ambient interface
- adeno-exocrine, endocrine
  - metabolism, nutrition, control
- cns (sequestered)

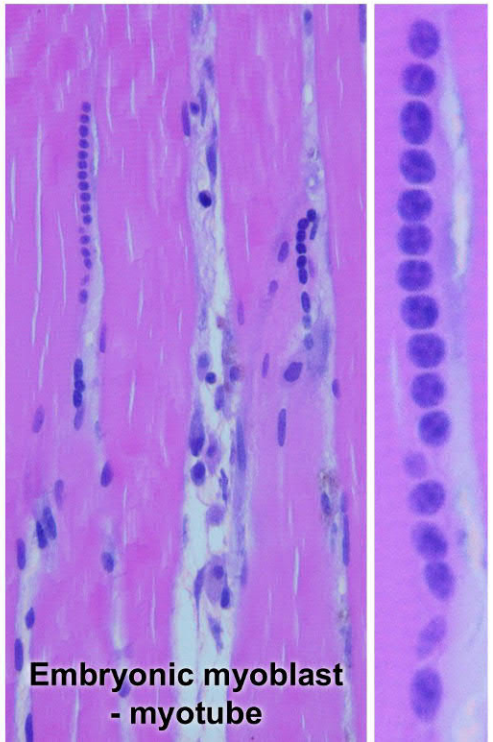
AMBIENT	
OUTER ORGANS	Epithelium (*ectoderm*)
	Lamina propria Organ-specific substrate (*mesoderm*)
PARIETES & EXTREMITIES	Concentric fascias Musculoskeletal (*parietal mesoderm*)
AMBIENT (extremities)	
COELOMS & BURSAS	Serosas Synovia (*parietal mesoderm*)
	Space
	Serosas (*visceral mesoderm*)
VISCERAL ORGANS	Organ-specific substrate Lamina propria (*mesoderm*)
	Epithelium (*ecto- & endoderm*)
AMBIENT ectoderm, upper aero-digestive	AMBIENT endoderm, abdo-pelvic viscera

Branched parenchyma – homeomorphic to a plane

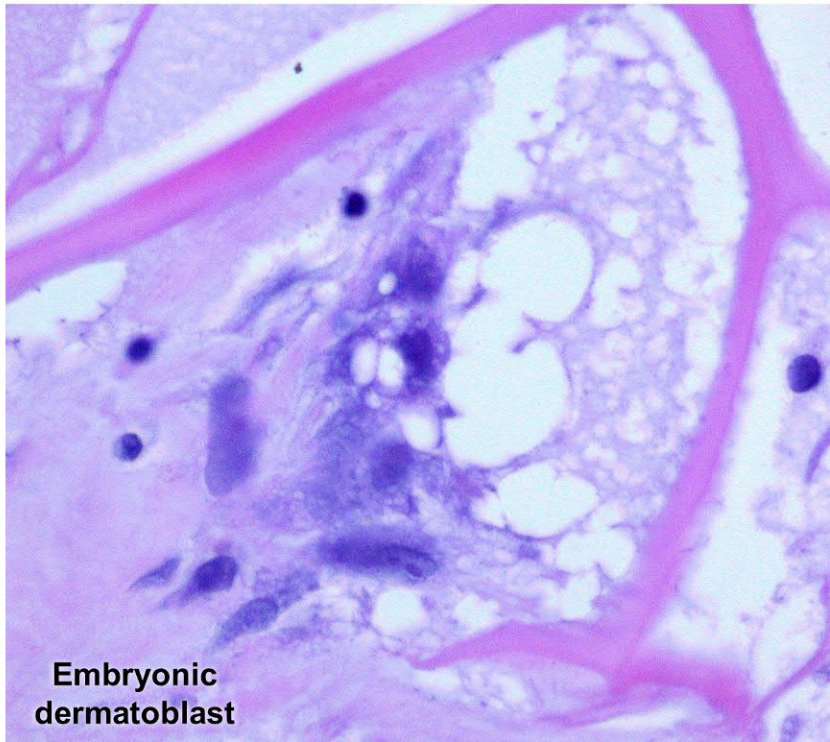


Epithelial discontinuity





Embryonic myoblast - myotube



Embryonic dermatoblast

AMBIENT	
OUTER ORGANS	Epithelium *(ectoderm)*
	Lamina propria
	Organ-specific substrate
	Adventitia *(mesoderm)*
PARIETES & EXTREMITIES	Concentric fascias
	Musculoskeletal *(parietal mesoderm)*
AMBIENT (extremities)	
COELOMS & BURSAS	Serosas Synovia *(parietal mesoderm)*
	Space
	Serosas *(visceral mesoderm)*
VISCERAL ORGANS	Adventitia
	Organ-specific substrate
	Submucosa
	Lamina propria *(mesoderm)*
	Epithelium *(ecto- & endoderm)*
AMBIENT ectoderm, upper aero-digestive	**AMBIENT endoderm, abdo-pelvic viscera**

SKIN

Epidermis
(or other epithelia)

BM

DERMIS
Papillary dermis
(lamina propria)

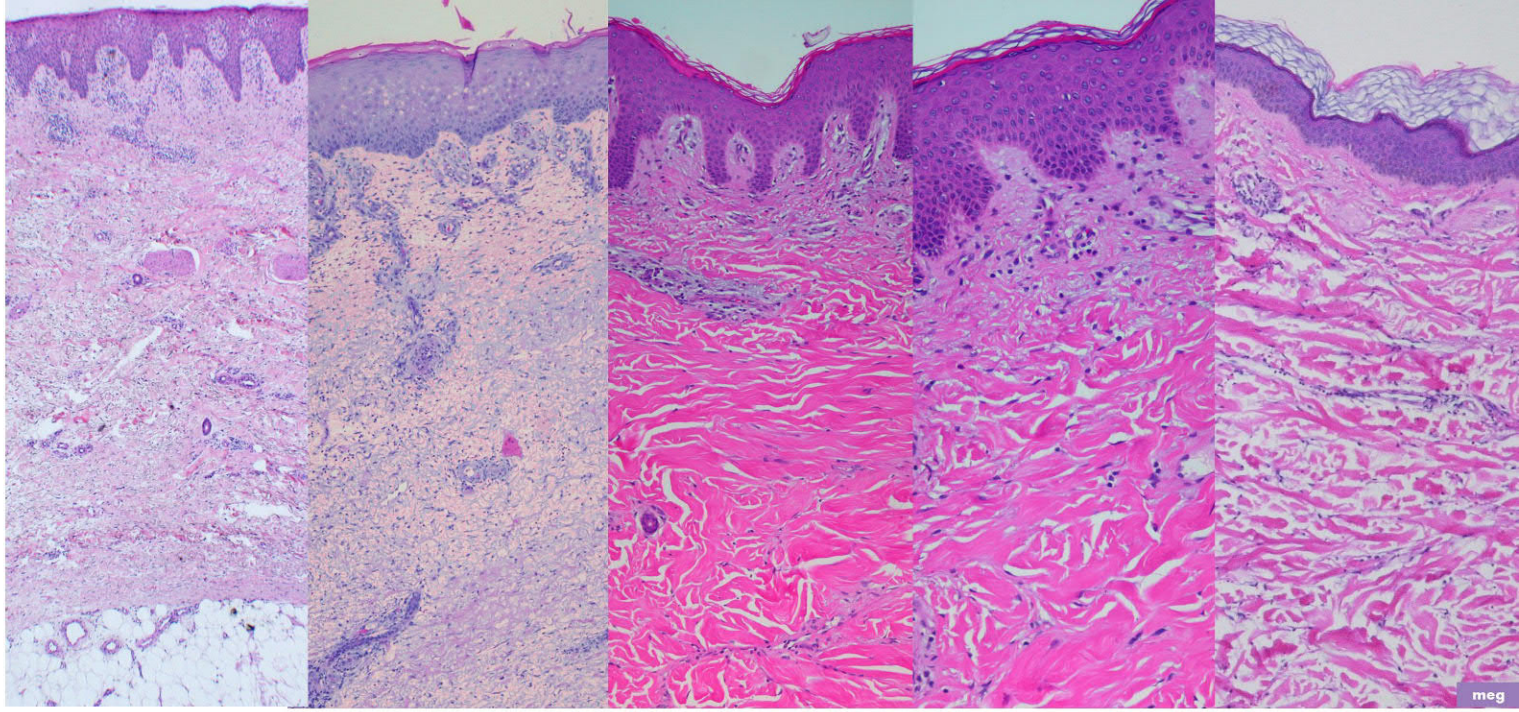
Reticular dermis
(1° embryonic substrate)

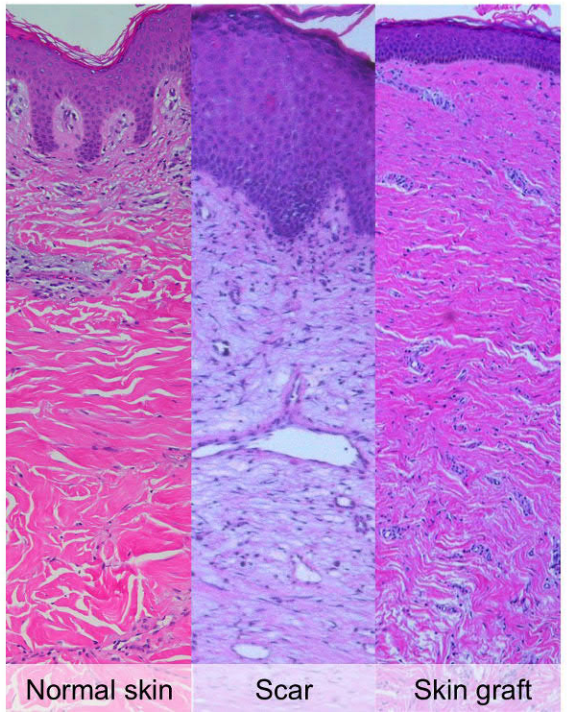
HYPODERMIS
(subcutaneous)
Camper's fascia
(adipose)

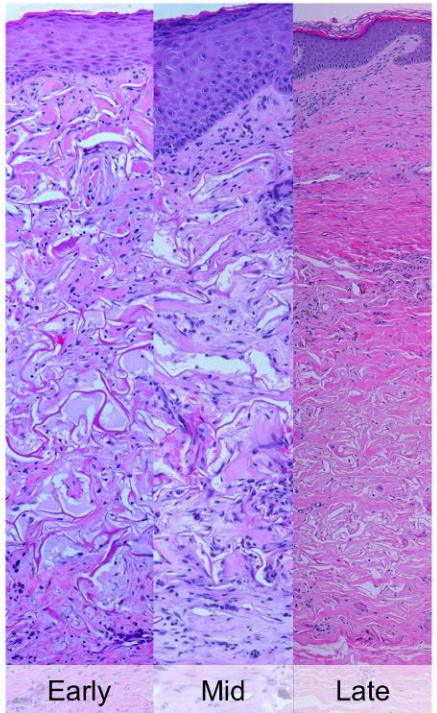
Scarpa's fascia
(fibrous lamina)

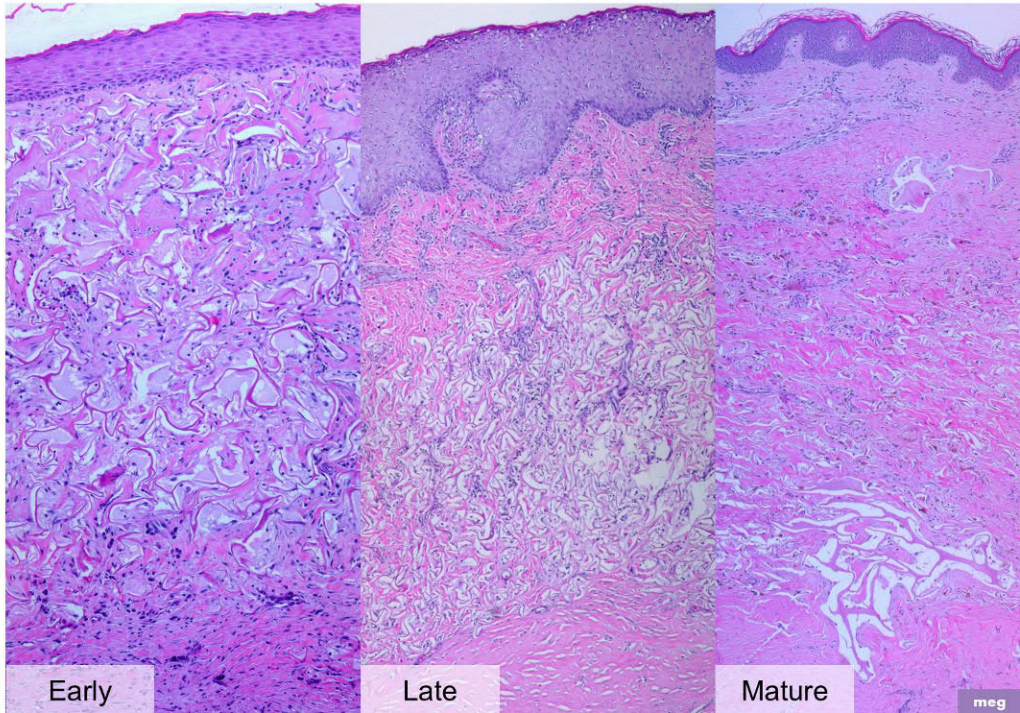
(adipose lamina)

MSK
Deep muscular fascia
Muscles
Bones & joints

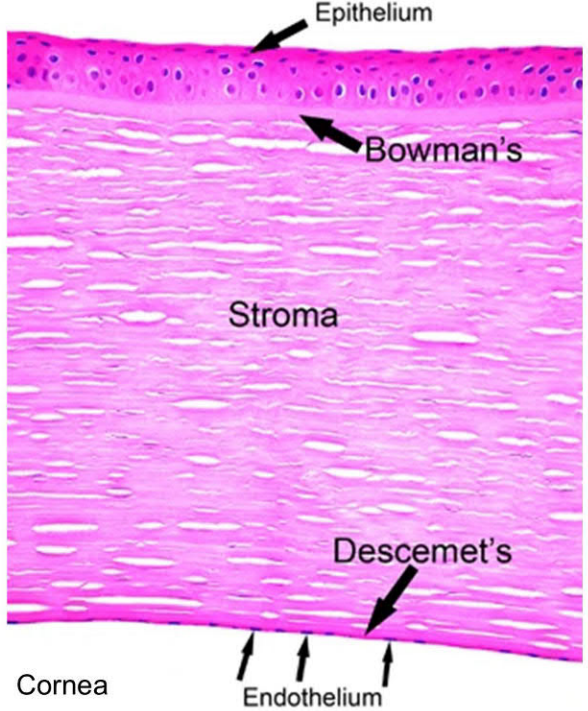






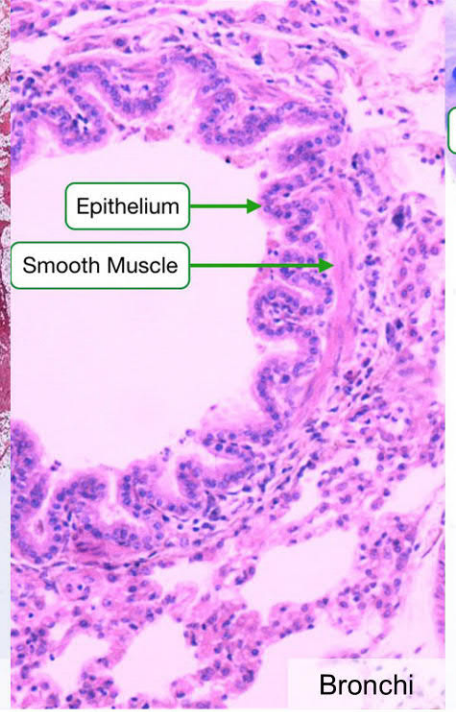


AMBIENT	
OUTER ORGANS	Epithelium *(ectoderm)*
	Lamina propria Organ-specific substrate Adventitia *(mesoderm)*
PARIETES & EXTREMITIES	Concentric fascias Musculoskeletal *(parietal mesoderm)*
AMBIENT (extremities)	
COELOMS & BURSAS	Serosas Synovia *(parietal mesoderm)*
	Space
	Serosas *(visceral mesoderm)* Adventitia
VISCERAL ORGANS	Organ-specific substrate Submucosa Lamina propria *(mesoderm)*
	Epithelium *(ecto- & endoderm)*
AMBIENT ectoderm, upper aero-digestive	**AMBIENT endoderm, abdo-pelvic viscera**

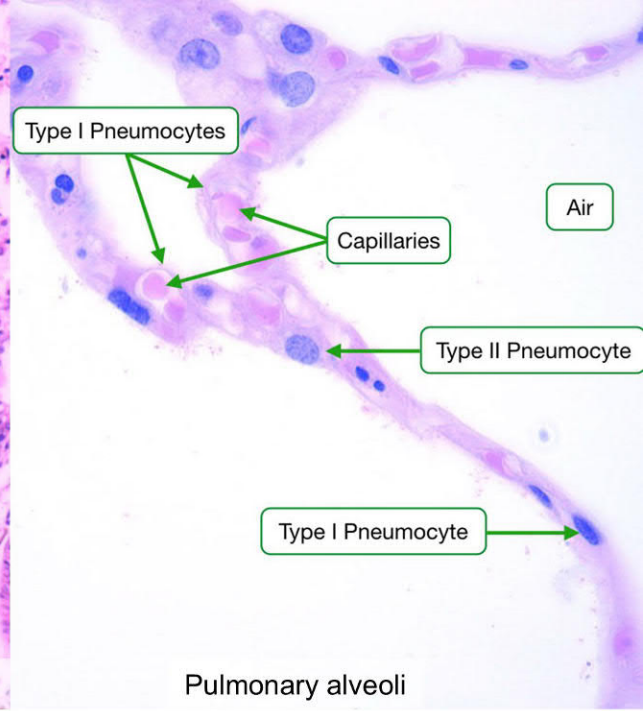


Cornea


Trachea

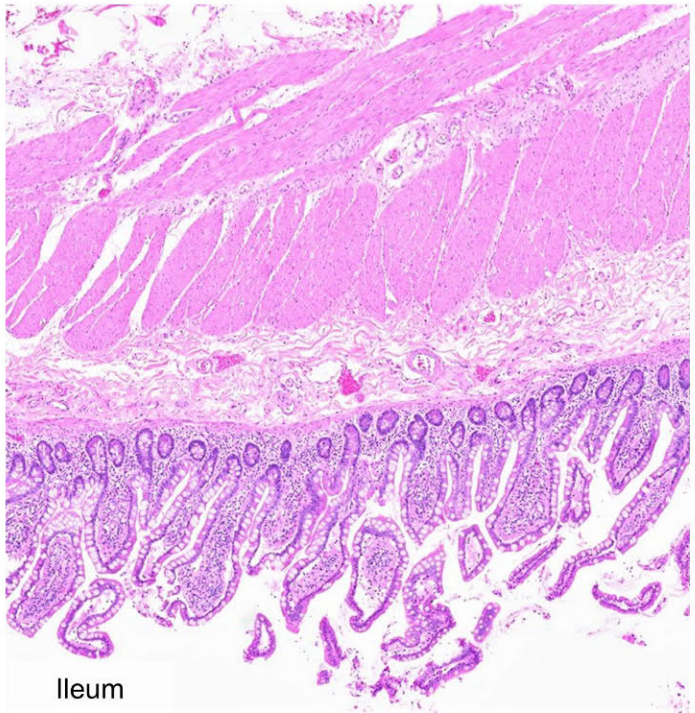


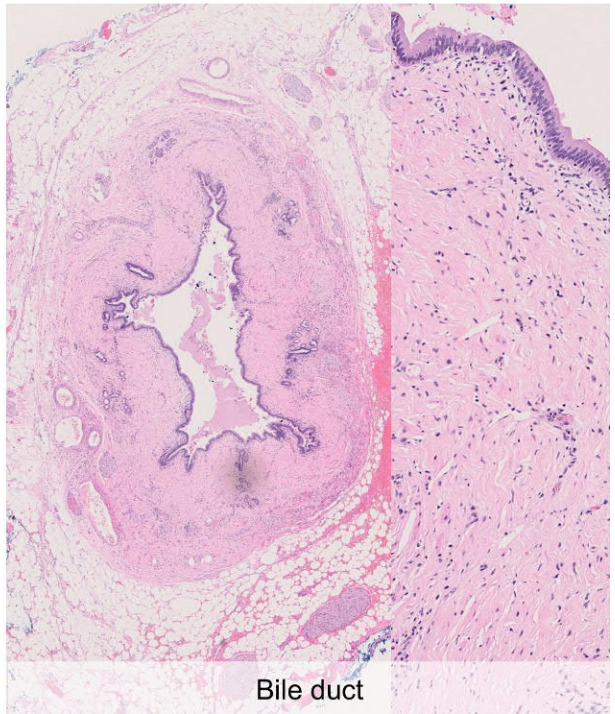
Bronchi

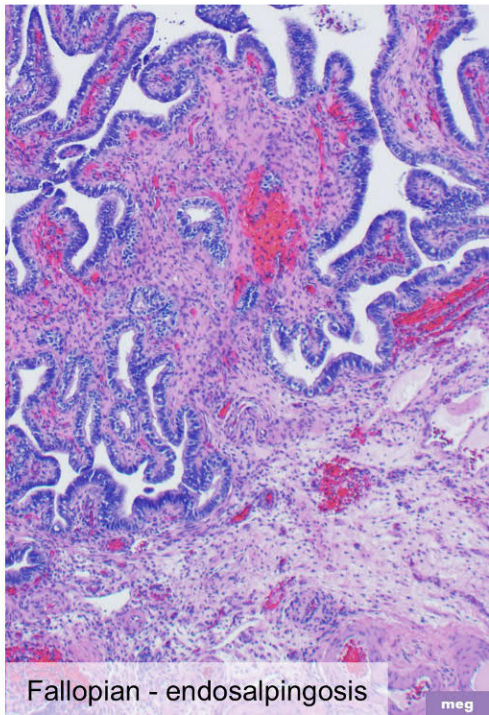


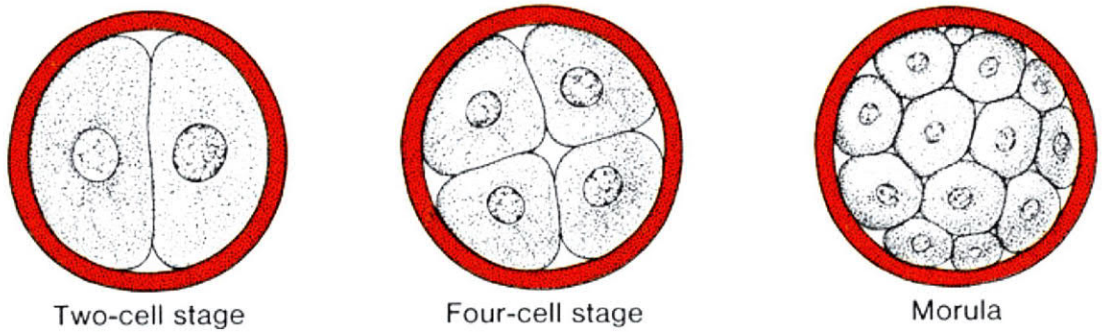
Pulmonary alveoli

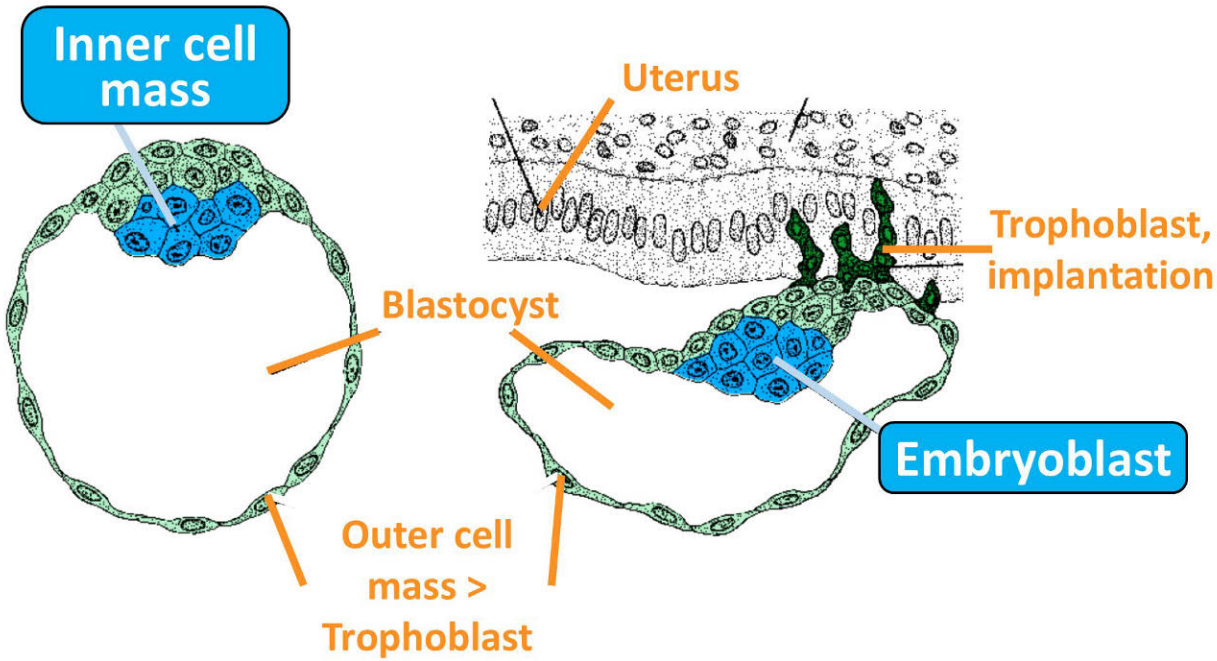
Serosa ---------- Adventitia
Muscularis propria circular longitudinal ---------- Submucosa ---------- Muscularis mucosae ---------- Papillary lamina propria
BM
Mucosal epithelium
BOWEL


Ileum


Bile duct

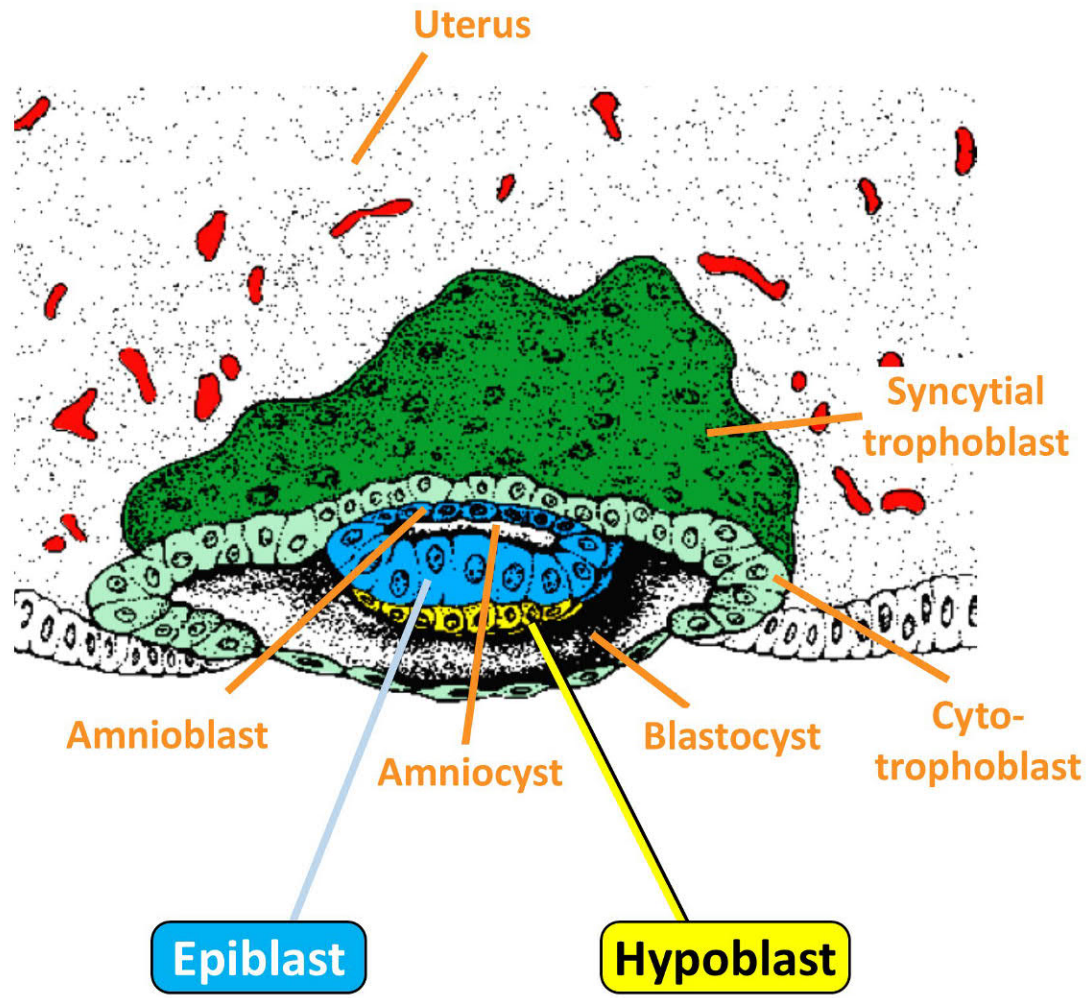

Fallopian - endosalpingosis



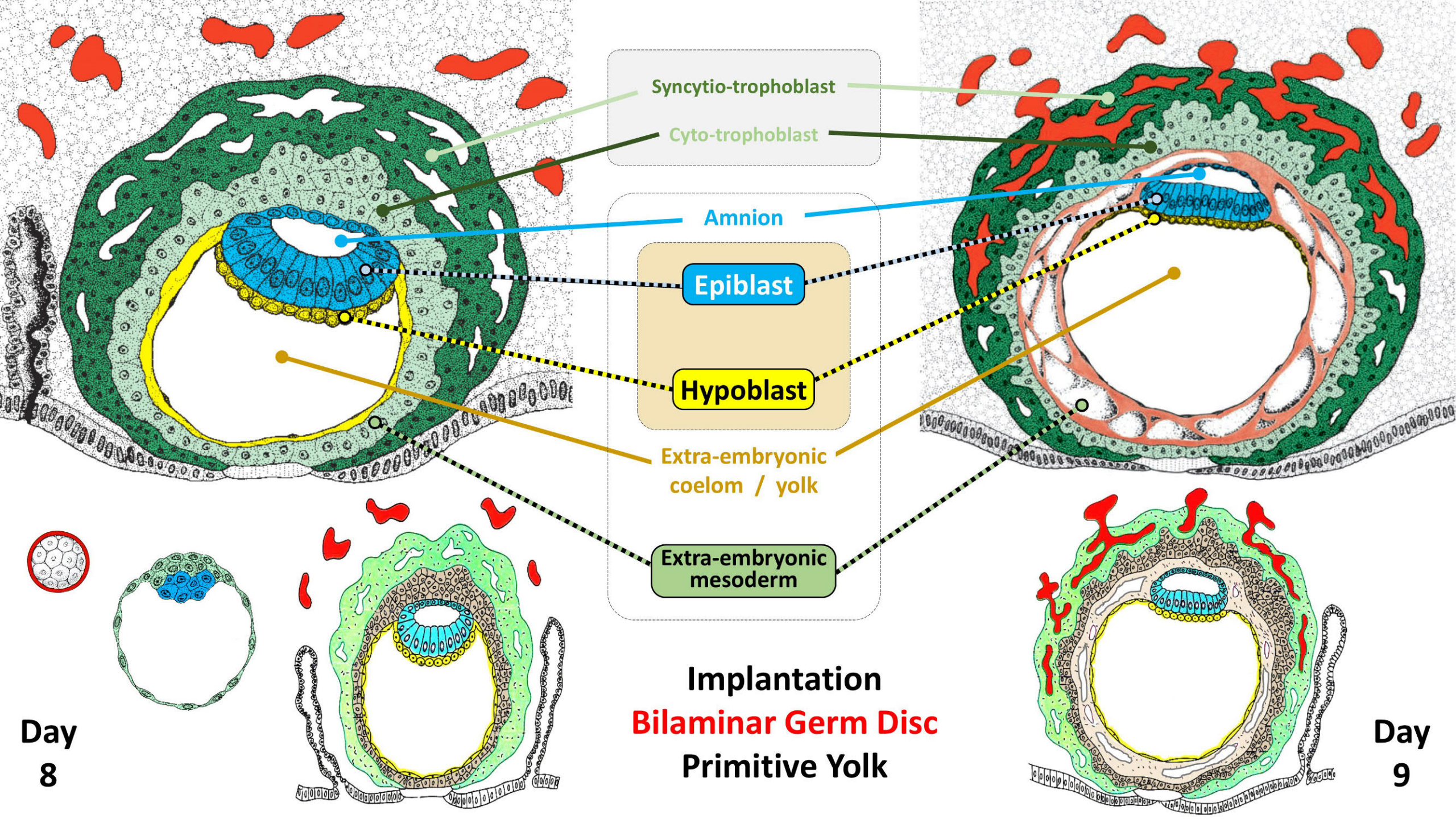


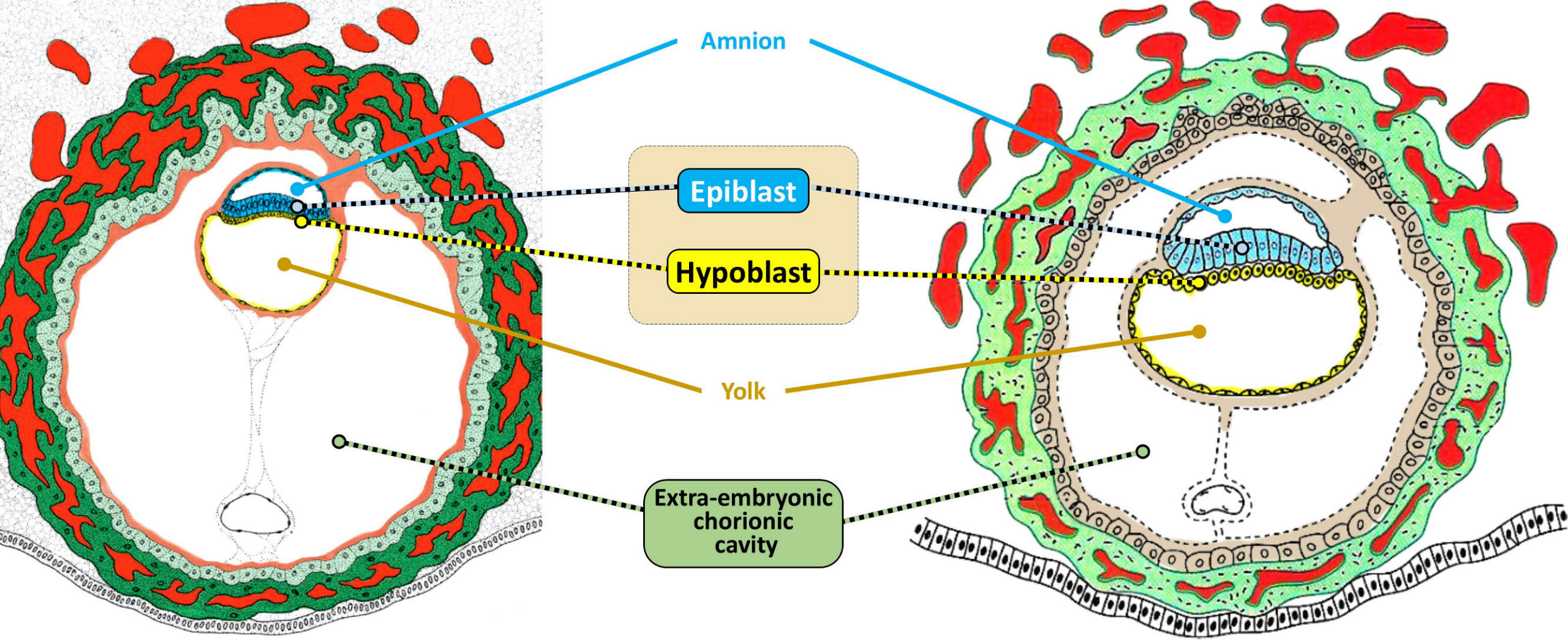
Embryoblast

1 Week



Bilaminar Germ Disc


Syncytio-trophoblast
Cyto-trophoblast
Amnion
Epiblast
Hypoblast
Extra-embryonic coelom / yolk
Extra-embryonic mesoderm
Day 8
Implantation
Bilaminar Germ Disc
Primitive Yolk
Day 9



Proto-placenta

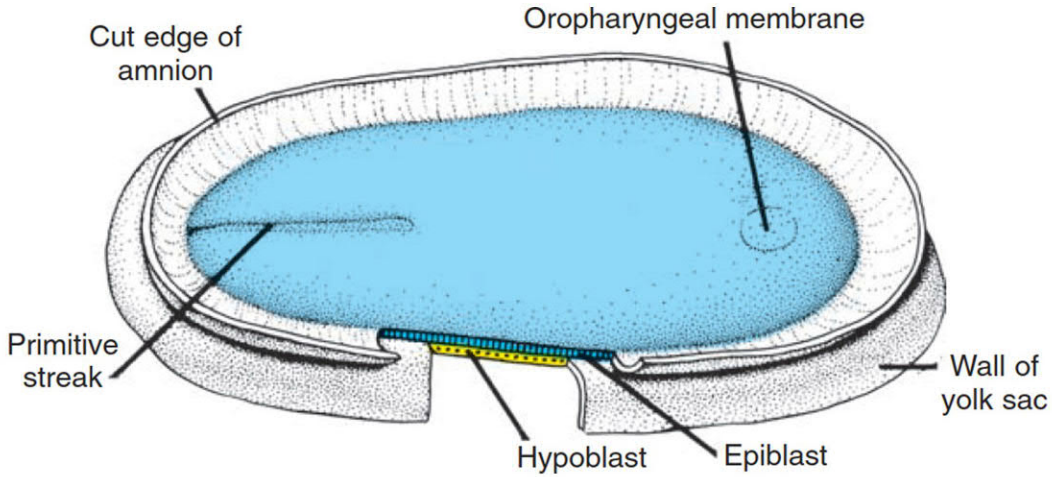
Bilaminar Germ Disc

Chorion

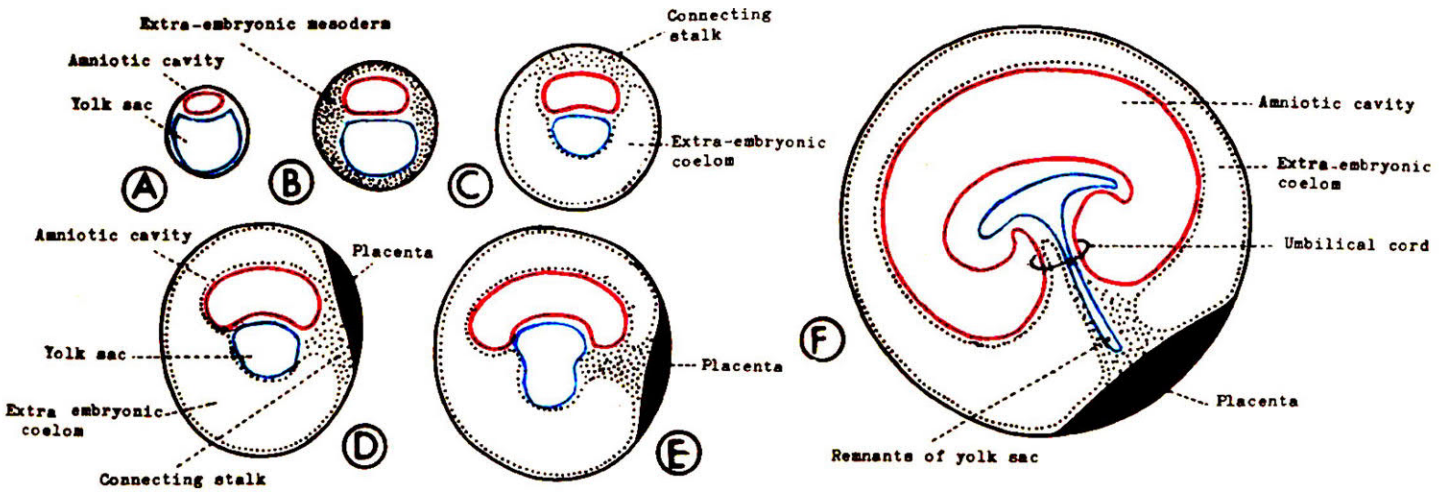
Yolk

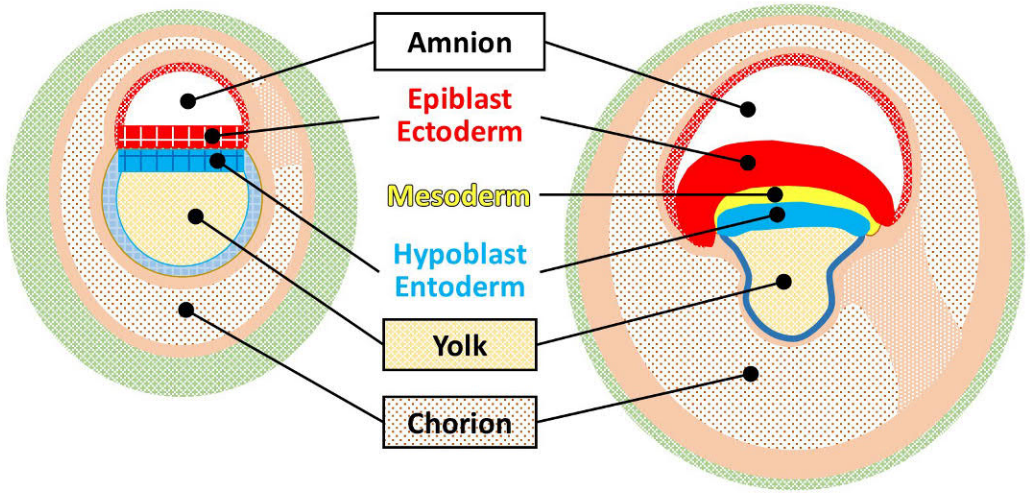
2 Weeks

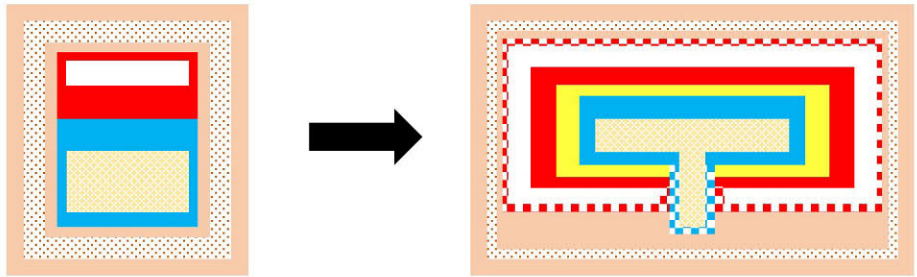
Axiality - Laterality



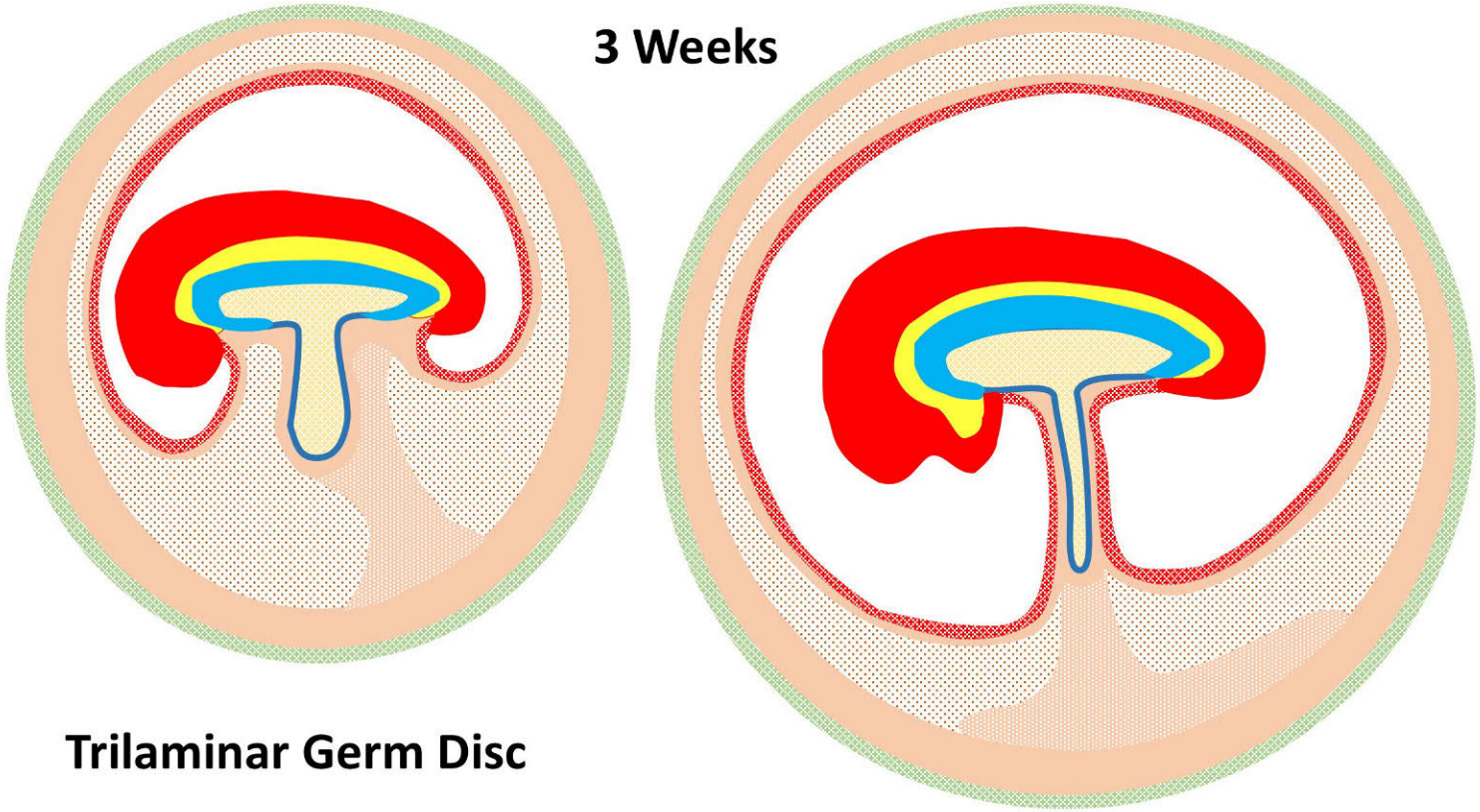
Embryogenesis



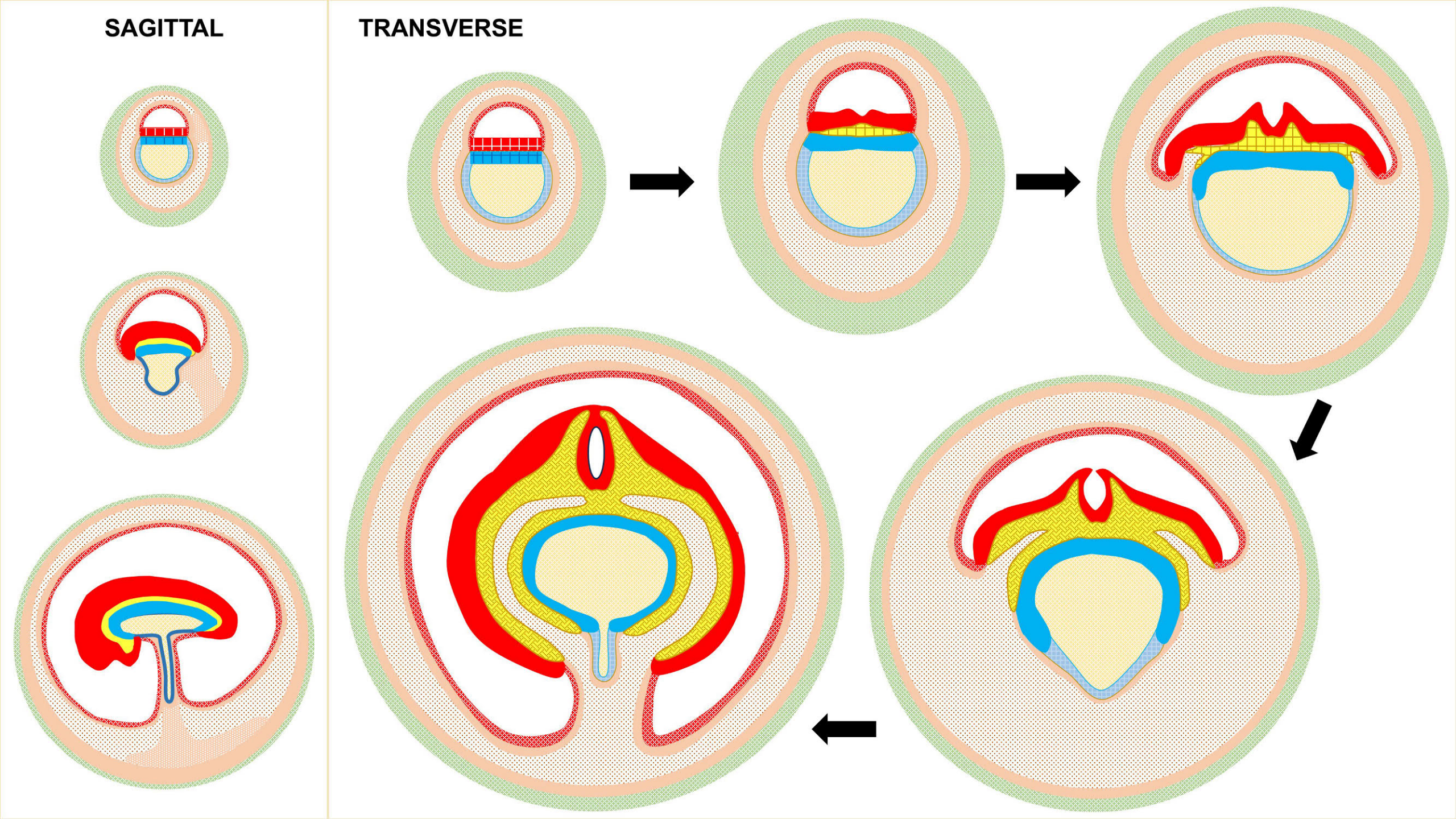


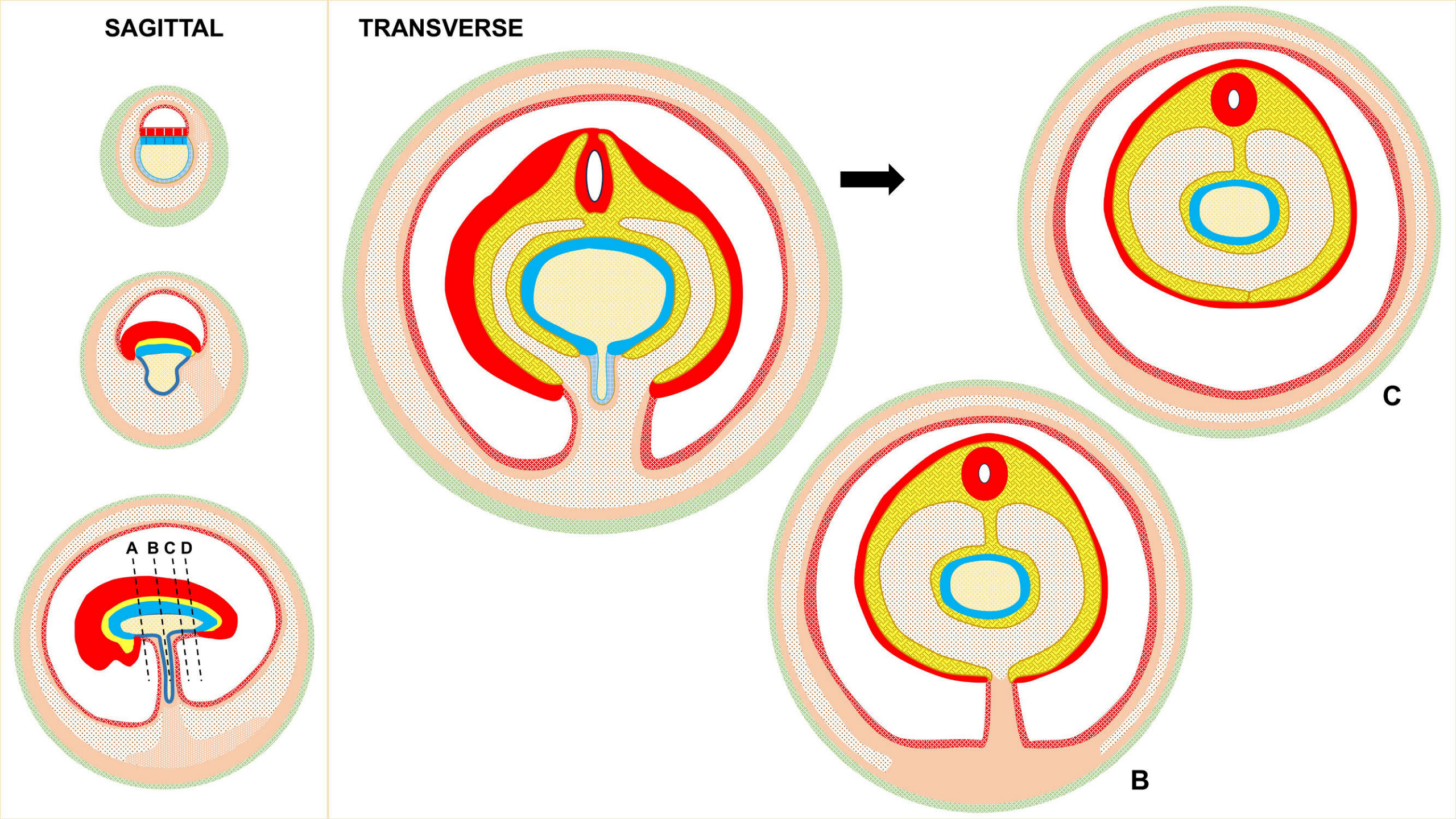


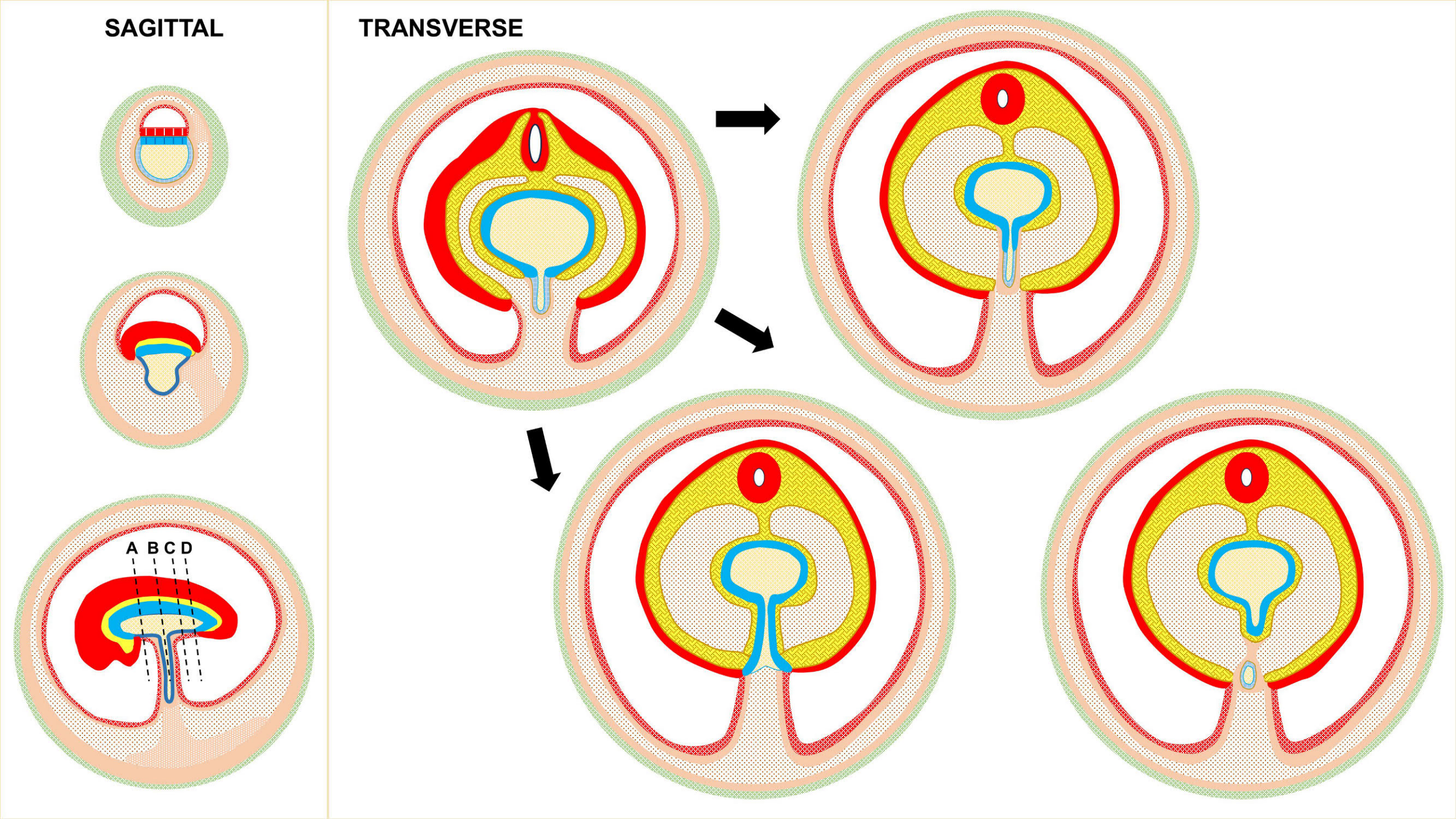
3 Weeks

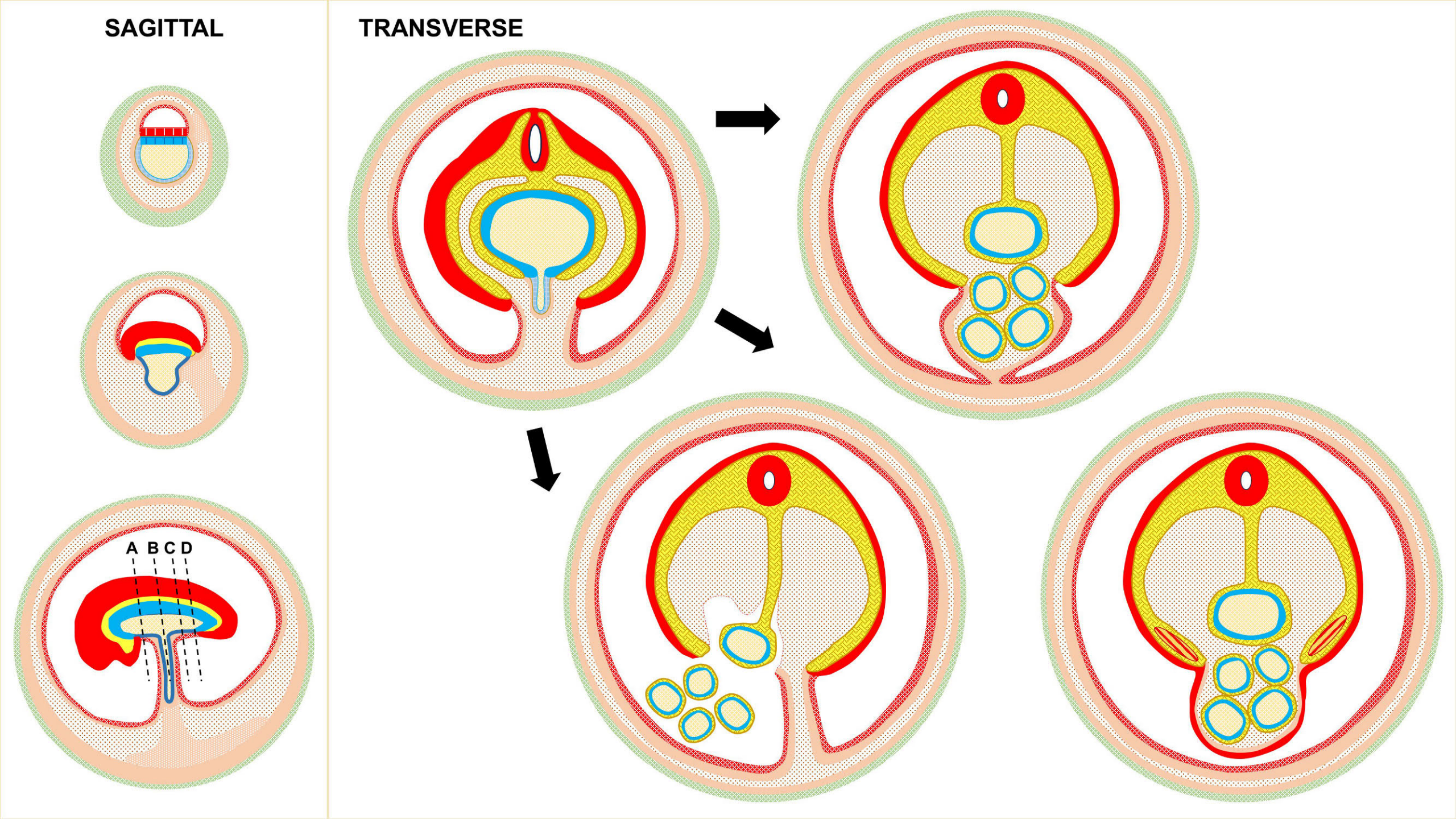


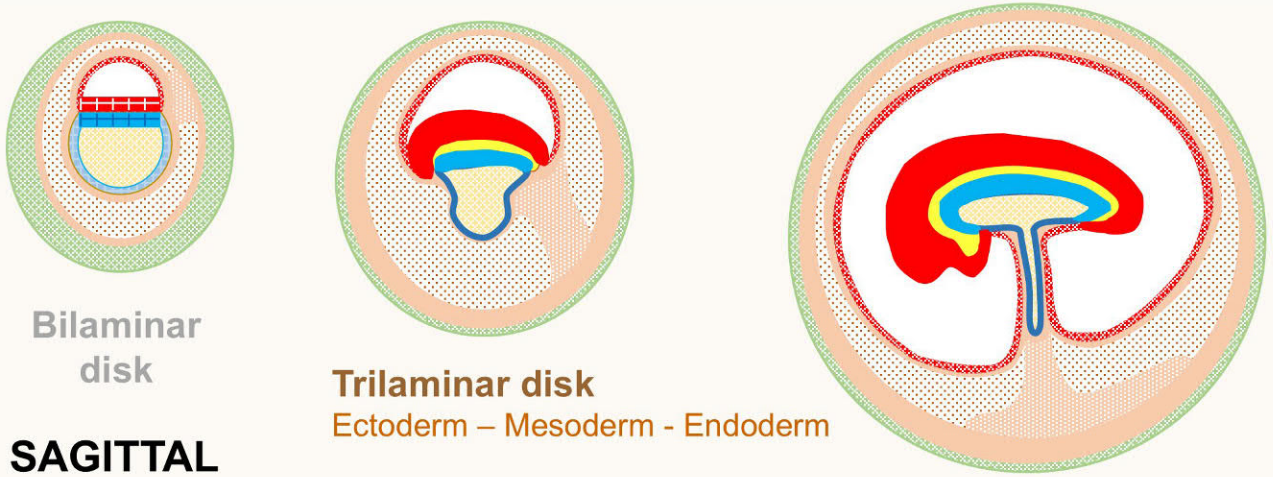
Trilaminar Germ Disc

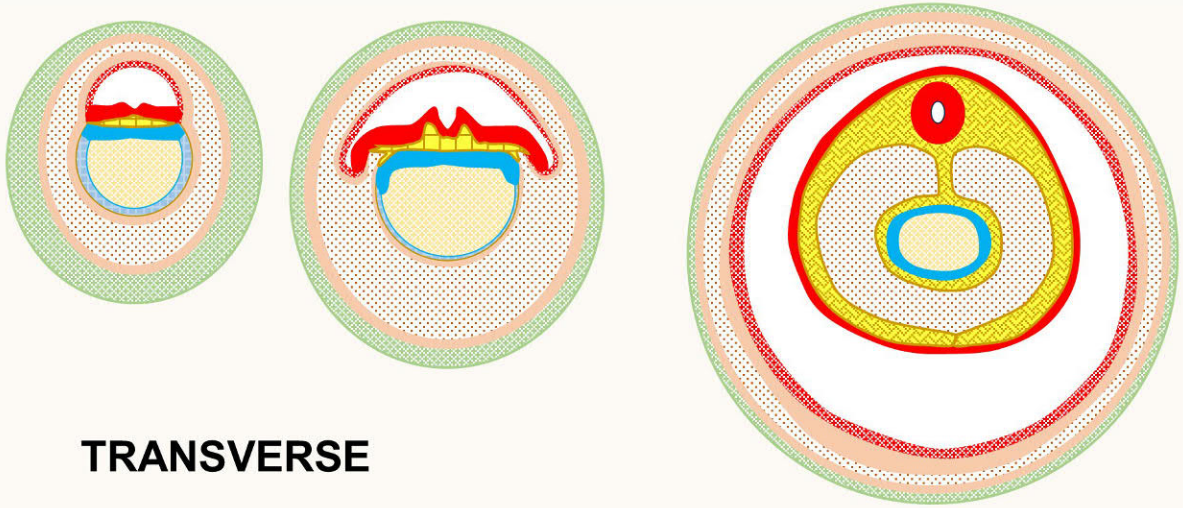

SAGITTAL
TRANSVERSE

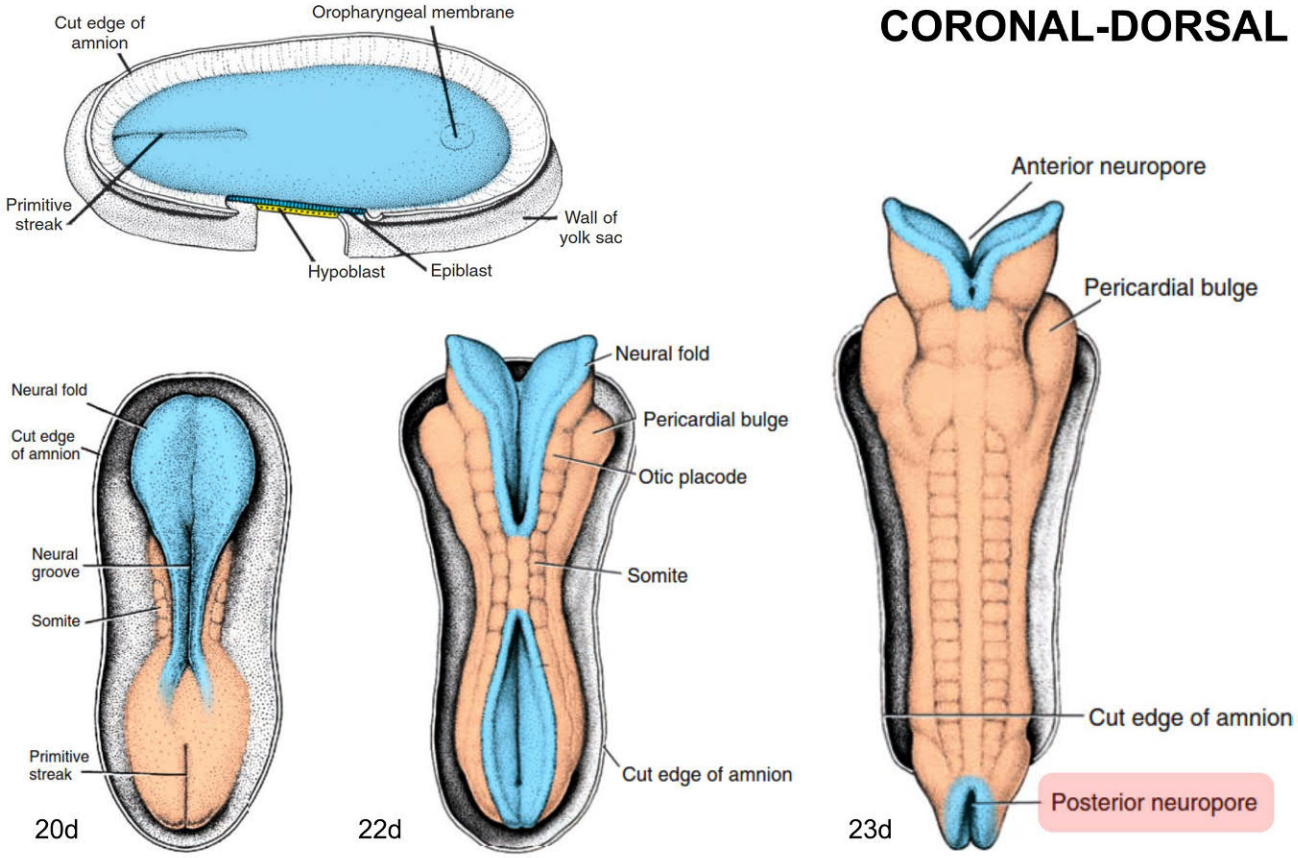

SAGITTAL
TRANSVERSE
A B C D
C
B

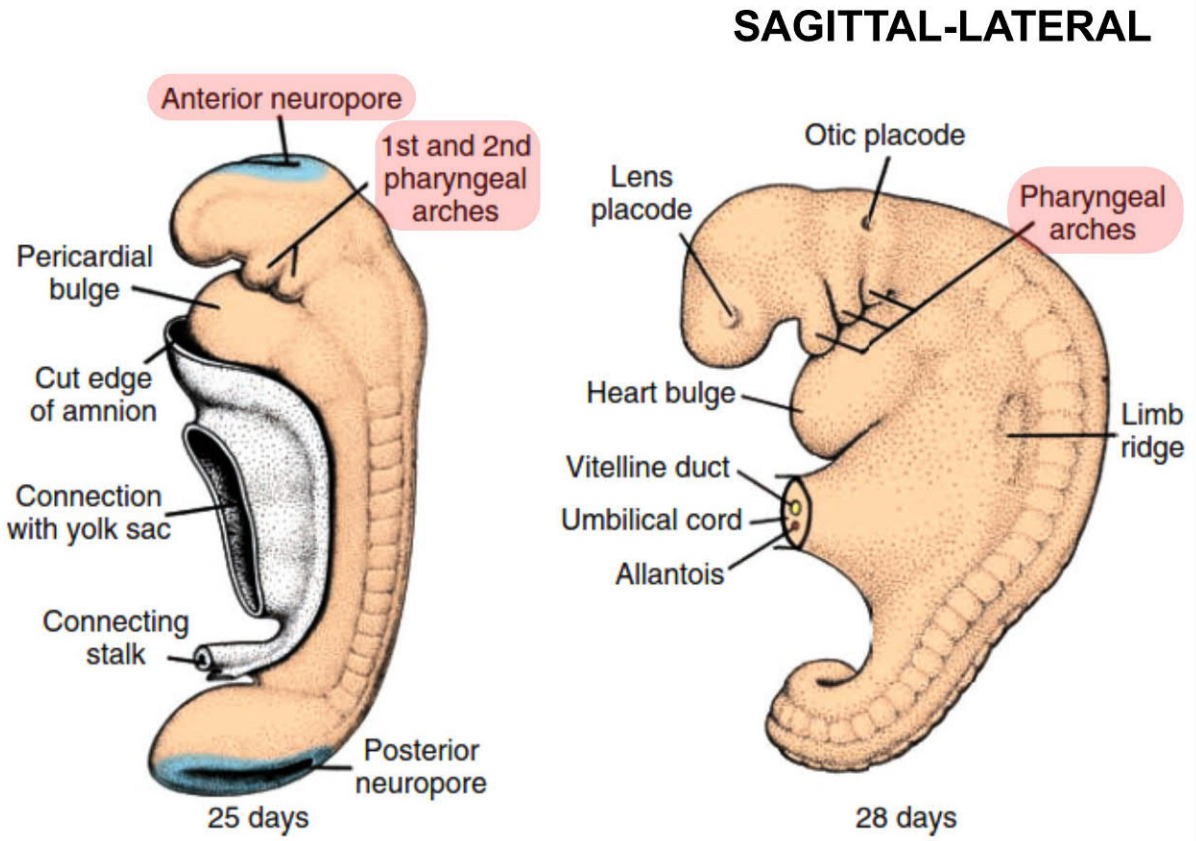

SAGITTAL
TRANSVERSE
A B C D


SAGITTAL
TRANSVERSE
A B C D


Bilaminar disk
Trilaminar disk
Ectoderm – Mesoderm - Endoderm
SAGITTAL


TRANSVERSE


CORONAL-DORSAL
Cut edge of amnion
Oropharyngeal membrane
Primitive streak
Wall of yolk sac
Hypoblast
Epiblast
Neural fold
Cut edge of amnion
Neural groove
Somite
Primitive streak
20d
Neural fold
Pericardial bulge
Otic placode
Somite
Cut edge of amnion
22d
Anterior neuropore
Pericardial bulge
Cut edge of amnion
Posterior neuropore
23d


SAGITTAL-LATERAL
Anterior neuropore
1st and 2nd pharyngeal arches
Pericardial bulge
Cut edge of amnion
Connection with yolk sac
Connecting stalk
Posterior neuropore
25 days
Otic placode
Lens placode
Pharyngeal arches
Heart bulge
Limb ridge
Vitelline duct
Umbilical cord
Allantois
28 days

Conceptual - Topological Embryology

BODY PLAN

Topology ::

total body homeomorphism to a torus
organs & tissues – homeomorphism to a plane

trilaminar

ectoderm	epithelia & derived
mesoderm	mesenchyme & derived
endoderm	epithelia & derived

fusion ventral, dorsal, rostral, caudal, arches

Anatomy ::

stroma vs. parenchyma

mesenchyme :
(mesoderm)
stroma
* anatomical binding
(fibroblasts :: ground-connective matrix)
* vascular distribution
(angiocytes :: vessels)
other common services
defense
energy storage
force & motion
fascias
musculoskeletal
serosas & coeloms

parenchyma :
(ectoderm, endoderm)
epithelia
ambient interface
adeno-exocrine, endocrine
metabolism, nutrition, control
cns (sequestered)

Physical Embryology

Key events ::

Ventral folding & fusion of inner plate
into respiratory, gastro-intestinal, genitourinary.
(hypoblast – endoderm, & visceral mesoderm)
Hypoblast-yolk, extra-embryonic bowel closes.
Chorion-allantois, extra-embryo urinary closes.

Ventral folding & fusion of outer plate
into skin & musculoskeletal body shell.
(epiblast – ectoderm, with parietal mesoderm)

Dorsal folding & fusion of epiblast-ectoderm
with sequestration of midline tube.
(neuroectoderm – neural tube and cns)
Closure of anterior & posterior neuropores.

Coeloms, serosas, bursas.
(from parietal-visceral cavitation of mesoderm;
. . . chest-abd-pelvis, to host mobile organs)

Ventral folding & fusion of branchial arches
into face and neck structures.
(gap between rostro-cephalic neuroectoderm and cephalad end of endodermal tube)

Trophoblastic and extra-embryonic structures.
Placenta
Umbilicus & cord

Circulation.
Placental-fetal, somatic vessels, heart

Visceral organogenesis
by hyperplasia & ducto-lobular branching.
(ectoderm & endoderm)

Mesenchymal & distributed organogenesis.
(hematopoiesis, host defense, etc.)

Somites & segmentation.
Musculoskeletal.
Limb buds.

► Embryological Pathology & Clinical Sequelae ◄

► Midline fusion defects ::
esophageal atresia, trachea-esophageal fistulas
bifid sternum & pseudarthrosis • cardiac exstrophy / ectopia cordis
diastasis recti, midline ventral hernias • omphalocele, gastroschisis
diastasis pubis, bladder exstrophy, cloacal anomalies • epi- & hypospadias
spina bifida, myelo- & meningocele

► Rostral & Lateral fusion defects ::
cleft lip & palate, other cranio-facial clefts, encephaloceles
branchial cysts & sinuses

► Persistence and sequestration anomalies ::
parietal sinuses, visceral sinuses, fistulas, sequestration cysts
thyroglossal duct
meckel's, vitelline-omphalomesenteric, urachal-allantoic
pilonidal

► Secondary & associated anatomical defects ::
multiple anomalies, syndromic deficits
secondary atrophy and asymmetries (e.g., mid face with cleft lip, lower body with spina bifida).

► Dualities ::
anatomical – vs – functional implications
morbid – vs – benign
congenita, praecox, tarda

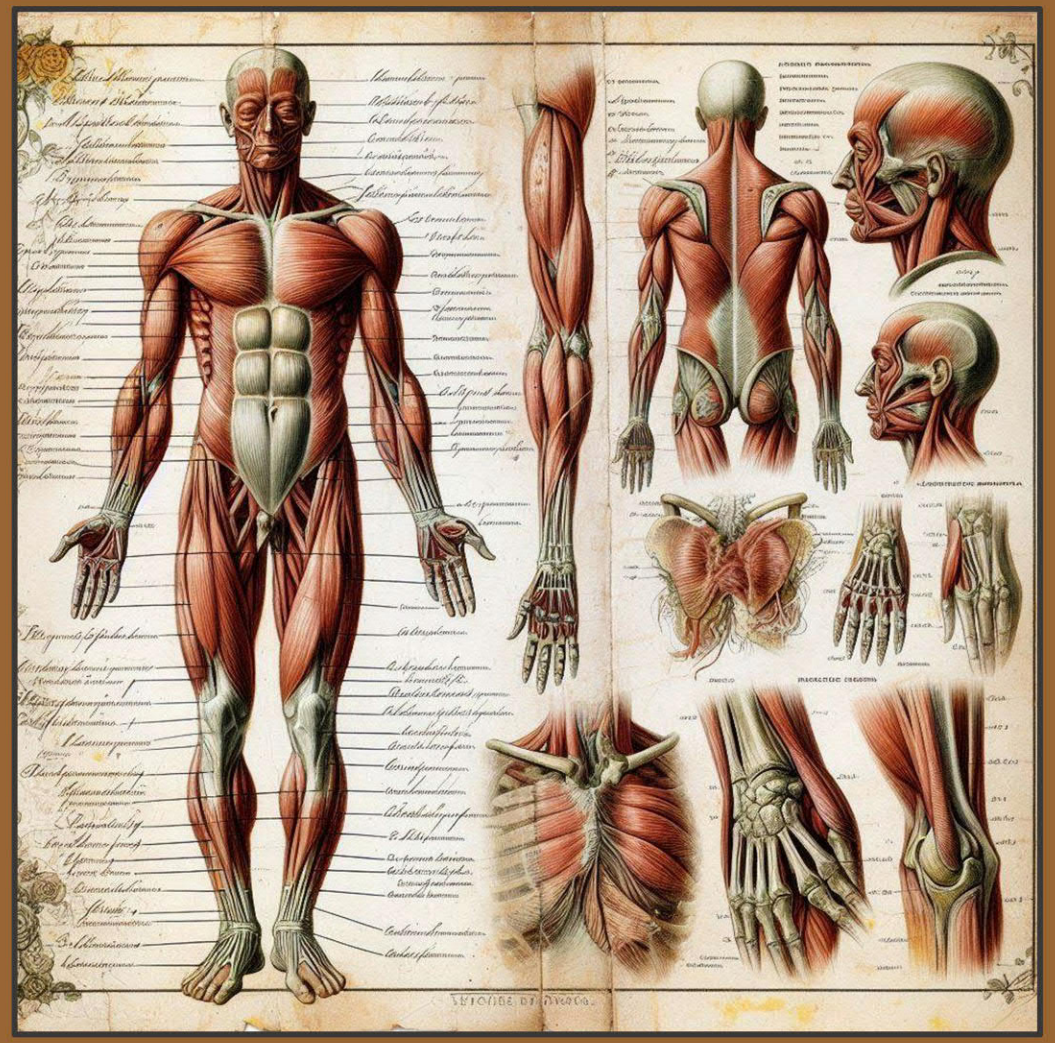
► Clinical sequelae & complications ::

essential :	vital coverage, reduction & stabilization
acute :	system specific, e.g. abscess, bleeding-perforation, incarceration, pressure
chronic – progressive :	system & site specific, e.g., speech-language-dental, herniation, urinary
neoplasia – cancer :	ectoderm (epithelia, glands) = carcinoma endoderm (visceral epithelia, organs) = carcinoma mesoderm (stroma, support, defense) = sarcoma, leukemia-lymphoma malignant transformation in fistulas, sinuses, diverticula, sequestrations, rests
incidental :	e.g., latex allergy
functional :	system & site specific, medical, physical, functional, social

► Clinical care ::

management :	incidental care – vs – comprehensive long-term management
surgery :	essential & acute complications – vs – reconstructive & rehabilitative
timing :	urgent, incidental-elective, staged reconstruction, graduated long-term plan

Anatomy



Embryology

Segmental

Vasculature

Wolff's Law

Four Horsemen of the Apocalypse, 1498, by Albrecht Dürer, (Nuremberg, 1471-1528).

The Final Judgment, 1865, by Gustave Doré, (France, 1832—1883).

E-DS-M-I

EDEMA

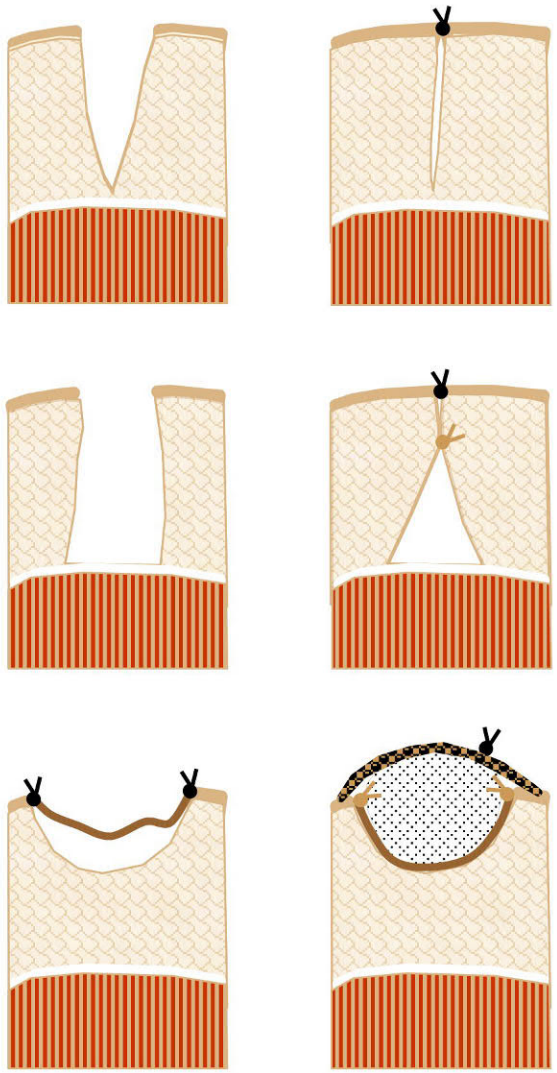
DEAD SPACE

MOTION

INFLAMMATION

DEAD SPACE

MOTION - INFLAMMATION



MANDATORY
for successful repair:

Tissue-to-Tissue Coaptation

Tissue Interface Stability Without Shear or Distraction

DEAD SPACE CONTROL

1 - Positive pressure from without.

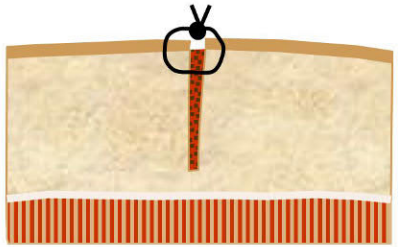
2 - Negative pressure from within.

3 - Gather and bind space.

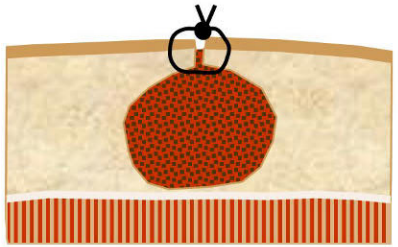
4 - Fill the space.
(flaps, biomatrices, cement)

Wound remodeling.
Proper dissection & preemptive avoidance.

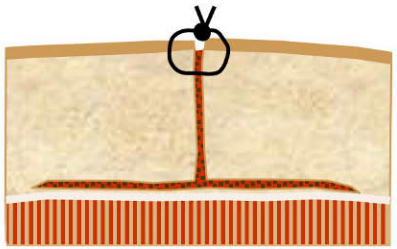
WOUND GEOMETRY & MECHANICS



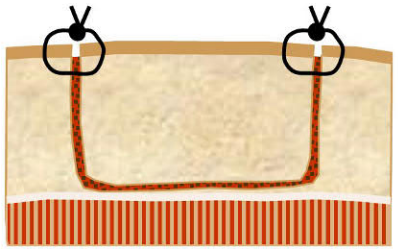
nominal dead space



overt dead space

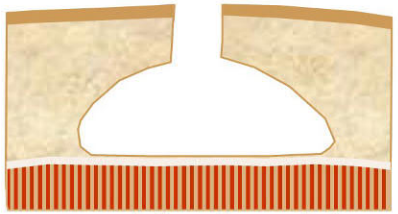


latent dead space, shear



latent dead space, shear

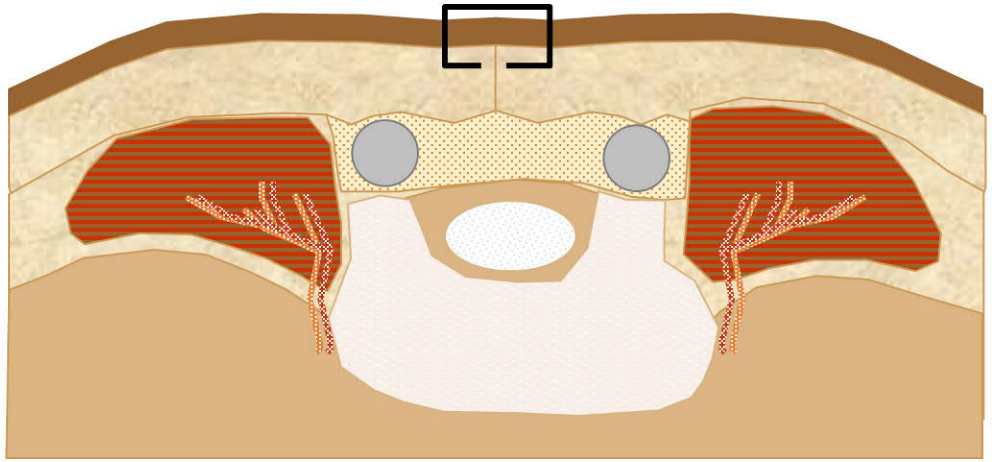
chronic scar & contracture, stiff



cavitary defect after pathology

excise scar to restore compliance

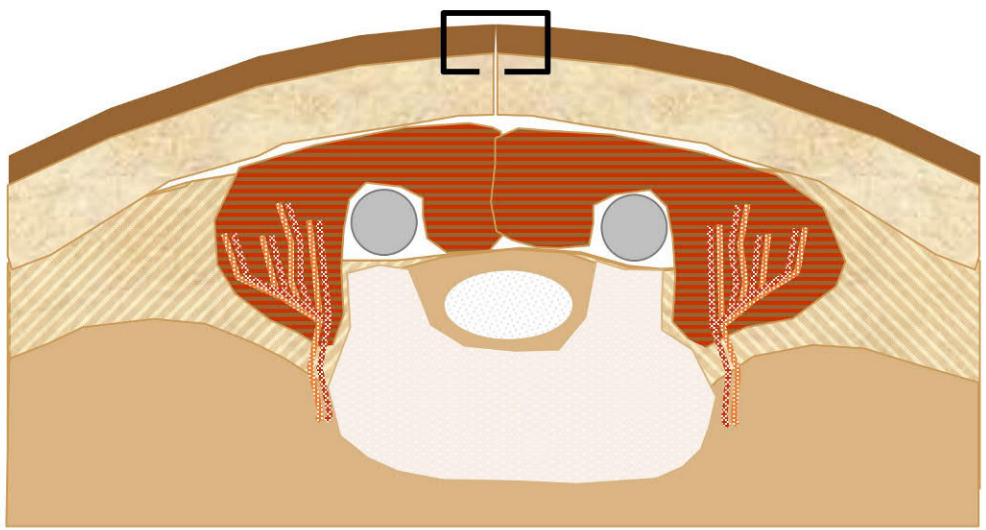
what next ?

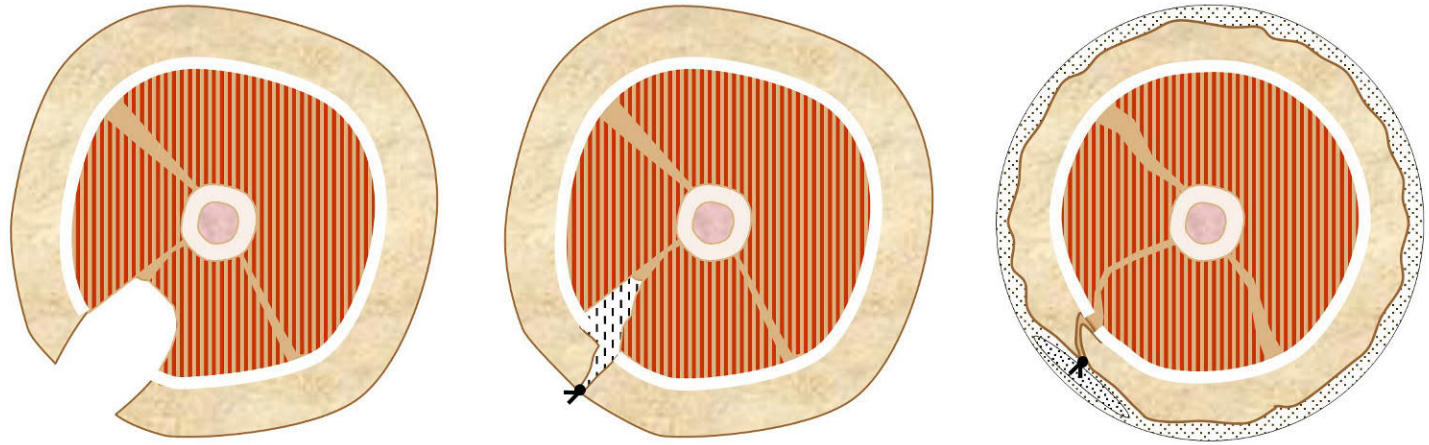


DEAD SPACE

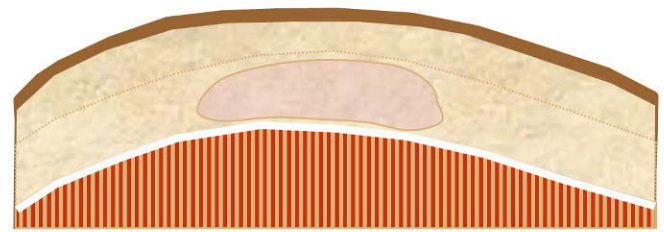
Unmitigated dead space = Abscess.

Fill it in or drain it, else the wound becomes a swamp.



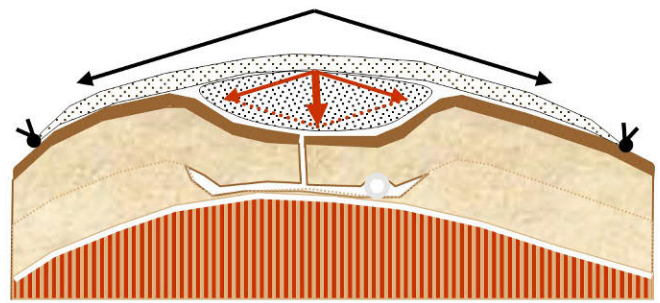


circumferential compression wrapping

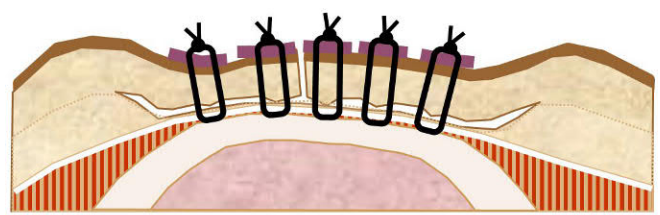


Tissue-to-tissue coaptation.

Tissue interface stability without shearing, distraction, or separation.



compression dressings



mattress sutures

DEAD SPACE CONTROL

Positive Pressure From Without.

Negative pressure from within.

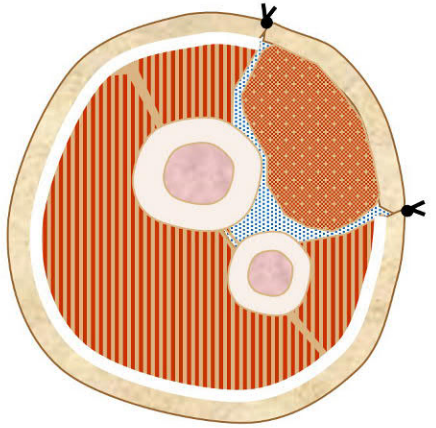
Gather and bind space.

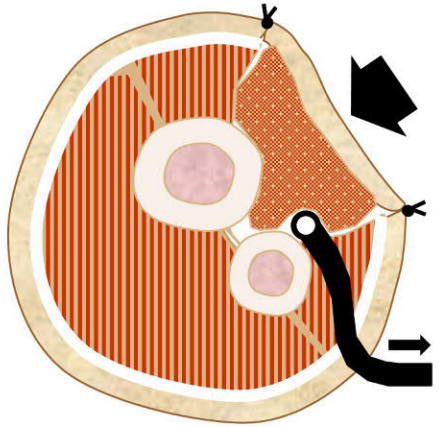
Fill the space.

Wound remodeling. Proper dissection & avoidance.

Tissue-to-tissue coaptation.

Tissue interface stability without shearing, distraction, or separation.



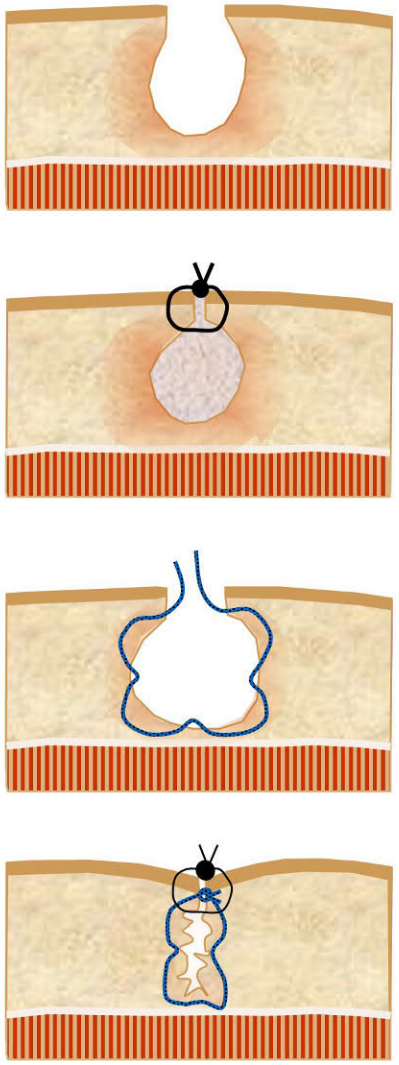


DEAD SPACE CONTROL

Positive pressure from without.

Negative Pressure From Within.

Gather and bind space.
Fill the space.
(flaps, biomatrices, cement)



DEAD SPACE CONTROL

Positive pressure from without.
Negative pressure from within.

Gather and Bind Space.

Fill the space.
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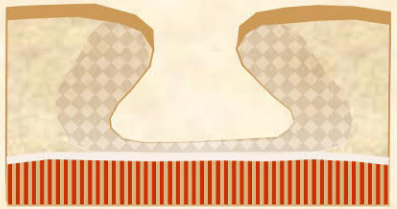
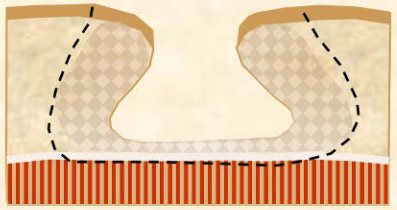
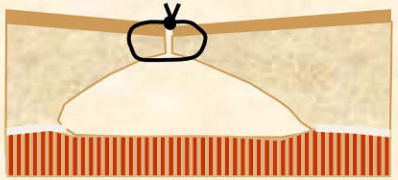


chronic scar & contracture, stiff

stiffness prevents reduction



excise scar to restore compliance

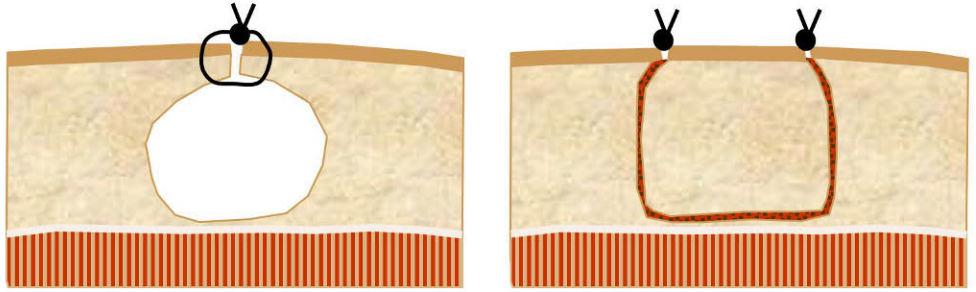


direct closure – drumskin effect

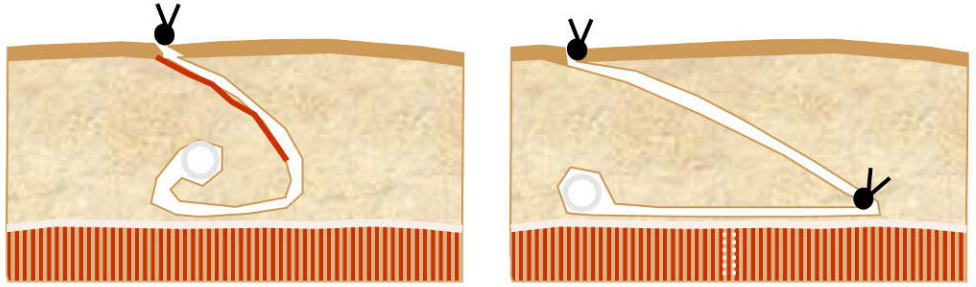
what next ?

DEAD SPACE CONTROL

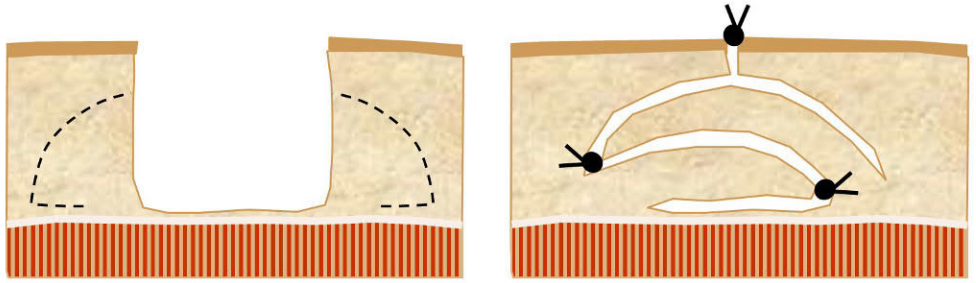
Fill the Space. (flaps, biomatrix, cement)



fill void with transposed flaps



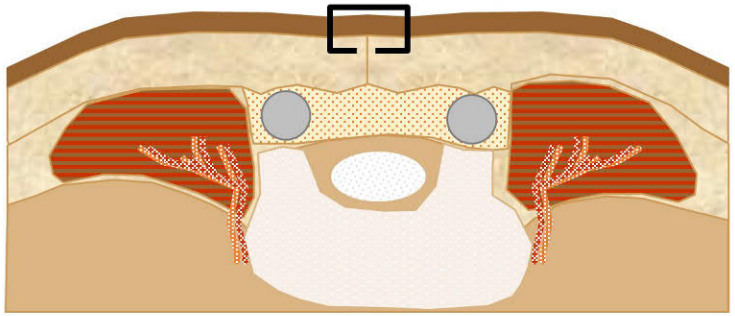
infolding and interleaving 1

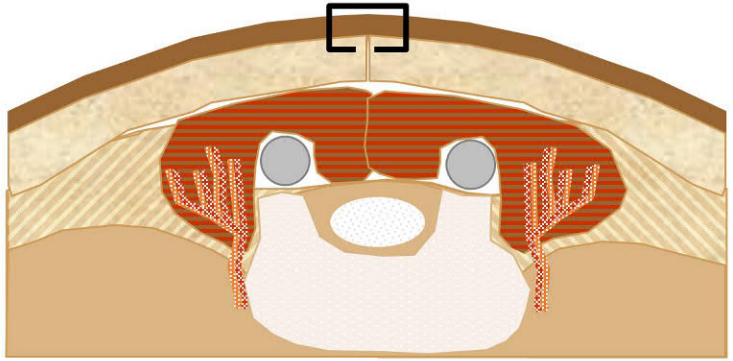


infolding and interleaving 2

DEAD SPACE CONTROL
Fill the Space - Biomatrix, Cement

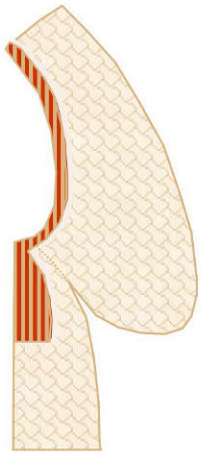
DEAD SPACE CONTROL
Fill the Space - Flaps





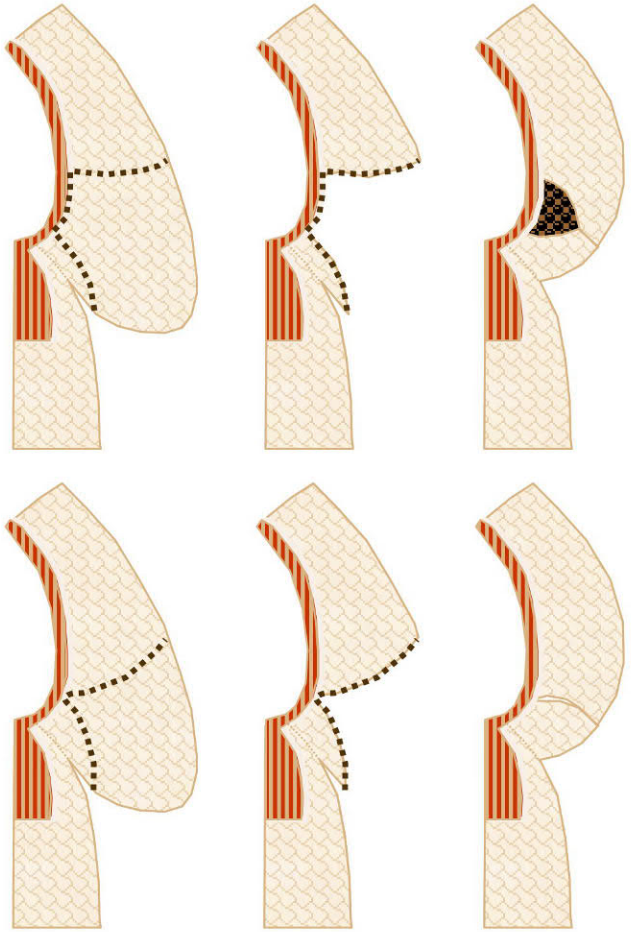
Tissue-to-tissue coaptation.

Tissue interface stability without shearing, distraction, or separation.

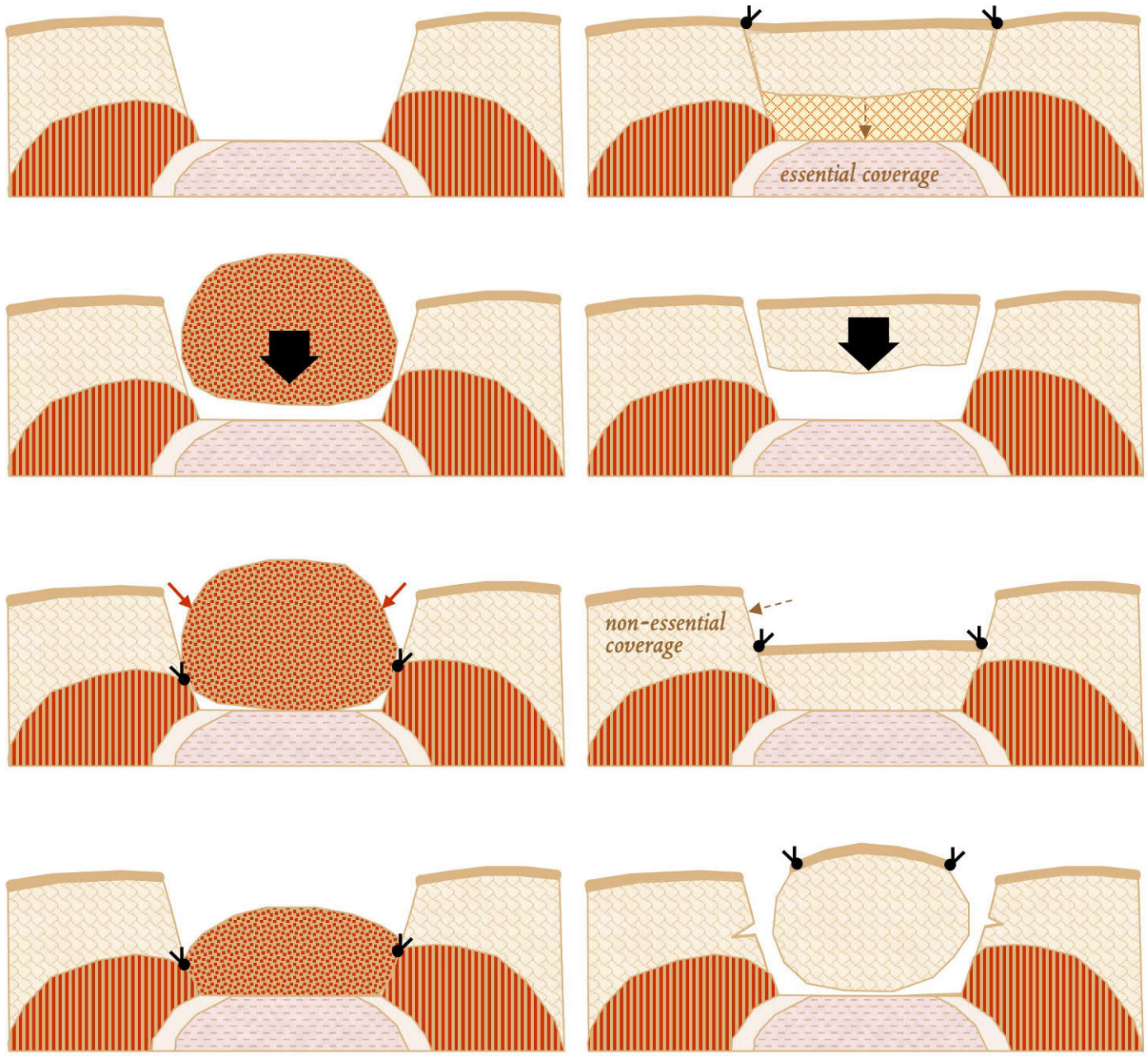


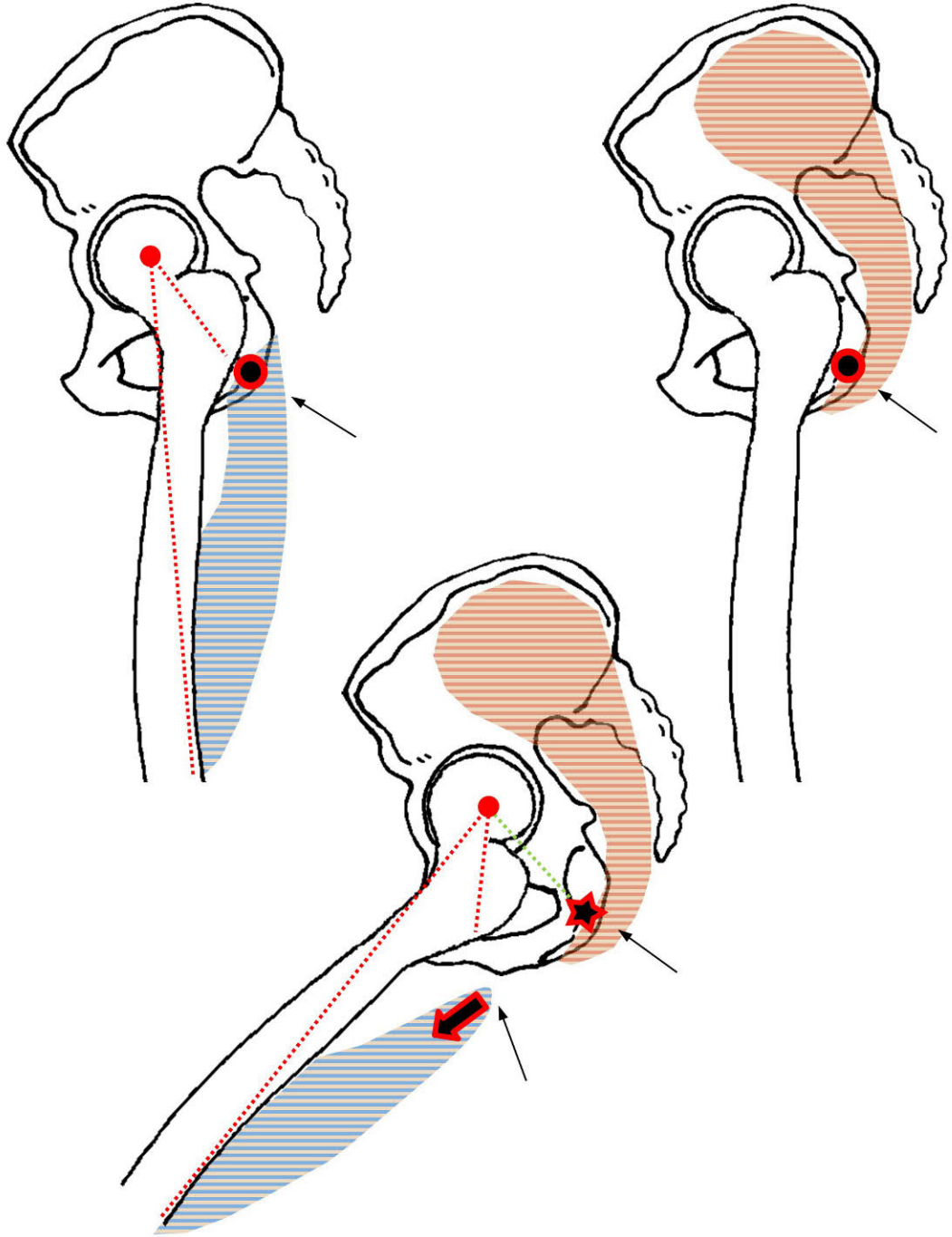
DEAD SPACE CONTROL

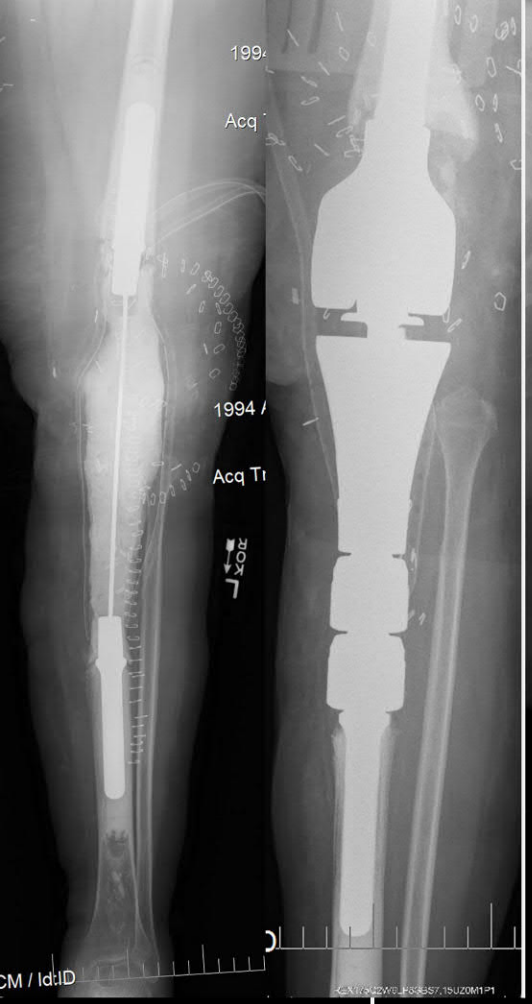
Wound Modeling - Preemptive Avoidance



Filling Space with Flaps :: Technicalities & Pitfalls



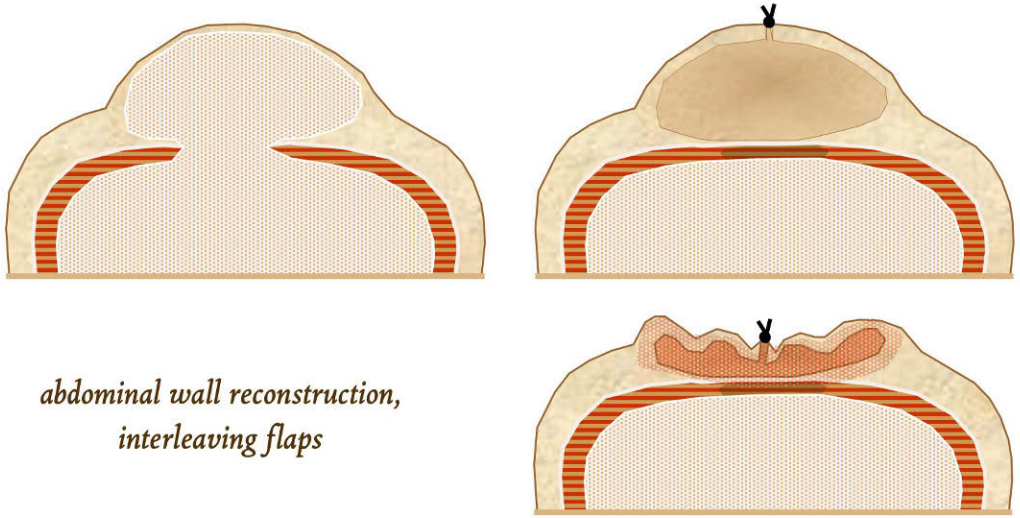




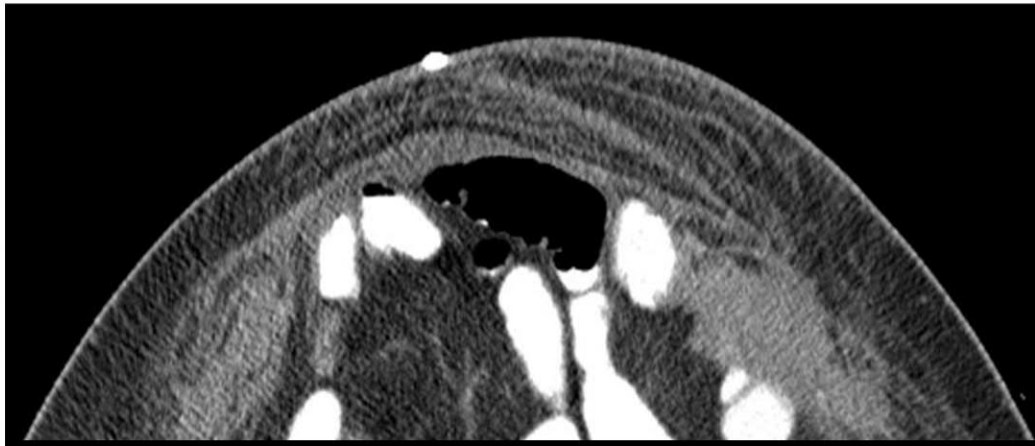
17 F, TKA after trauma

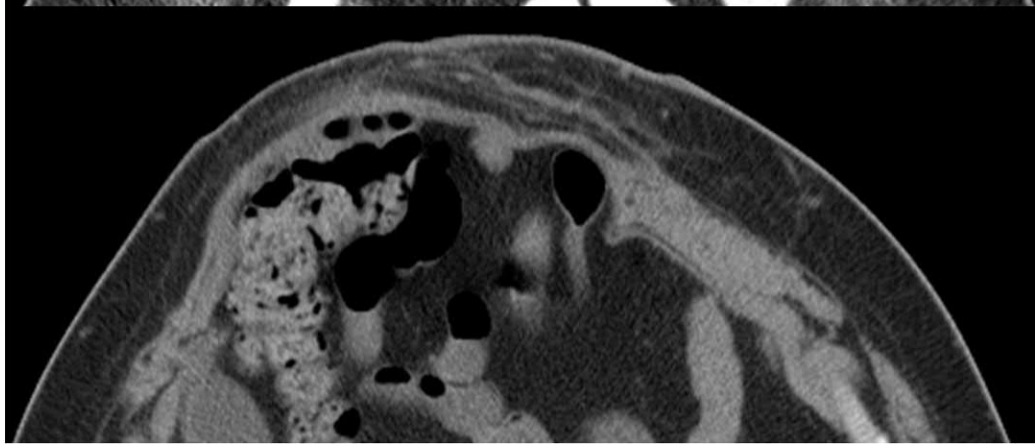
66 F, tumor resect THA, late failure

58 F, sarcoma resection and THA



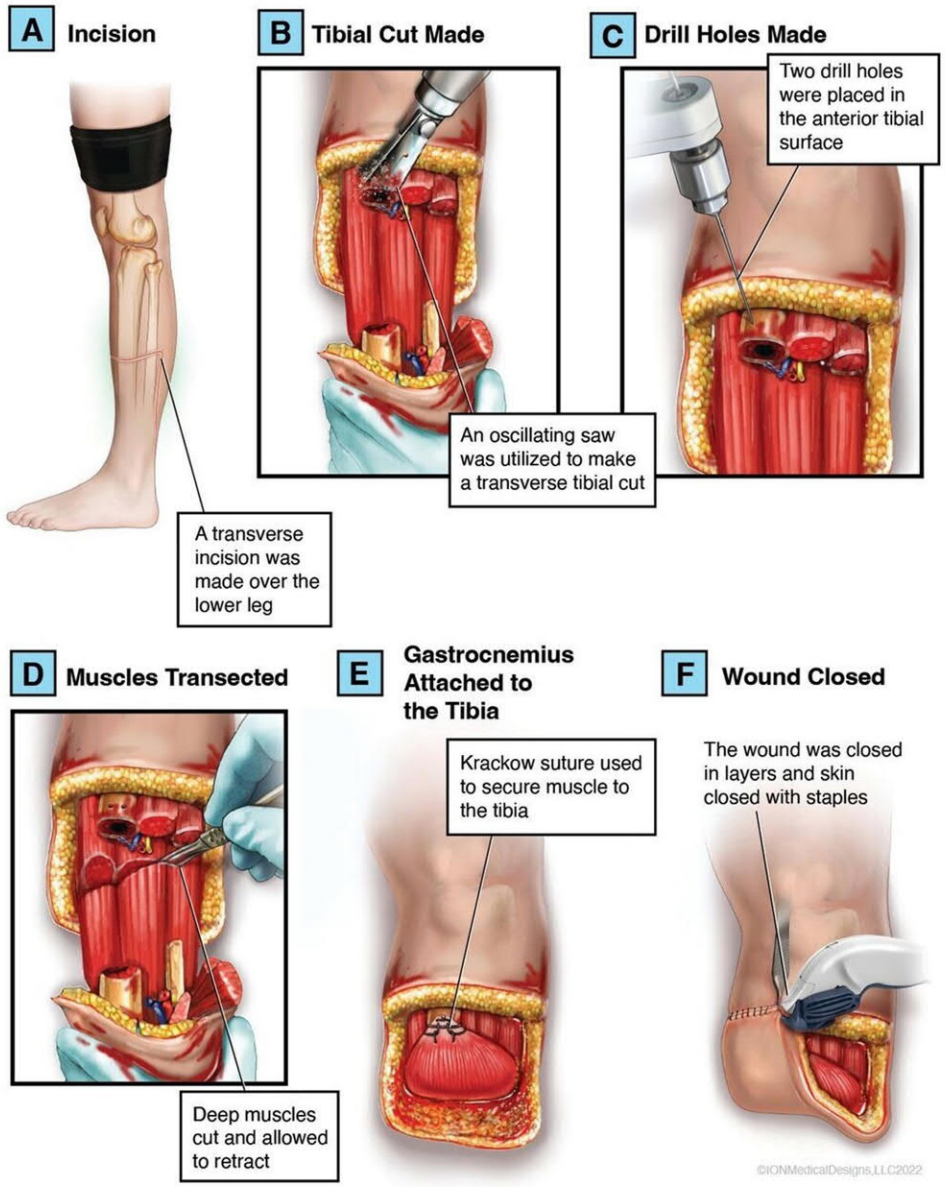
abdominal wall reconstruction, interleaving flaps

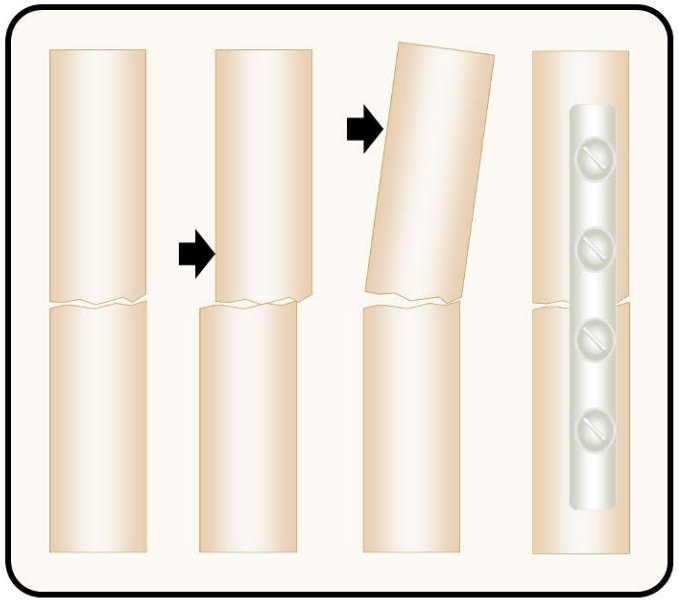


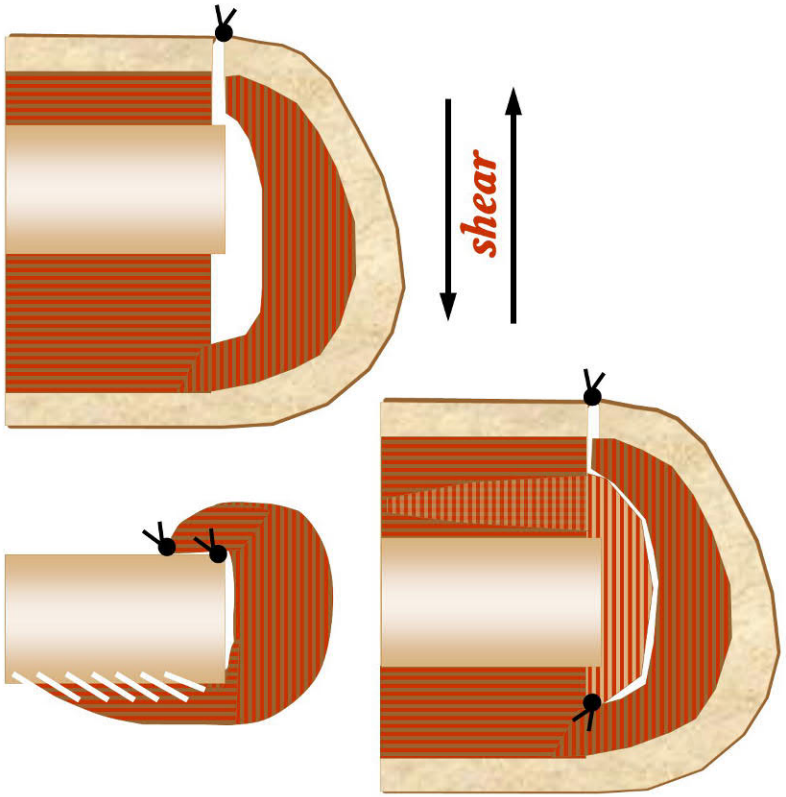


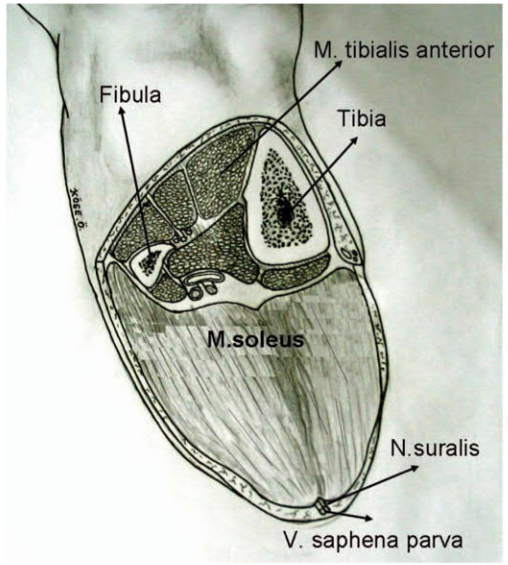
44 M, tibia defect after necrotizing fasciitis

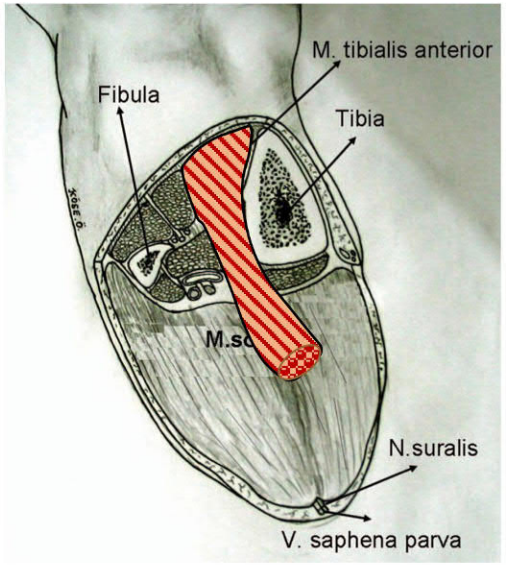
Left Below the Knee Amputation

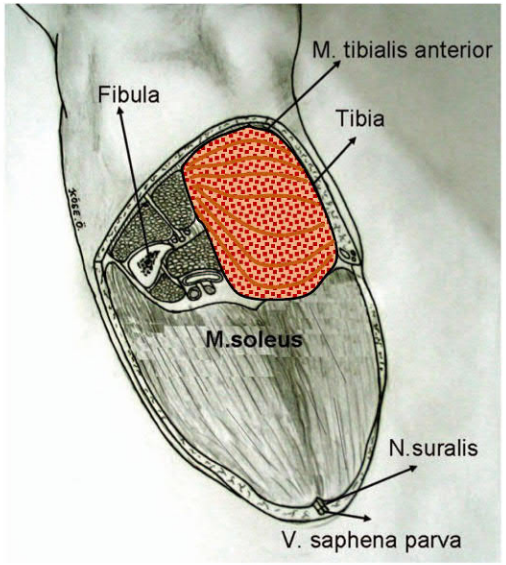


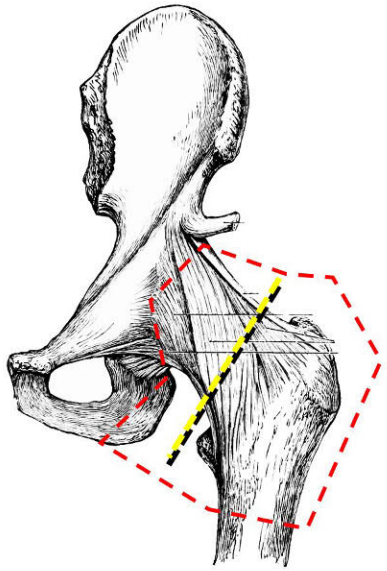


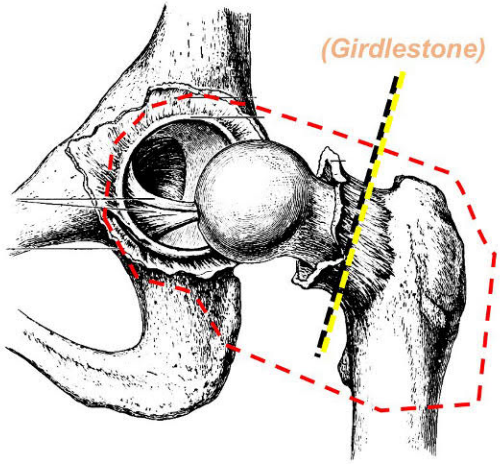


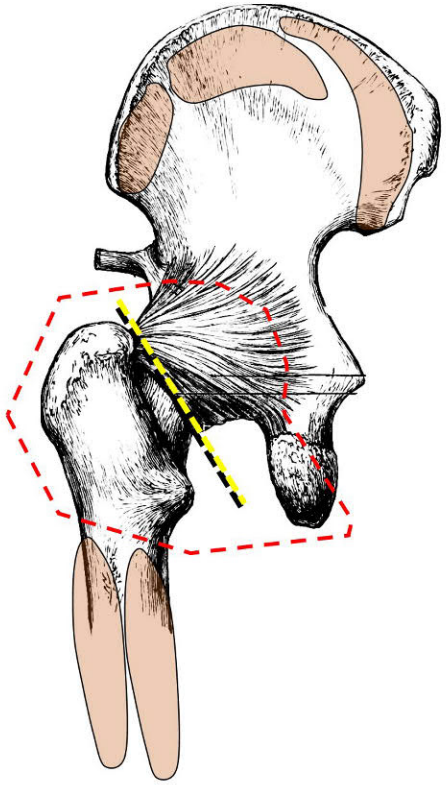


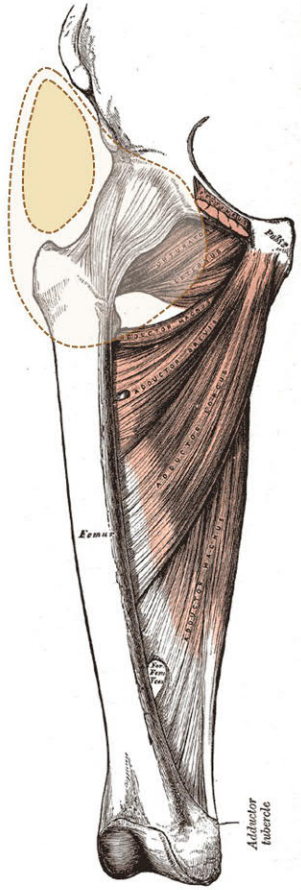


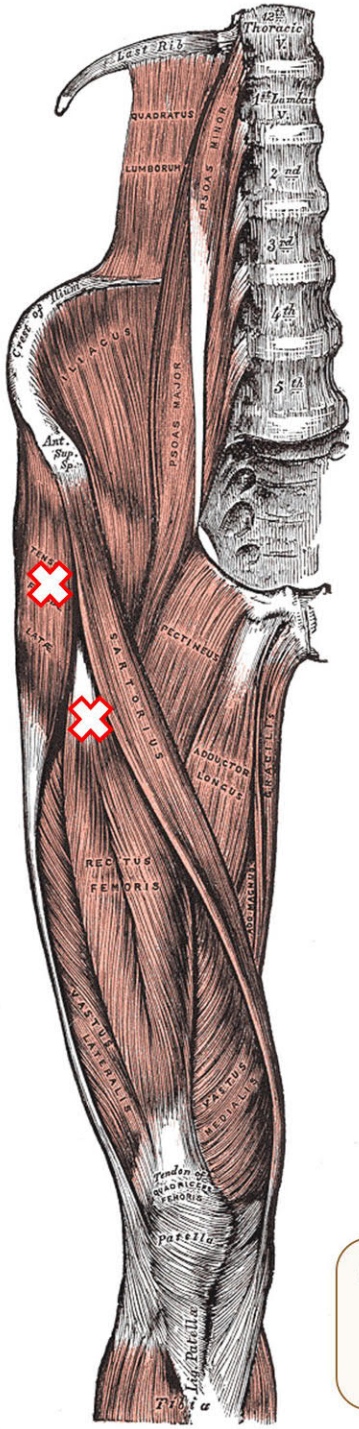


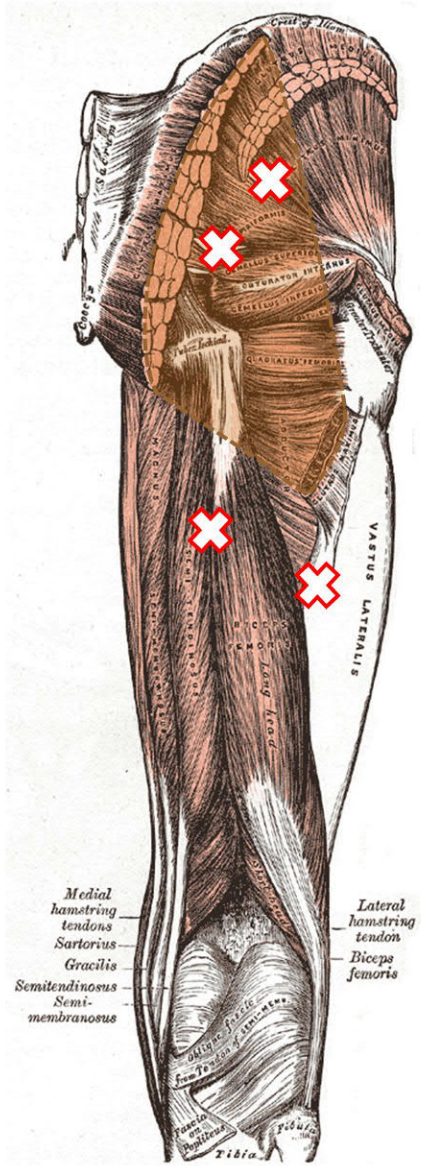


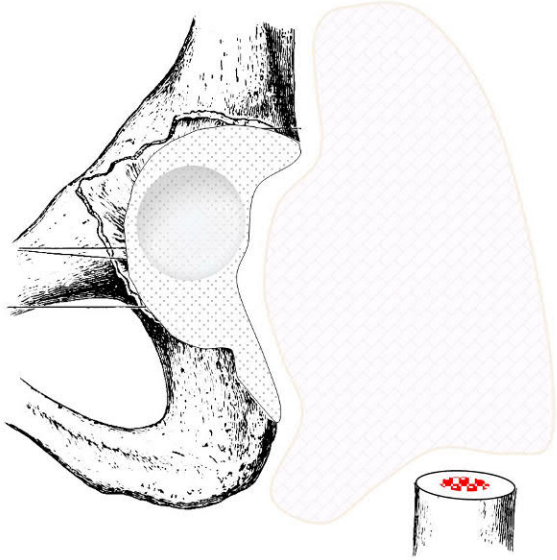


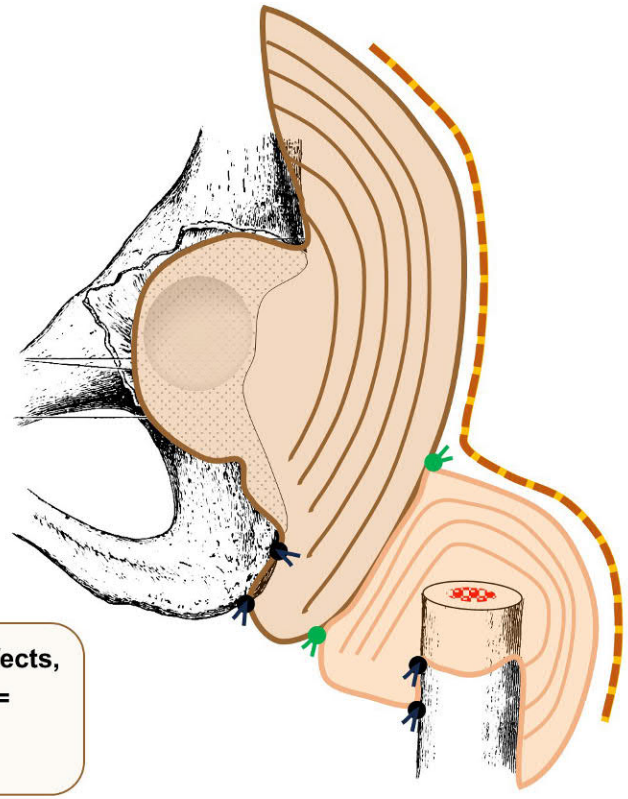












Segmental anatomy, large or complex defects, wounds with motion and dead space =

Multiple Flaps

Anatomy

Embryology

Segmental

Vasculature

Wolff's Law

ANATOMY : **Vasculature**

Physics of vasculogenesis

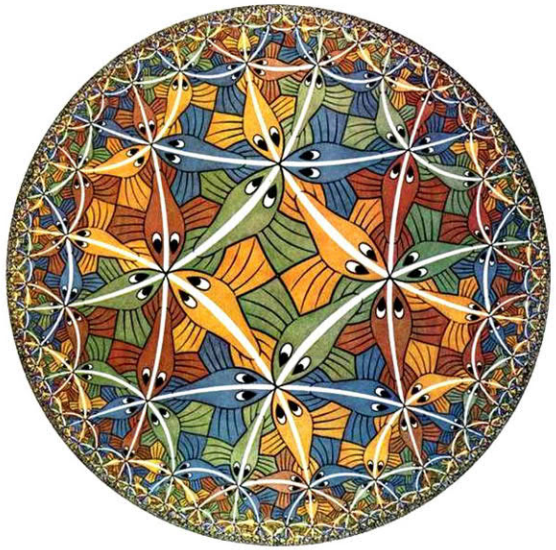
- Angiogenesis, VT model
- Angiosomes, collaterals

Vascular anatomy

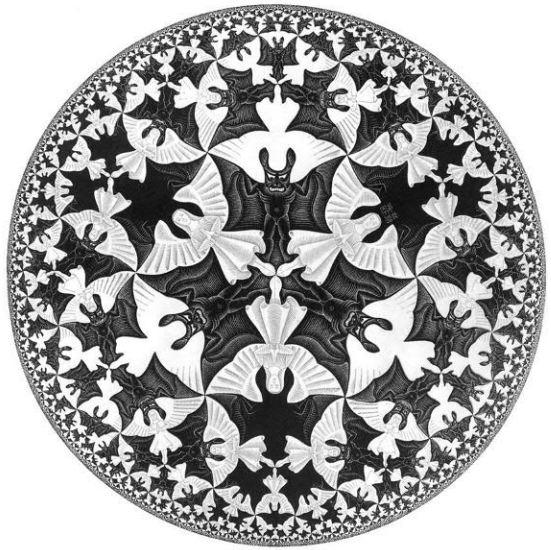
- Multi-layer fascias
- Tangential networks
- Vertical perforators

Clinical implications

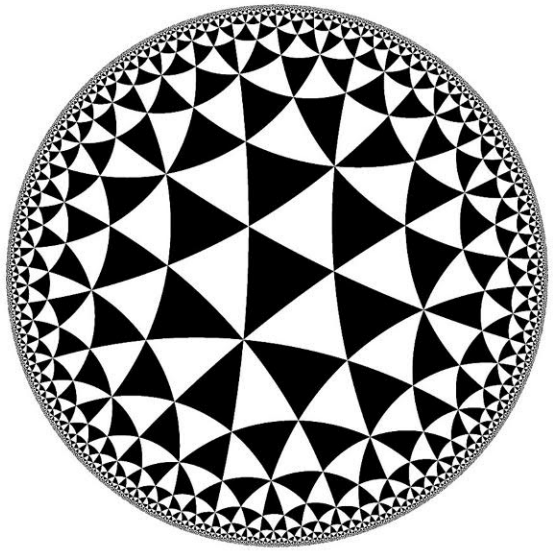
- Flap creation
  (*make it reach versus make it live*)
- Flap delays, crossing watersheds
  (*make it hurt versus kill it*)
- Flap thinning

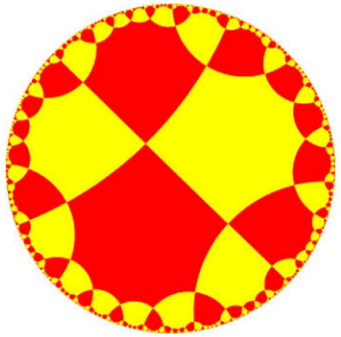


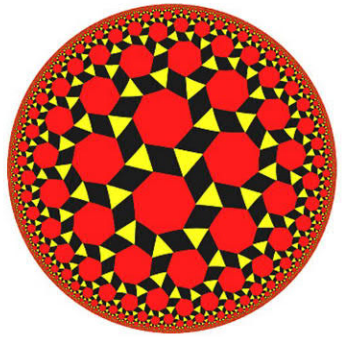
M.C. Escher, 1959
Circle Limit III, Heaven and Hell

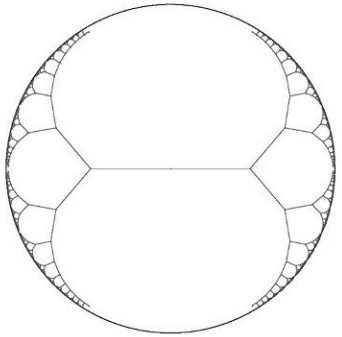


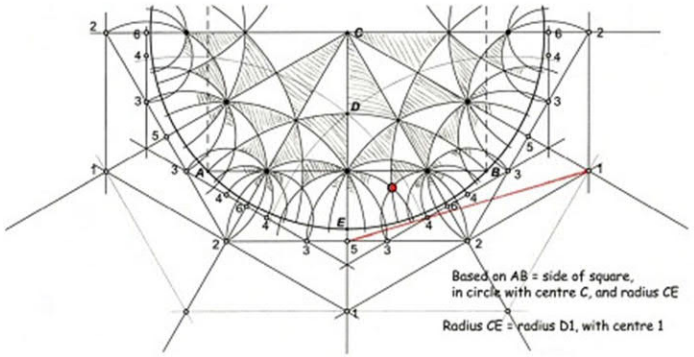
M.C. Escher, 1960
Circle Limit IV

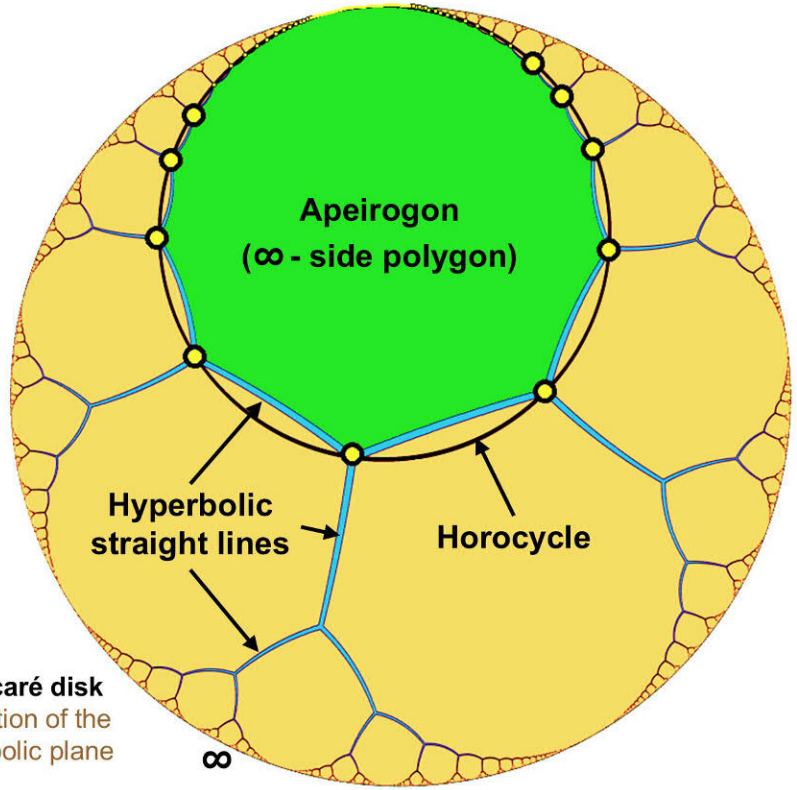




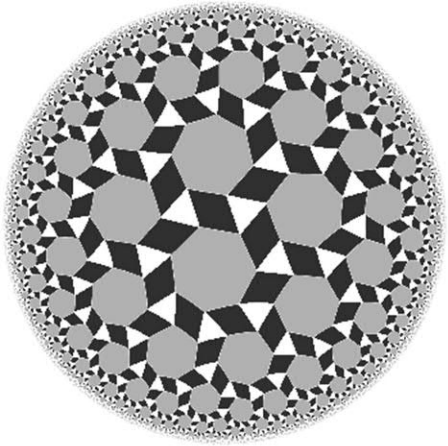




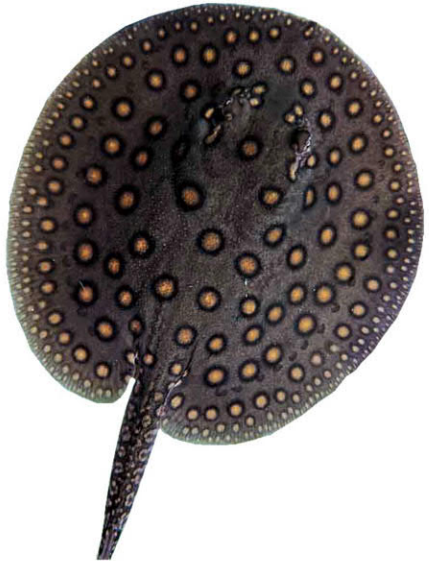




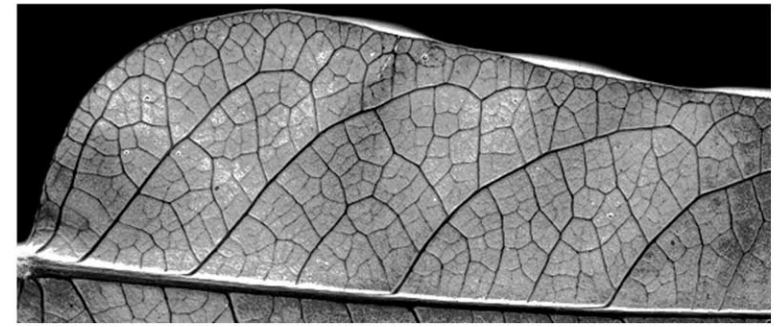
Poincaré disk
projection of the
hyperbolic plane



Hyperbolic tiling
on Poincaré disk

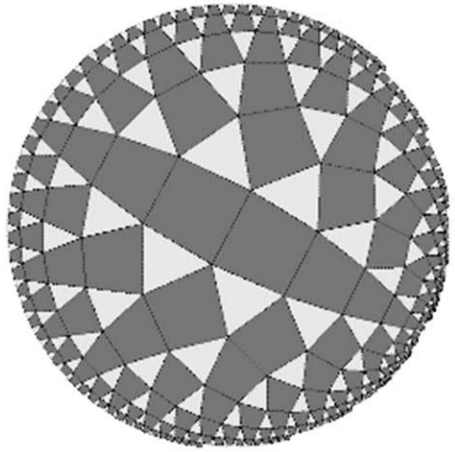


Stingrays
Potamotrygon spp.

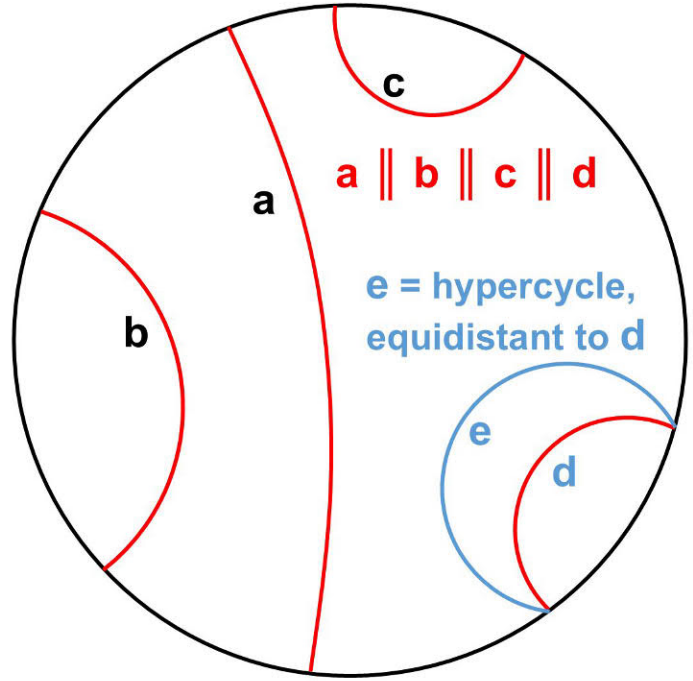


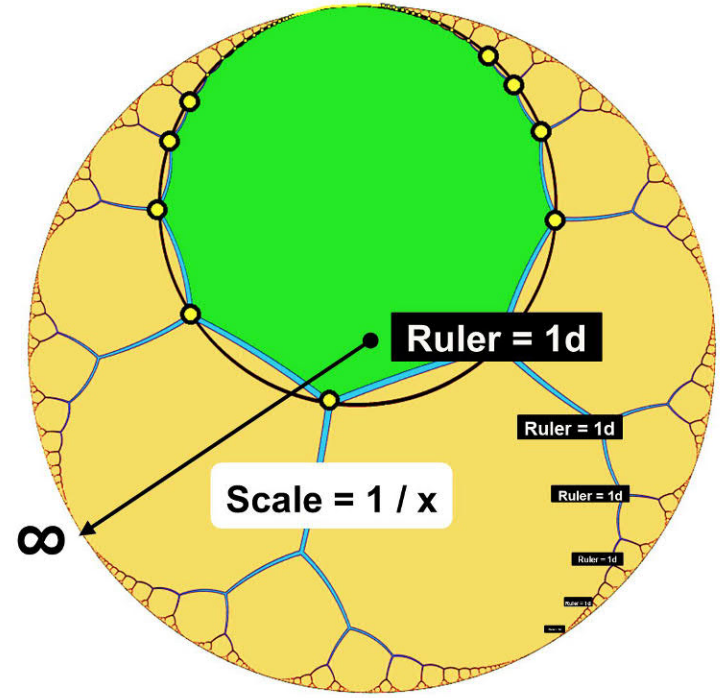
Math & Art : : Hyperbolic geometry ***f(x) = 1/x***

Biology : : Growth & Isauxesis



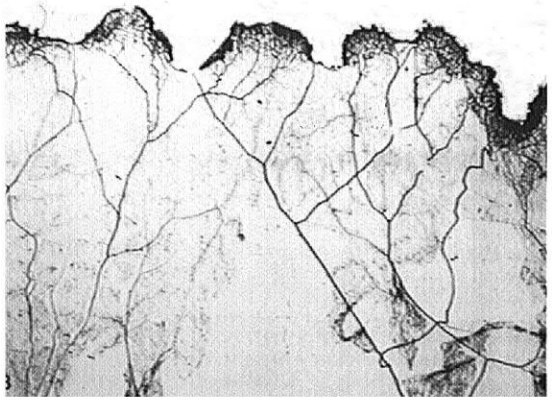
Optic neuron





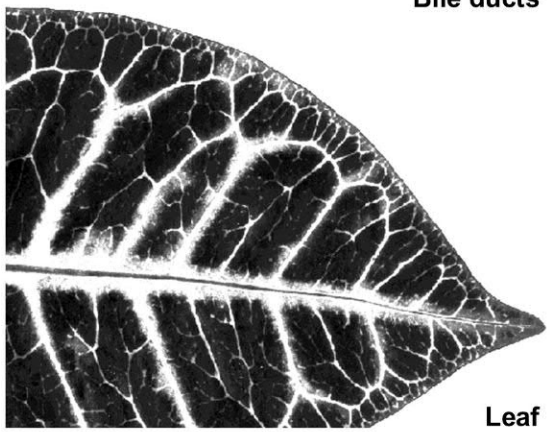
Bile ducts

Bronchi



Skin

Bile ducts

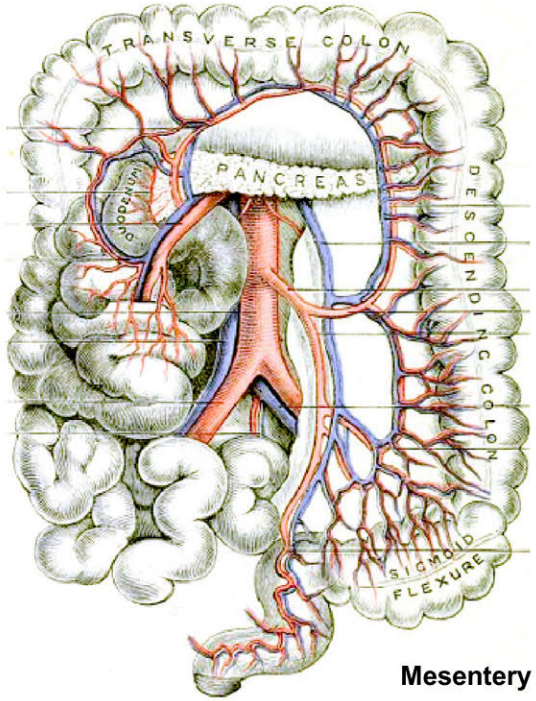


Leaf

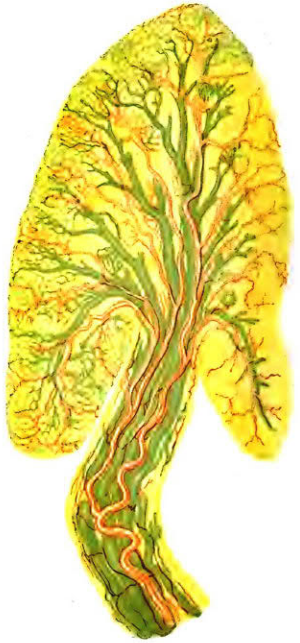
DEVELOPMENTAL ANGIOGENESIS & THE BIOPHYSICS OF VASCULAR NETWORK FORMATION

Marc Gottlieb
MD

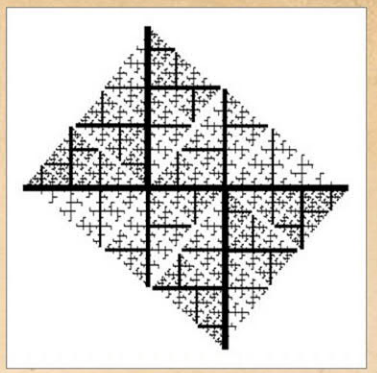
Phoenix
Arizona

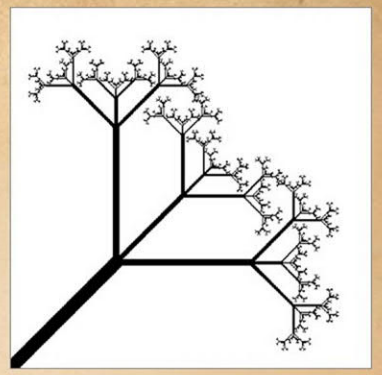


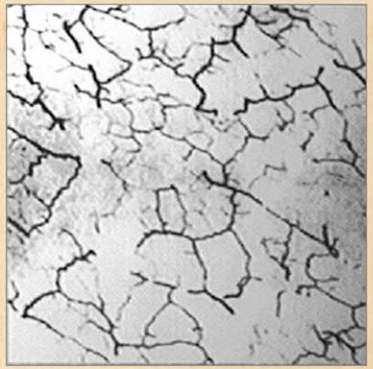
Mesentery

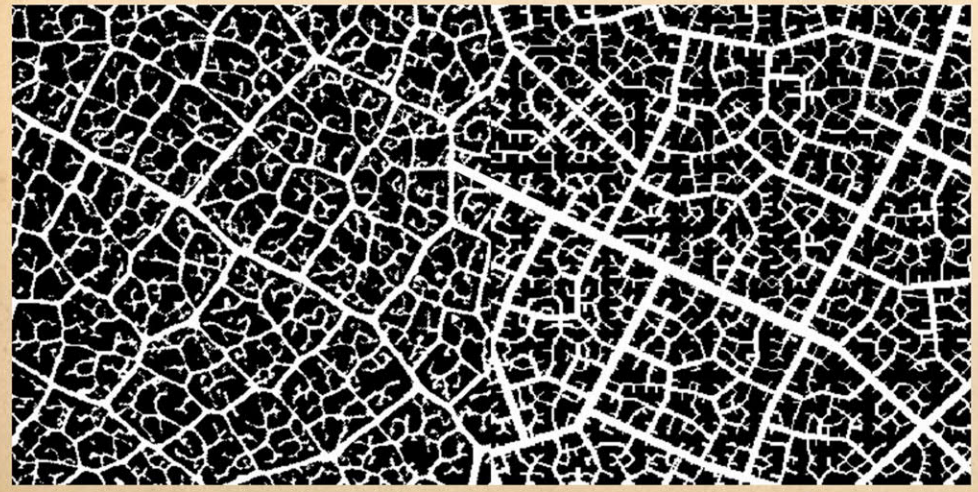


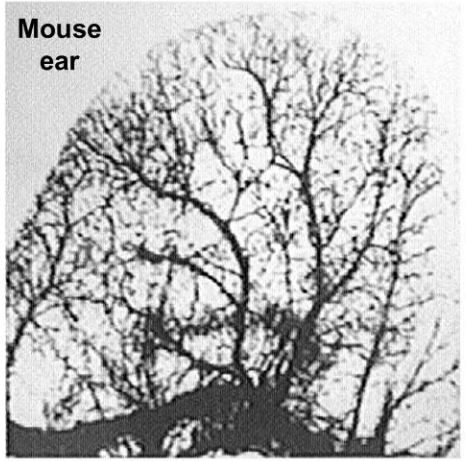
Ovary

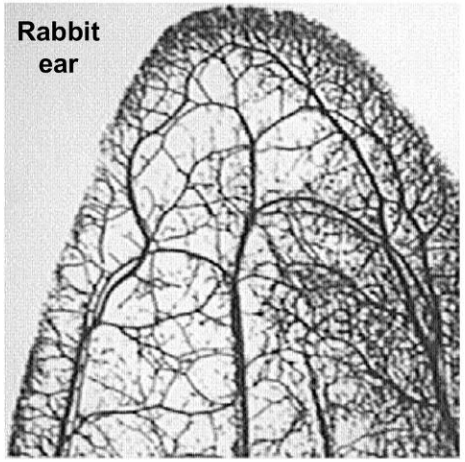


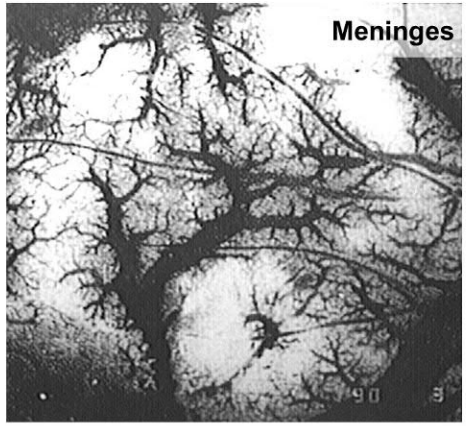


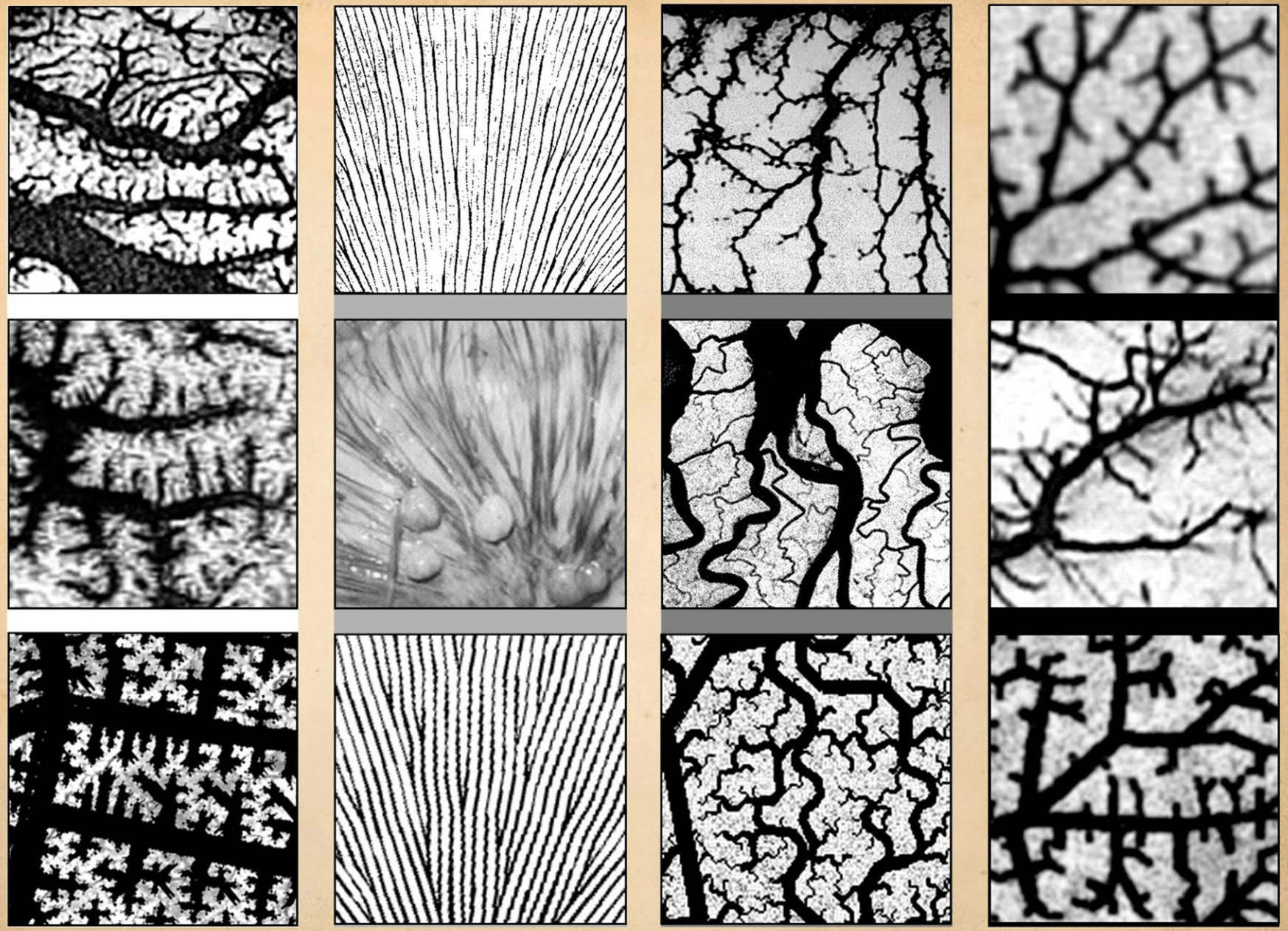


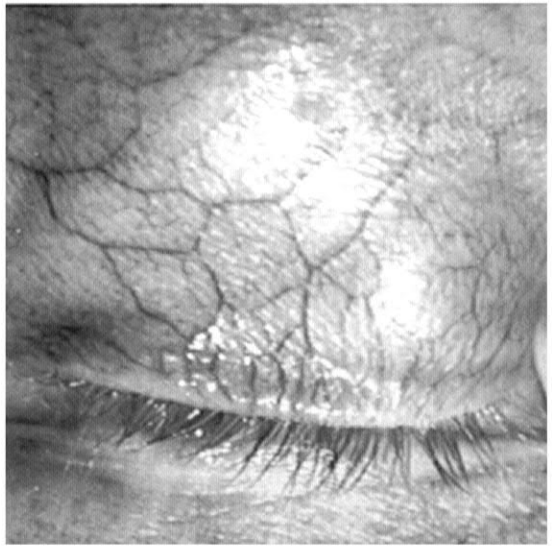


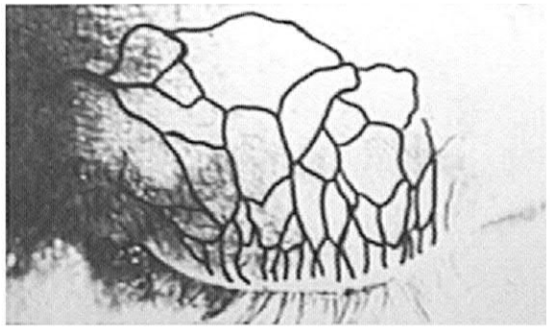

Mouse
ear


Rabbit
ear

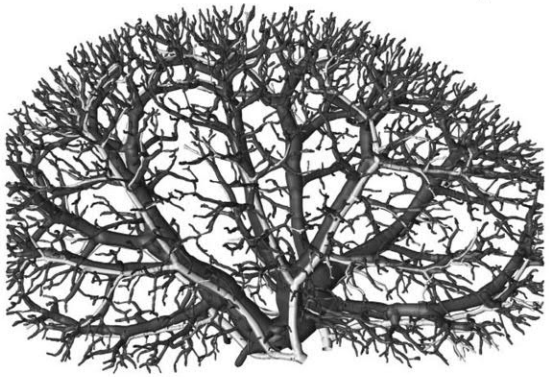

Meninges



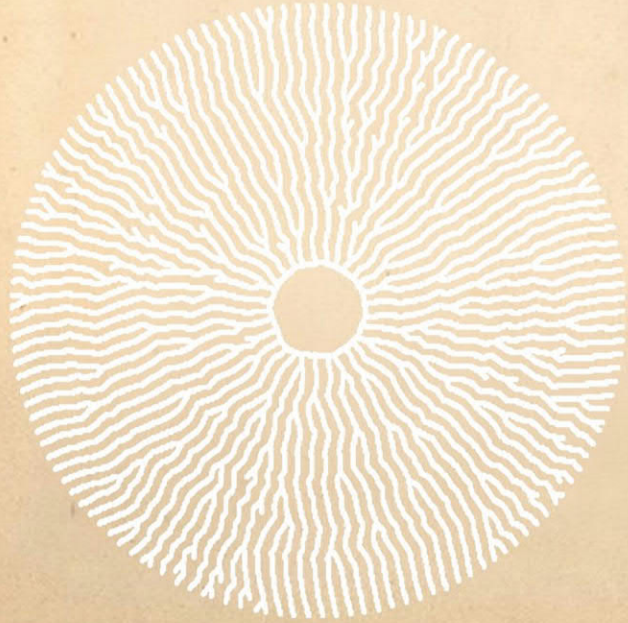


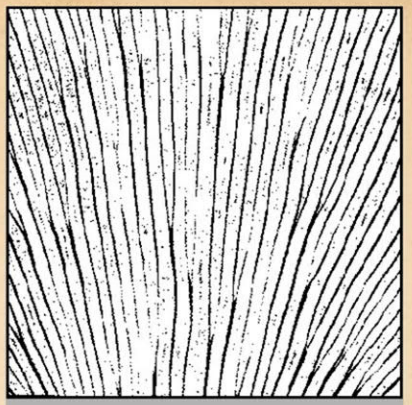


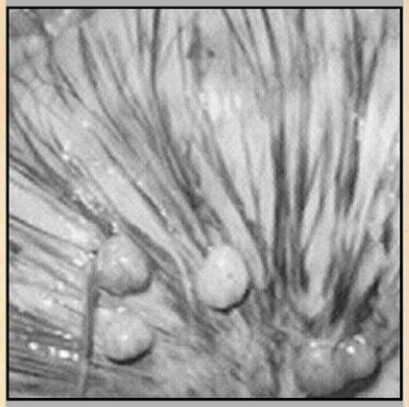
Eyelid



Kidney



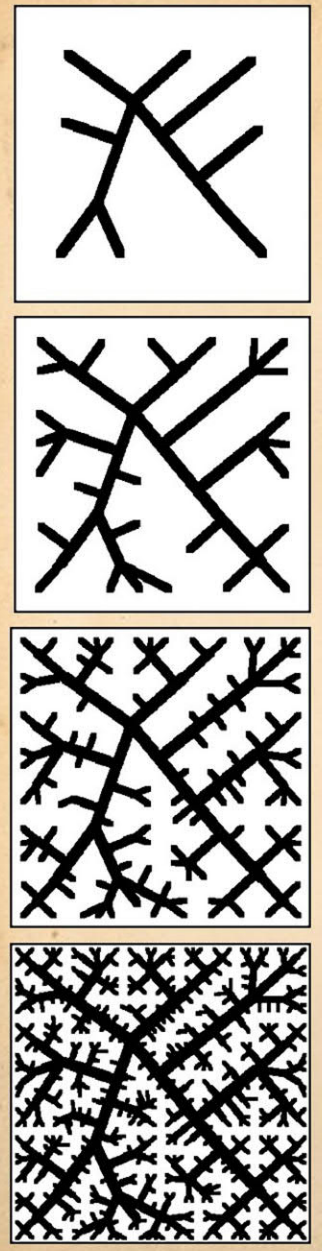




Angiogenesis is a life-and-death critical process.

VEGF & VEGFR genes are highly conserved across major taxa.

Multicellular life is impossible without angiogenesis and VEGF.

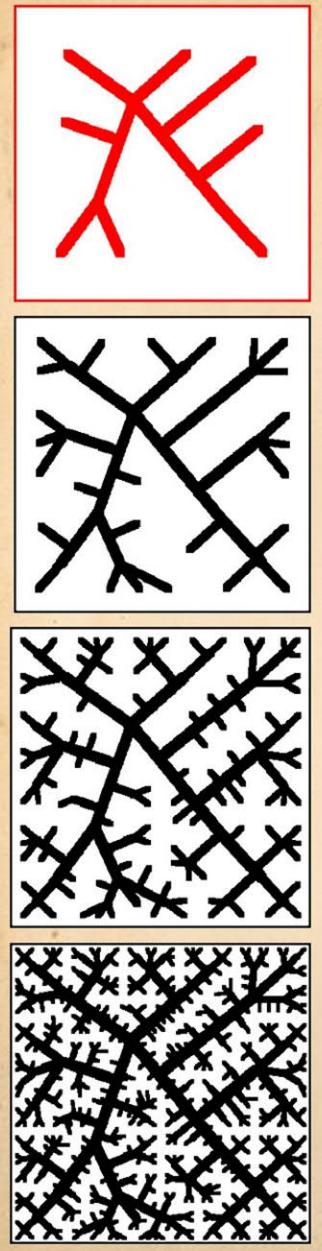


How do VEGF and the machinery of angiogenesis operate to create a vascular network?

How little information is needed to engineer vascular networks, and how efficient is the process?

How does the system ensure that the life-and-death accuracy of the process is conserved?

What are the geometries and topologies of vascular networks, and why do other structures share them?



How do VEGF and the machinery of angiogenesis operate to create a vascular network?

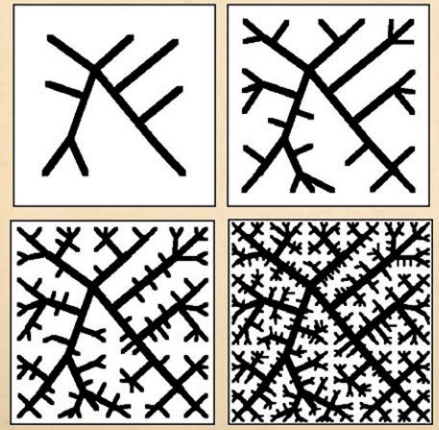
Developmental angiogenesis is a closed loop control system.

It depends on angiocytes, other cells, oxygen, angiogenic factors, and diffusion.

Angiogenesis is a purely reactive process, an error correcting response to perturbations created by growth.

THE VT MODEL OF ANGIOGENESIS

The Vascular neT Model of the Formation of Blood Vessels and Vascular Networks



ARIMEDICA

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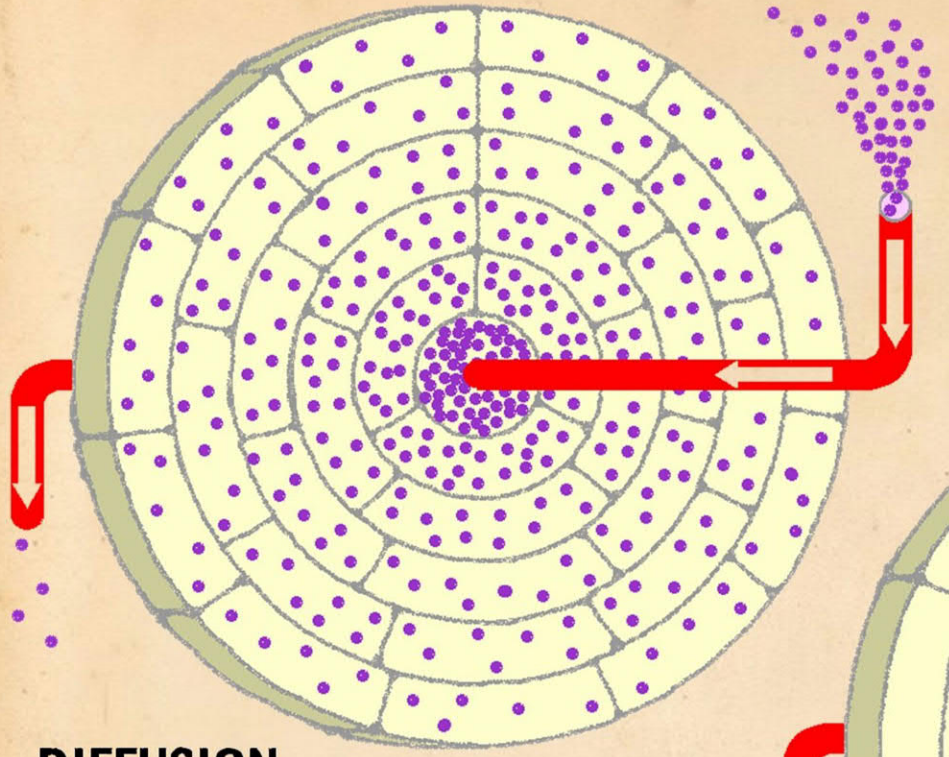
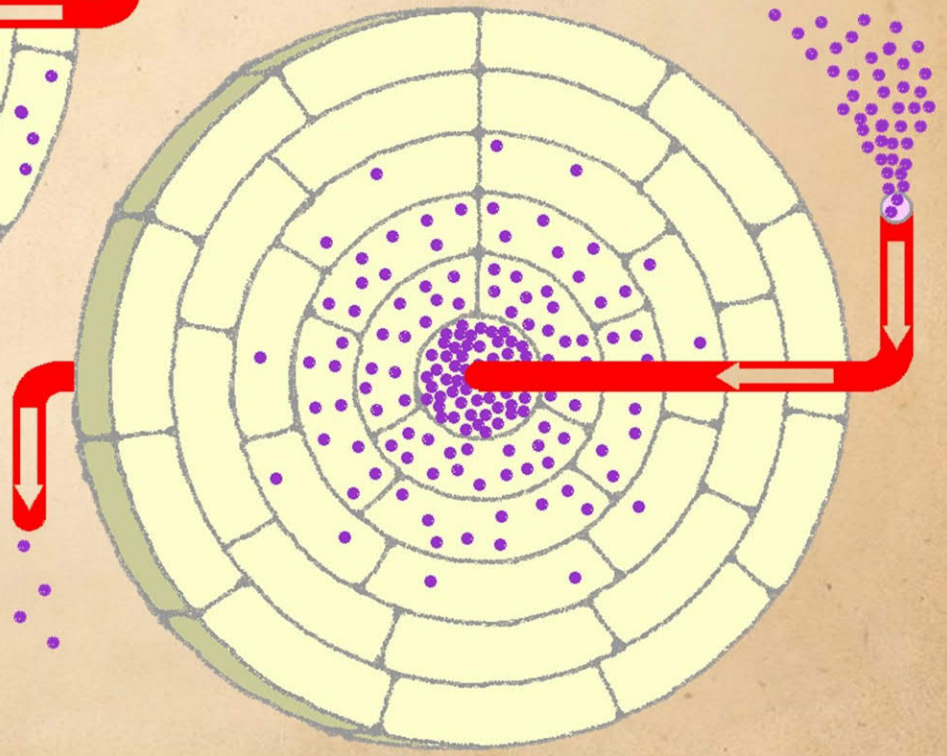
ANGIOGENIC PHYSIOLOGY - THE REAL NATURE

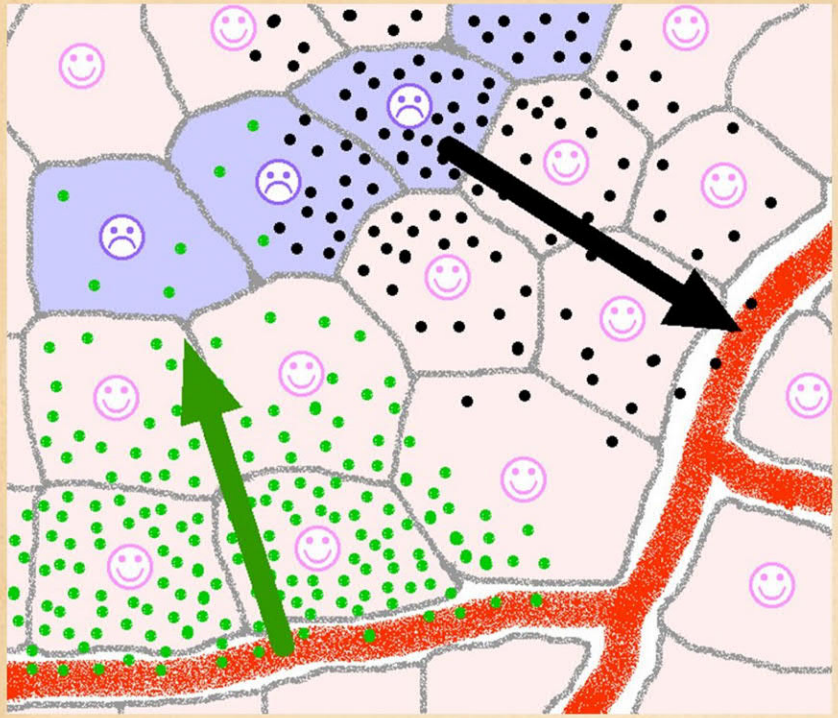


DIFFUSION
WITHOUT
CONSUMPTION



DIFFUSION
WITH
CONSUMPTION

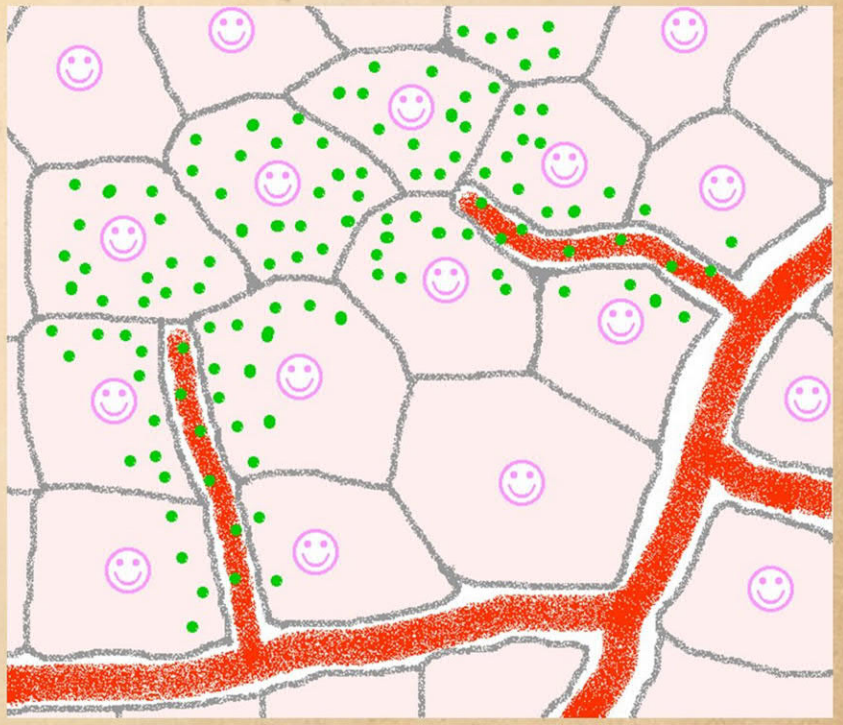
ANGIOGENIC PHYSIOLOGY - THE REAL NATURE



FORWARD DIFFUSION
OF OXYGEN

BACK DIFFUSION OF
ANGIOGENIC FACTORS

NEW
BLOOD VESSELS
RESTORE
OXYGEN SUPPLY



Auxesis

αύξησις

Increase

Isauxesis

ισαύξησις

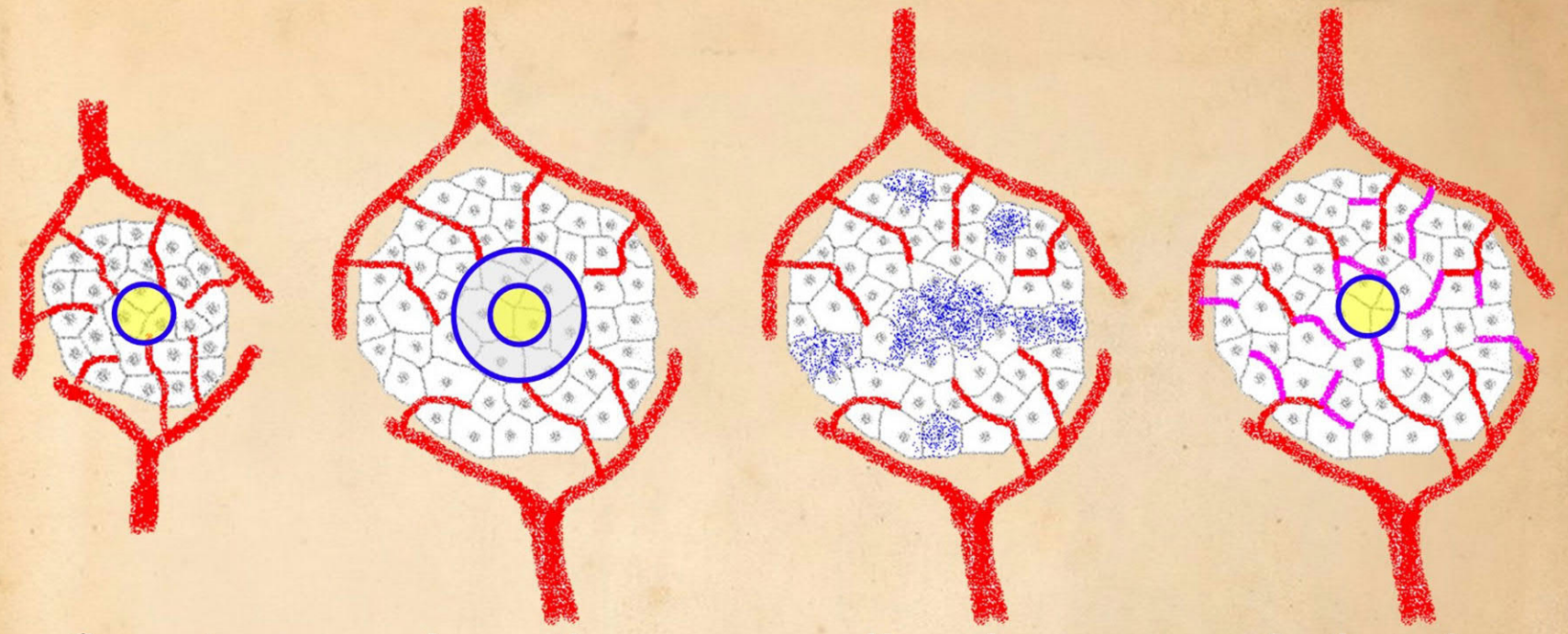
Equal increase

Once an embryonic structure is established, it grows at same rate as the host.

It is then part of the host for subsequent new structures that arise.

New structures arise from cells which are always at a base scale.

ANGIOGENIC PHYSIOLOGY - THE REAL NATURE

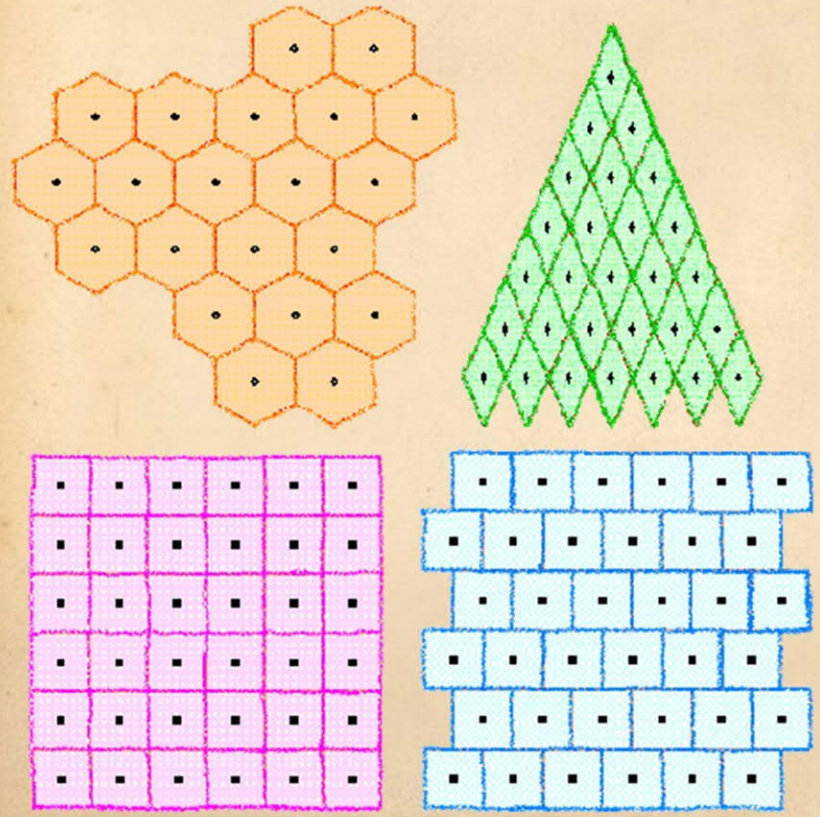


Current vessels	Isauxetic growth	Hypoxic cells	Angiogenic response
Short distances	Increased distances	Release AFs	Restored distances
Adequate oxygen	Inadequate oxygen	Tropic stimulus	Adequate oxygen

COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 1A

TISSUE & GROWTH MODELS

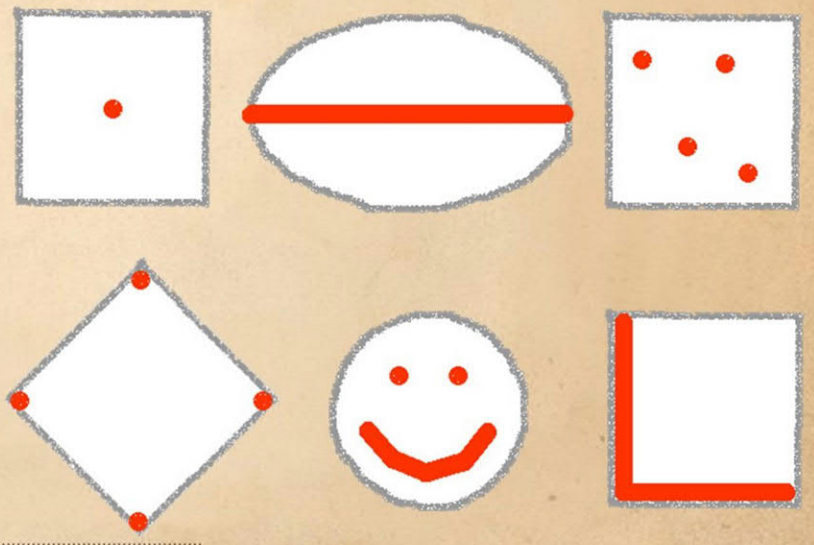


STEP 1

SETUP

Computer modeling of angiogenesis starts here.

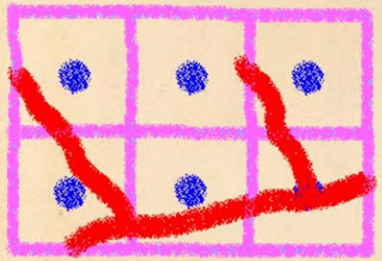
STEP 1B SEED VESSELS



COMPUTER ANGIOGENESIS - RECREATING NATURE

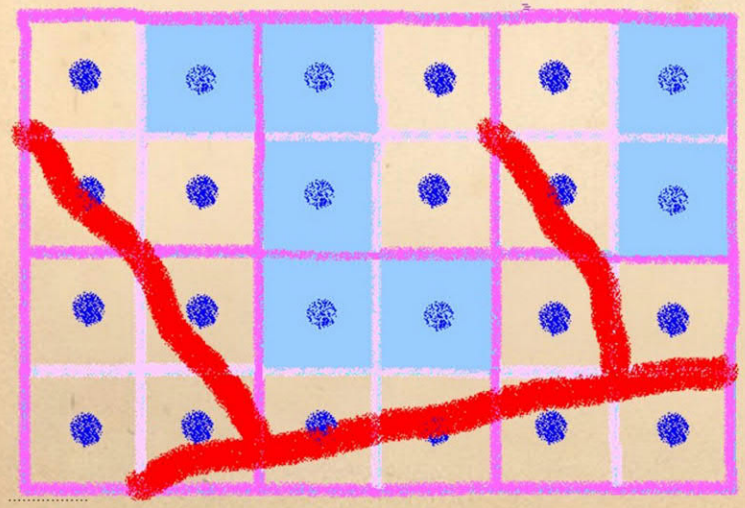
STEP 2
GROWTH

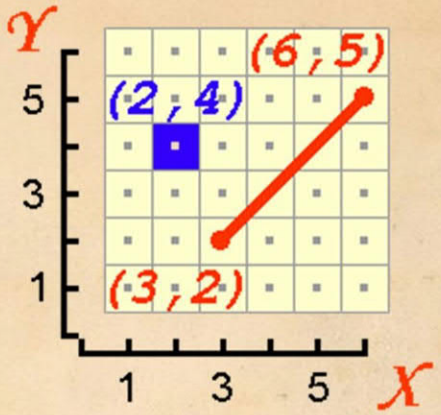
This is the start of the Main Loop
"ISAUXESIS"



STEP 2A

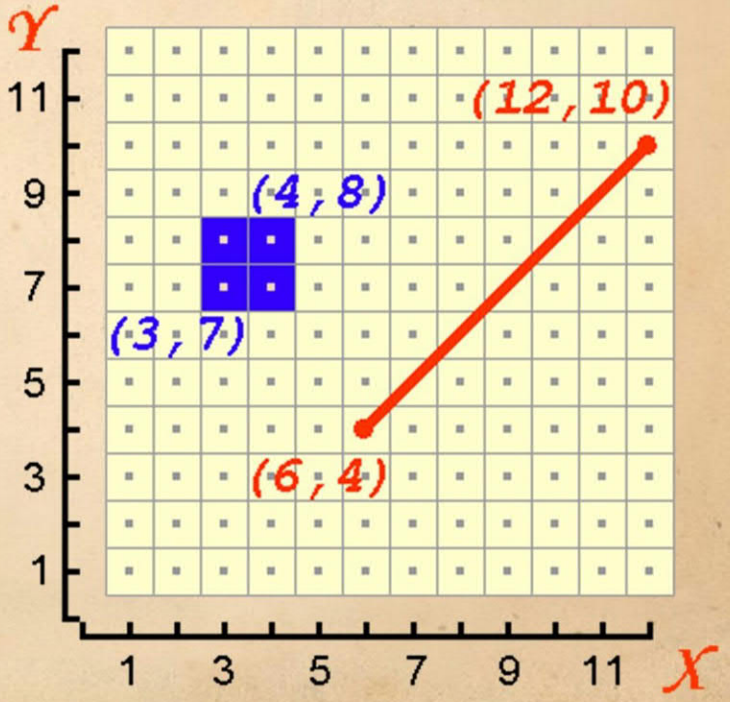
GROW THE TISSUE





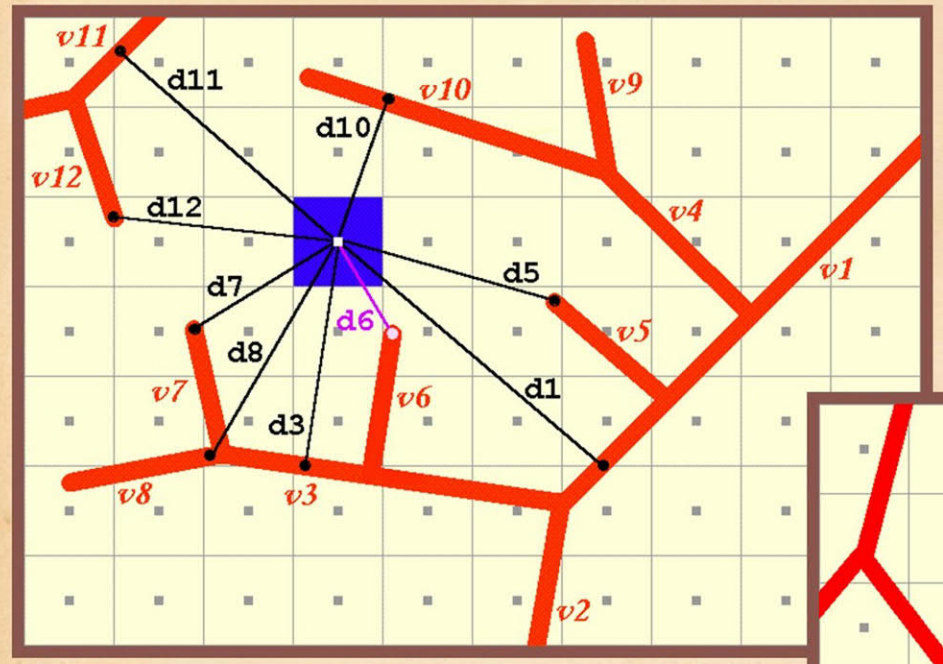
STEP 2B

MATCHING VESSEL GROWTH



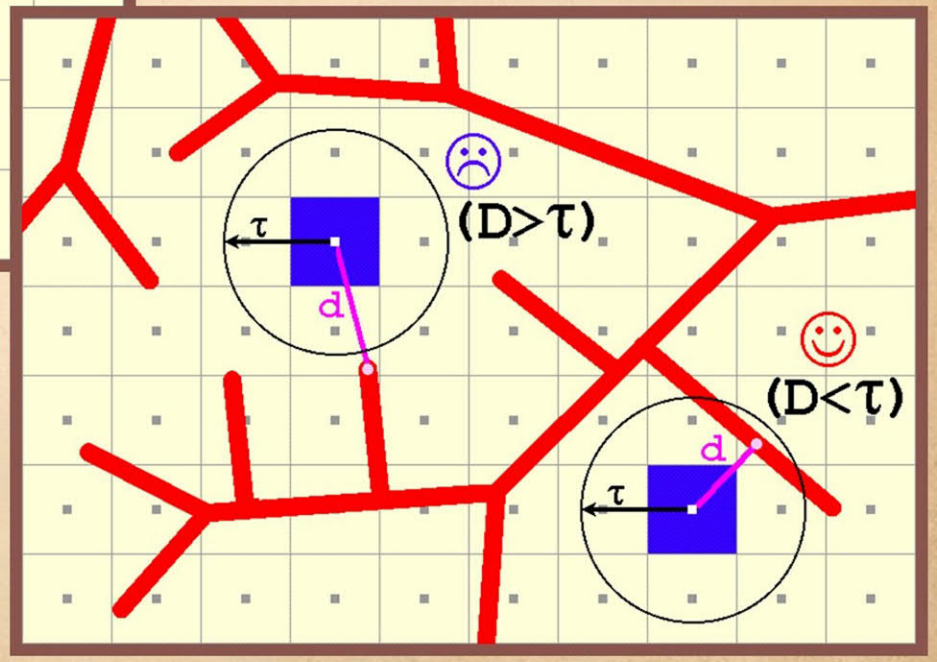
COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 3A FIND DISTANCE



STEP 3
ISCHEMIA TESTING

STEP 3B TEST FOR ISCHEMIA



Intrinsic Parameter # 1 τ

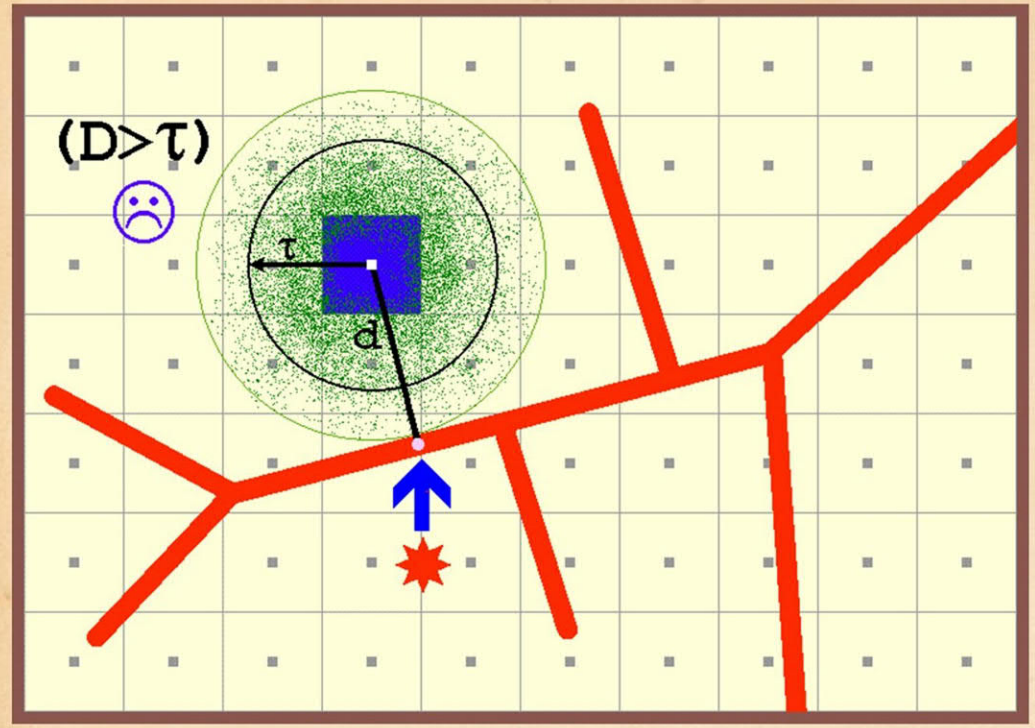
ischemia threshold

$D > \tau$

=

ischemia

COMPUTER ANGIOGENESIS - RECREATING NATURE



STEP 4
SPROUTING

STEP 4A **ORIGINATE**

parameters
=
one + *three*

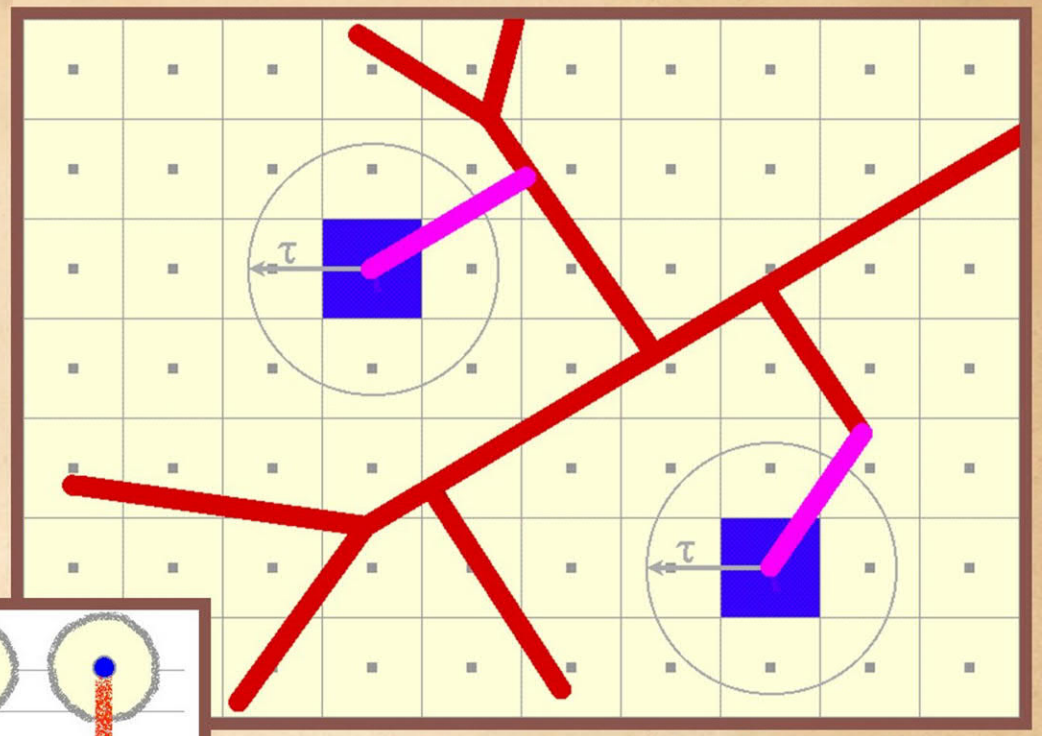
G	**Intrinsic Parameter # 1**	**Intrinsic Parameter # 2**	**Intrinsic Parameter # 3**
Extrinsic Element # 0	**τ**	**R**	**A**
growth model	ischemia threshold	vessel reach	multiple sprout zone

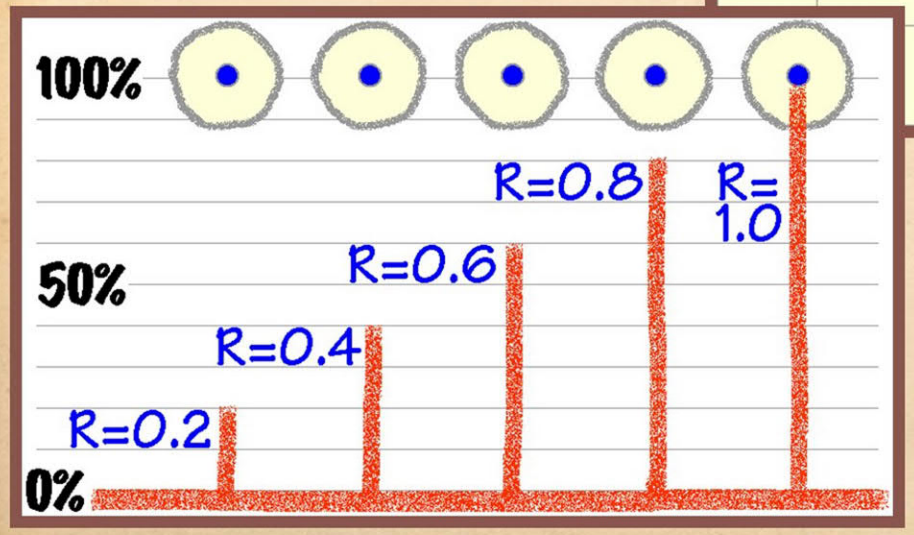
COMPUTER ANGIOGENESIS - RECREATING NATURE

STEP 4
SPROUTING

STEP 4B
VESSEL REACH

$$0 \leq R \leq 1$$





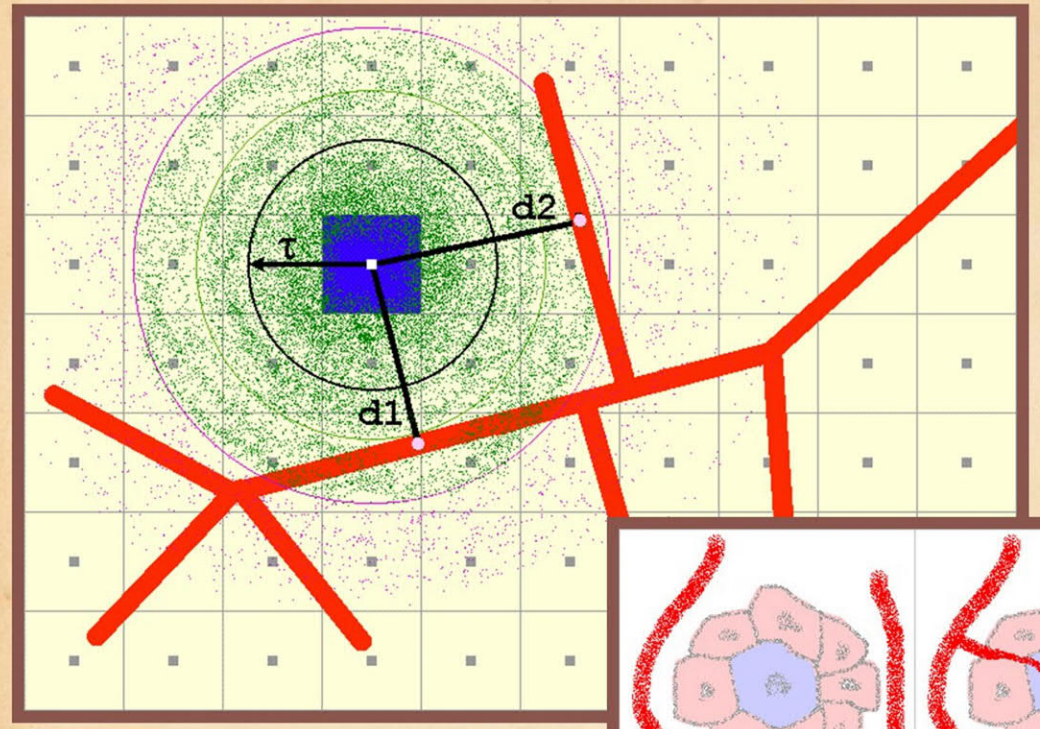
two constructs

Intrinsic Parameter # 2

vessel reach

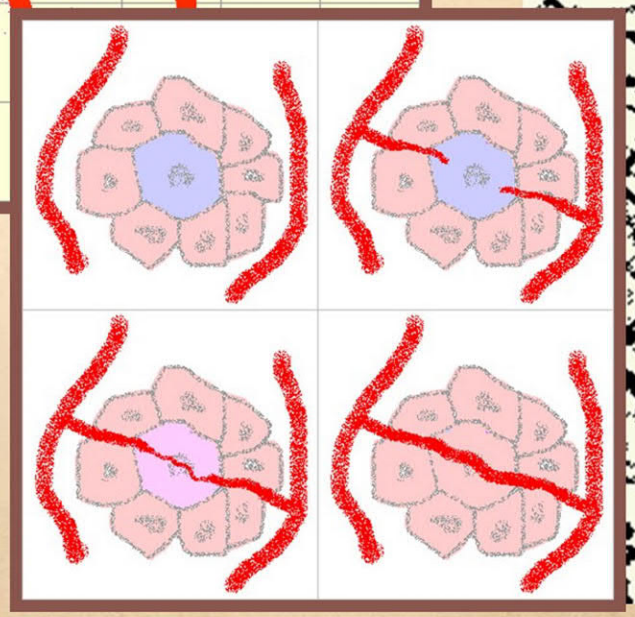
R

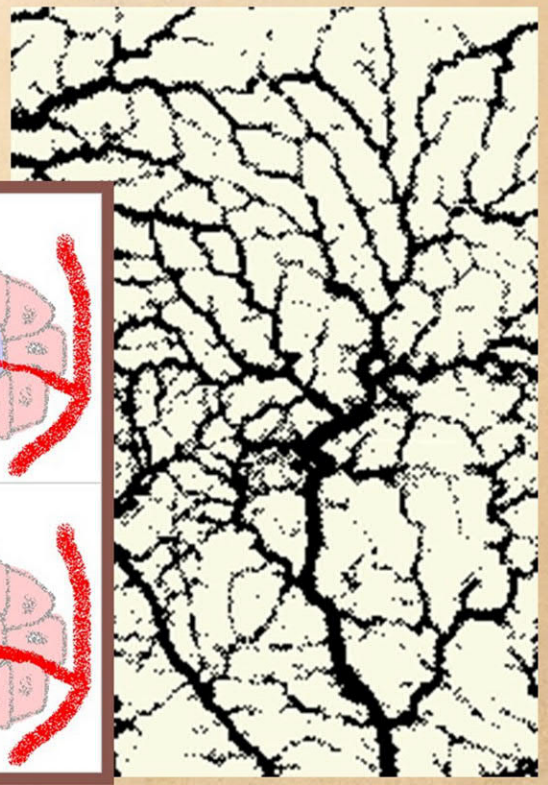
COMPUTER ANGIOGENESIS - RECREATING NATURE



STEP 4
SPROUTING

STEP 4C **MULTIPLES**





anastomoses

Intrinsic Parameter # 3

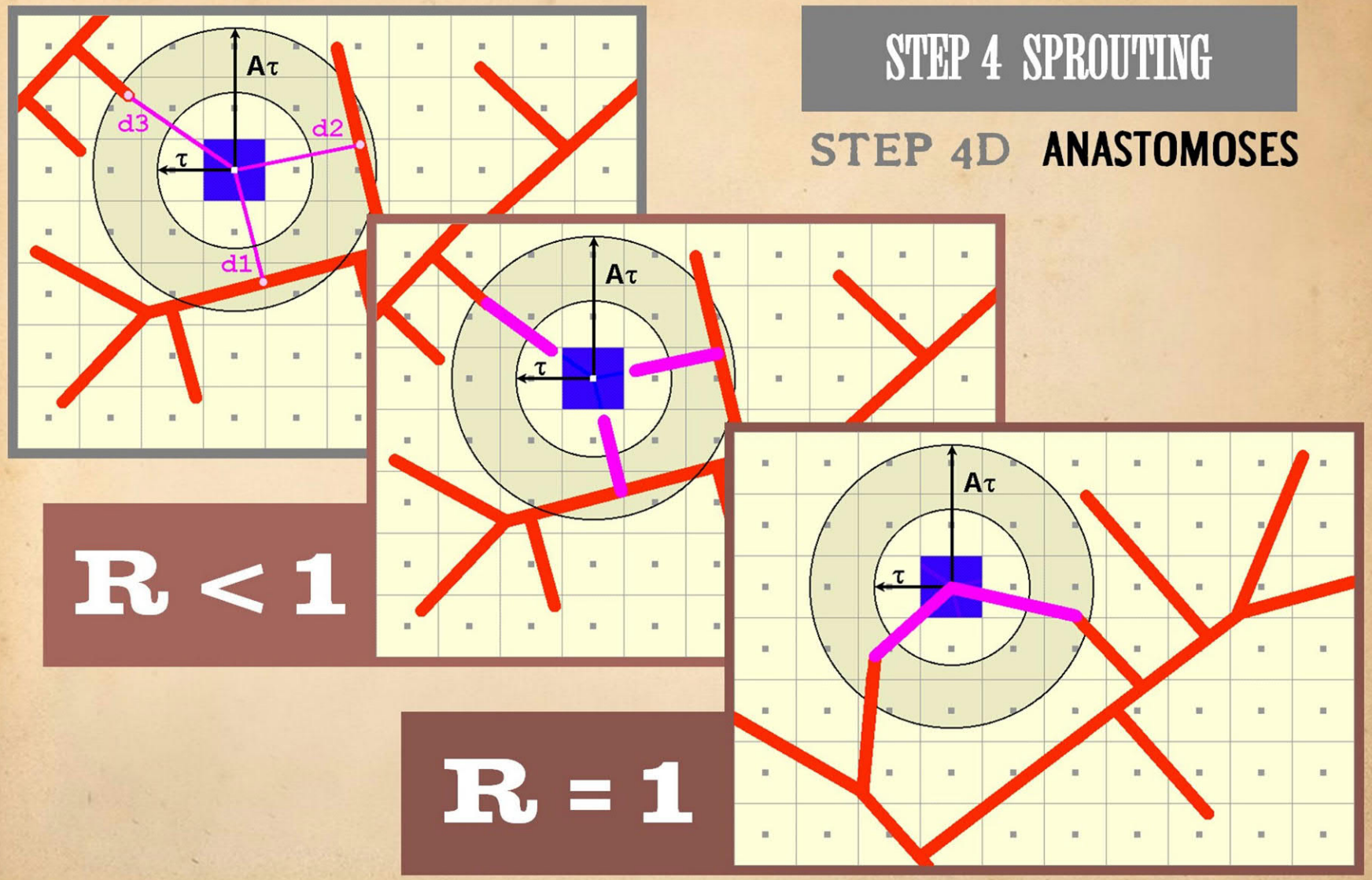
A

multiple sprout zone

COMPUTER ANGIOGENESIS - RECREATING NATURE

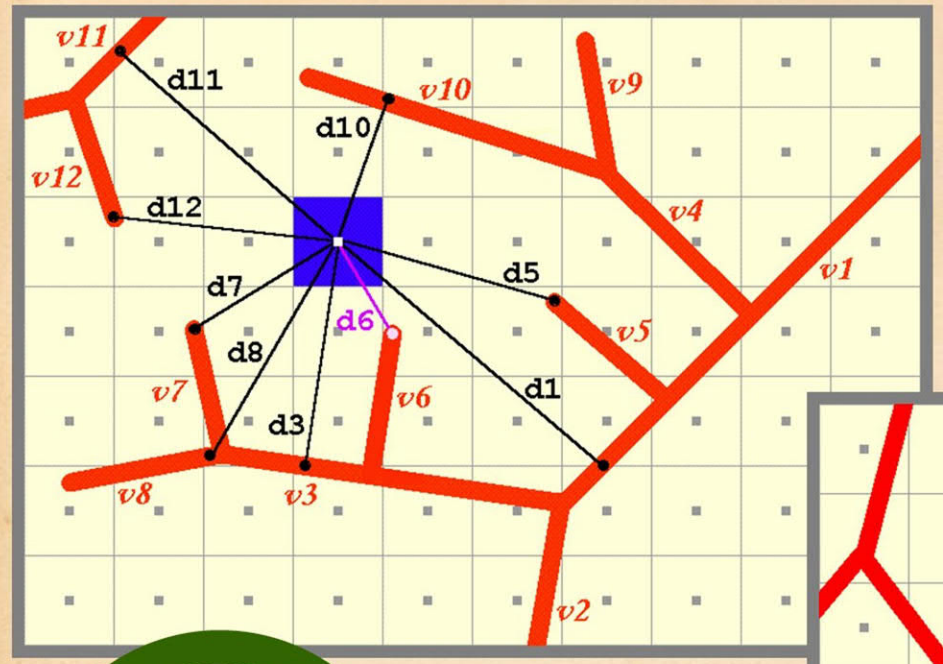
STEP 4 SPROUTING

STEP 4D ANASTOMOSES



COMPUTER ANGIOGENESIS - RECREATING NATURE

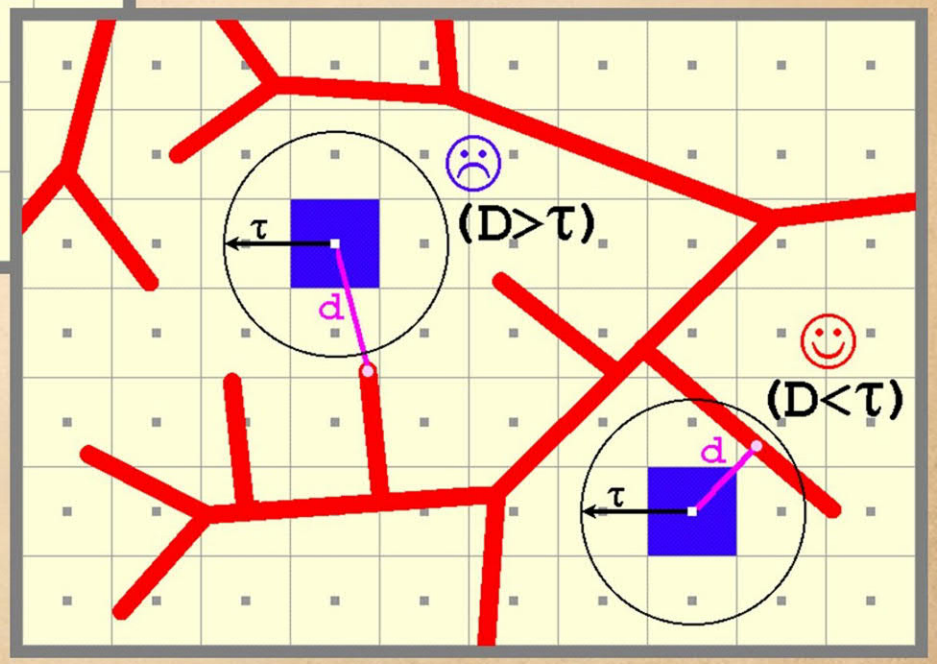
STEP 3A FIND DISTANCE

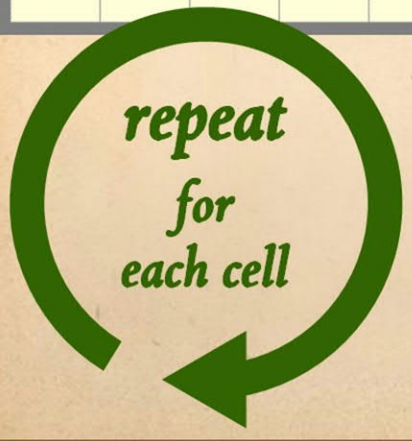


STEP 3 ISCHEMIA TESTING

iterate: cell - by - cell

STEP 3B TEST FOR ISCHEMIA





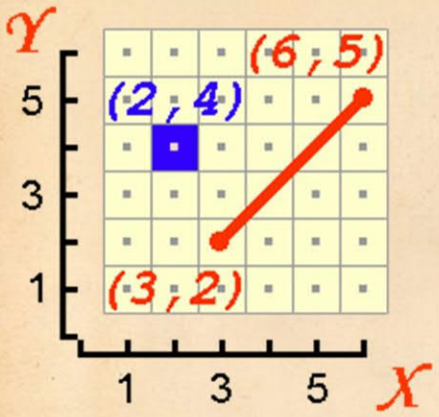
$$D > \tau$$

=

ischemia

COMPUTER ANGIOGENESIS - RECREATING NATURE

Back to the start of the Main Loop



STEP 2A

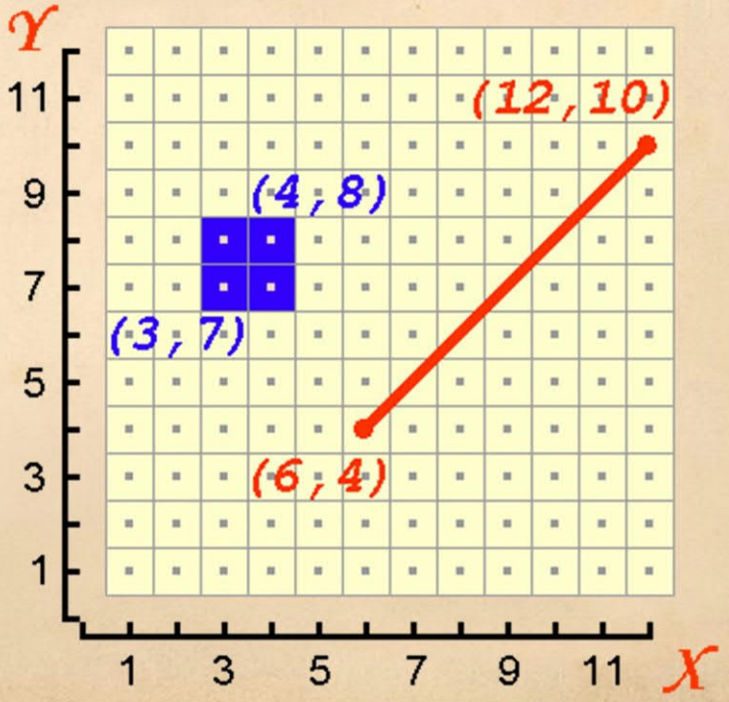
GROW THE TISSUE

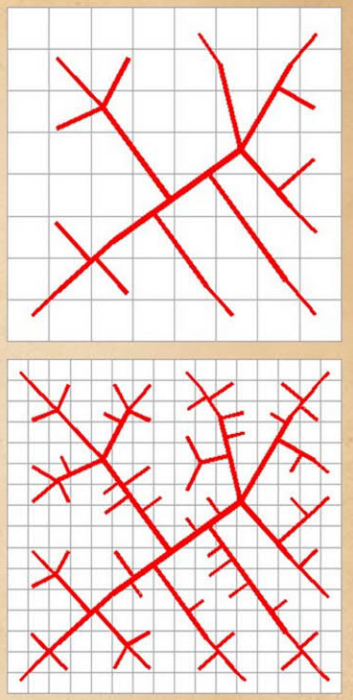
STEP 2B

MATCHING VESSEL GROWTH

iterate the growth cycle

STEP 2 GROWTH

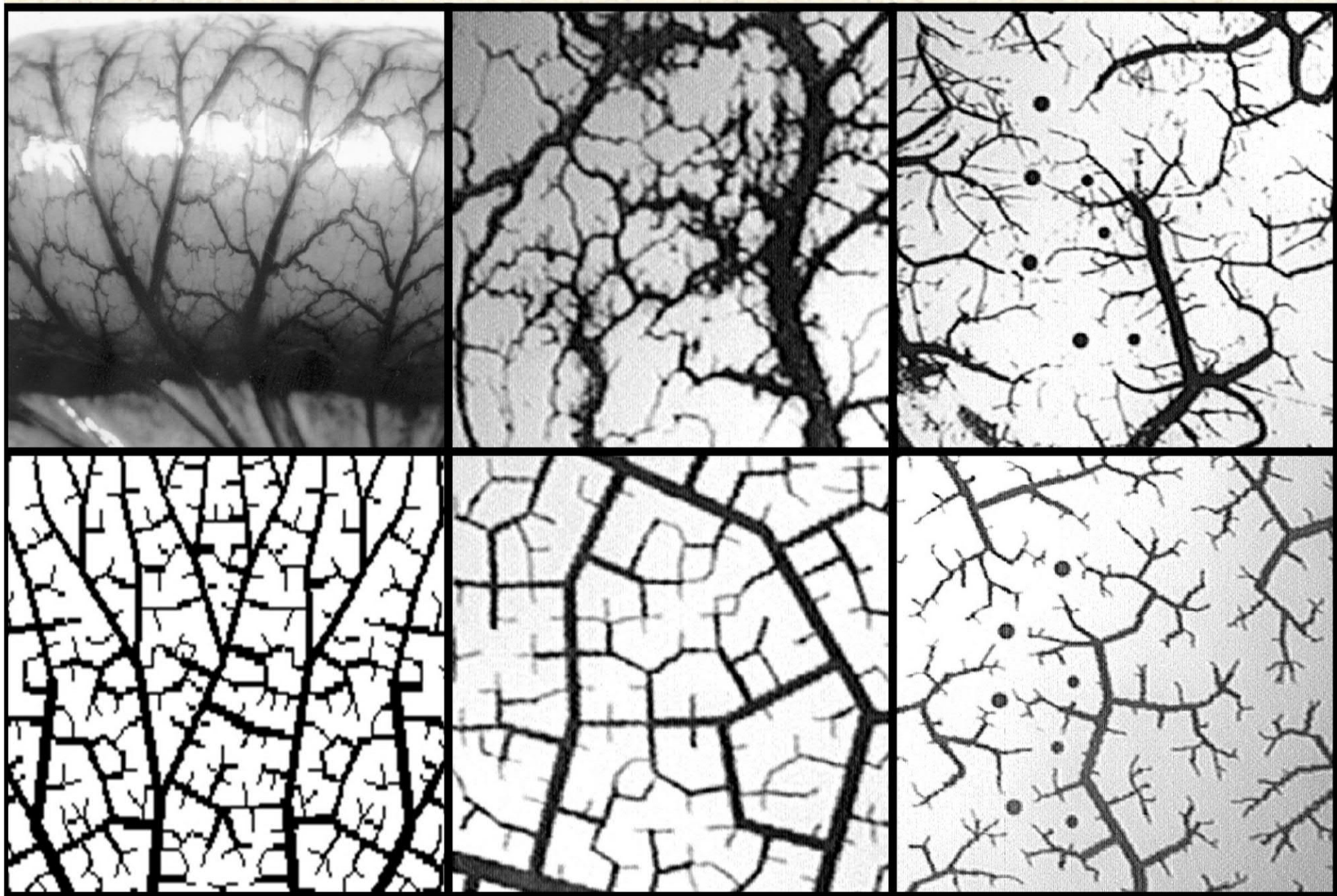




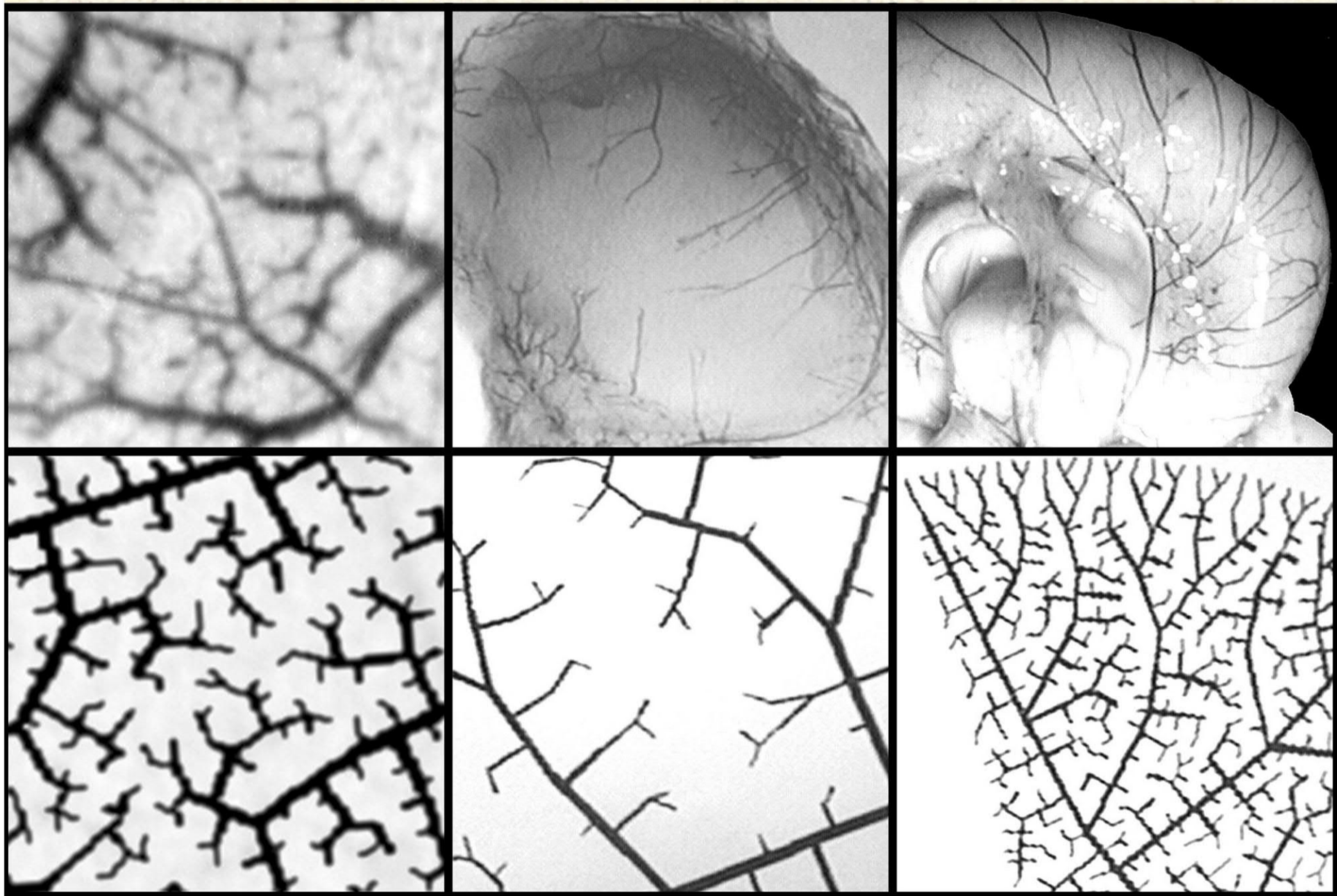
repeat

a new generation

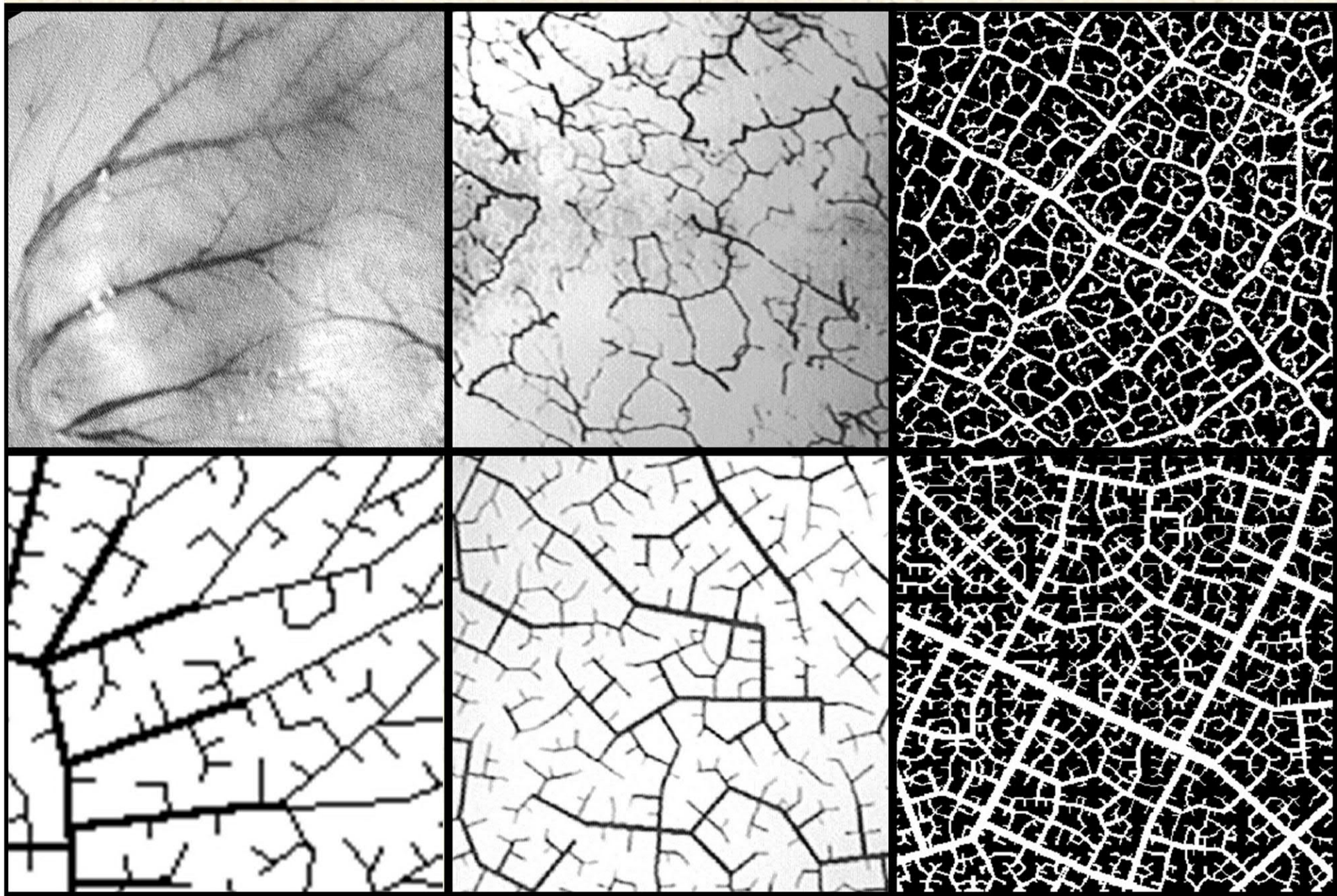
Real Vessels & Computer Vessels :: Side-by-Side

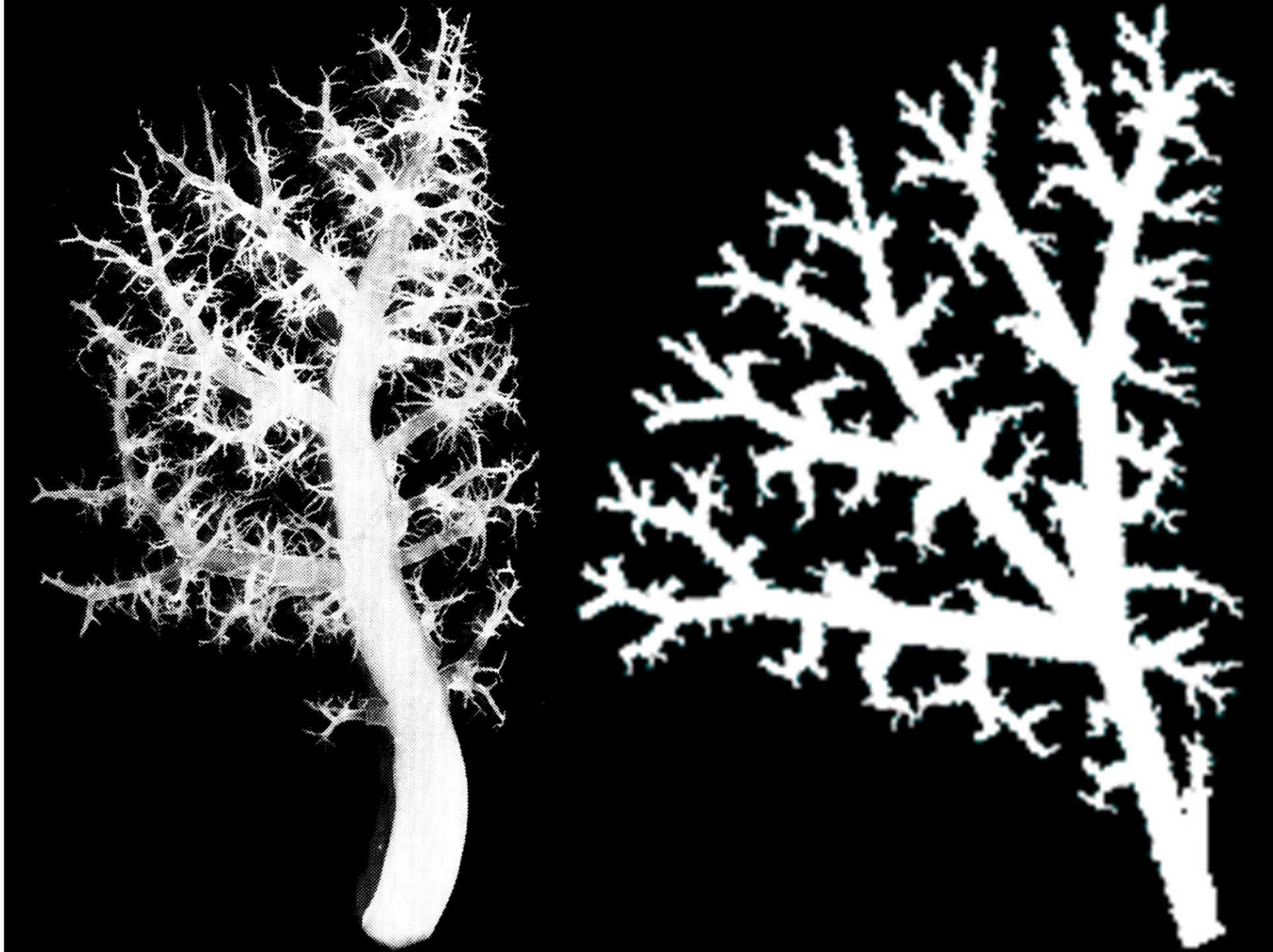


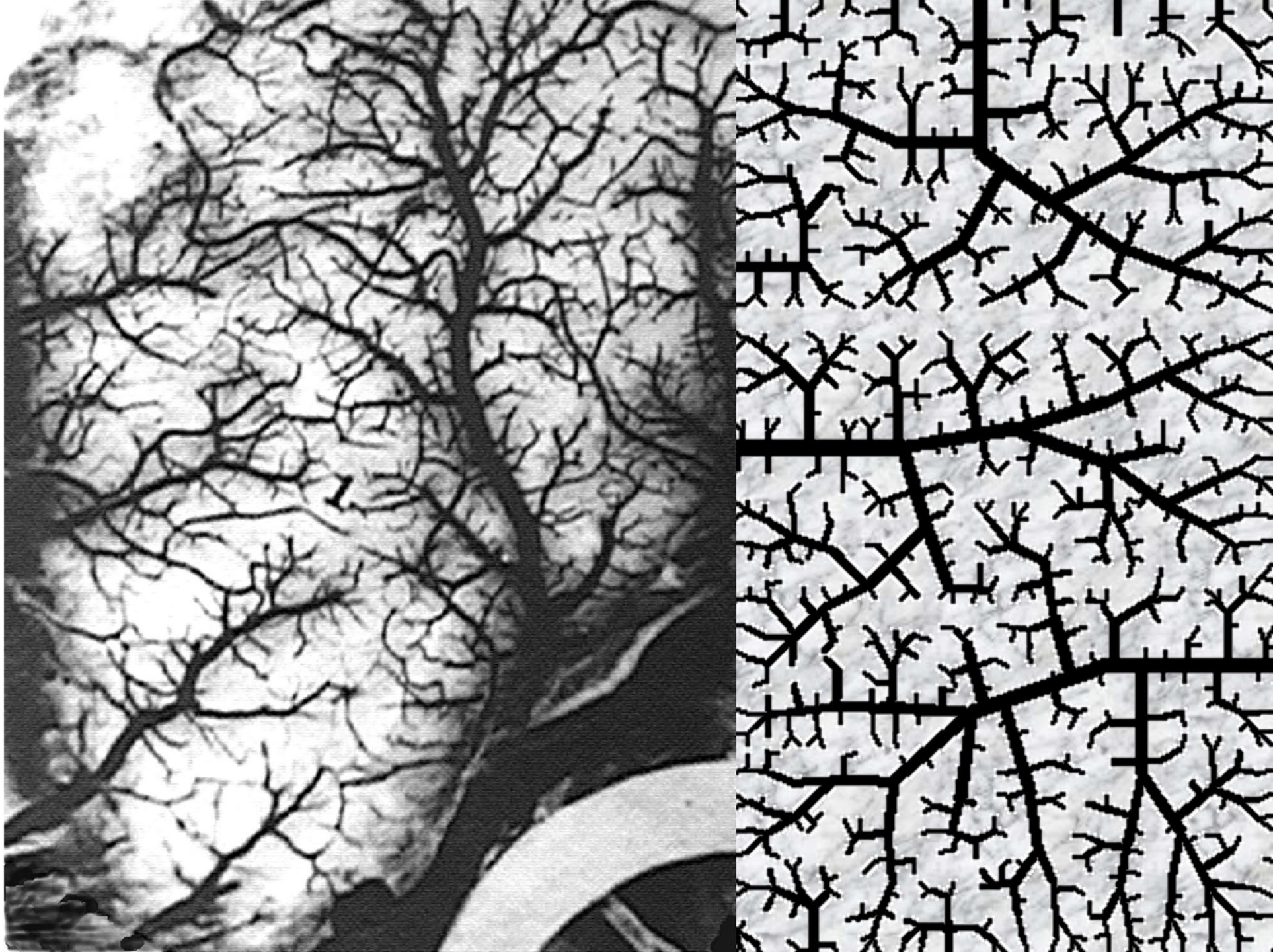
Real Vessels & Computer Vessels :: Side-by-Side



Real Vessels & Computer Vessels :: Side-by-Side





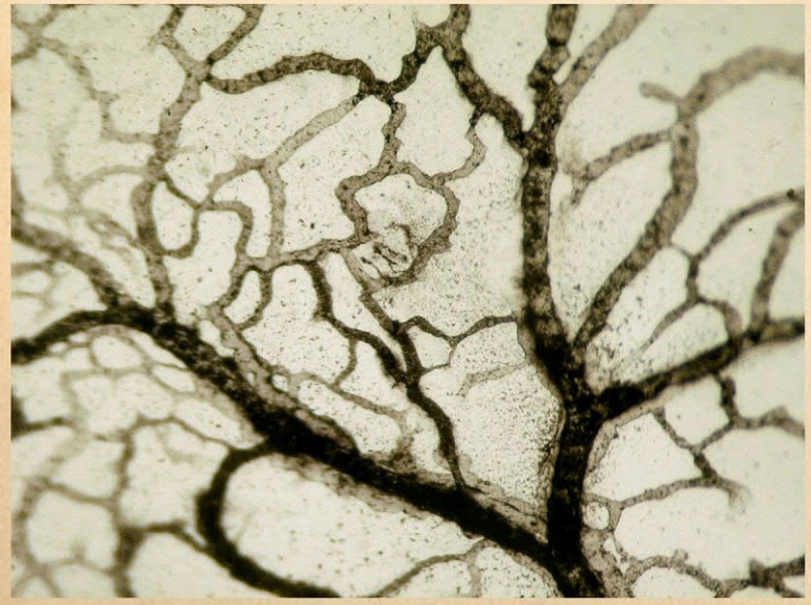


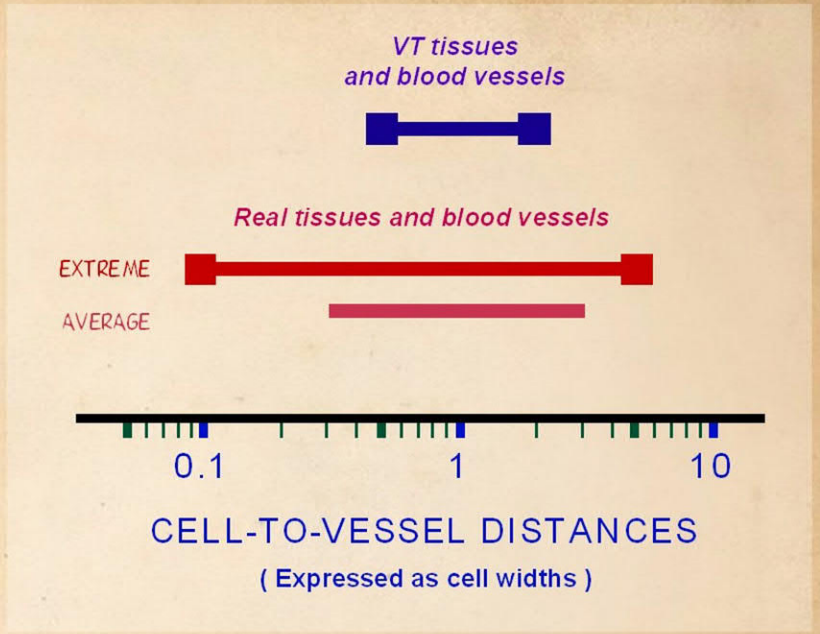
Arteries and veins

Capillaries

Vessel diameters

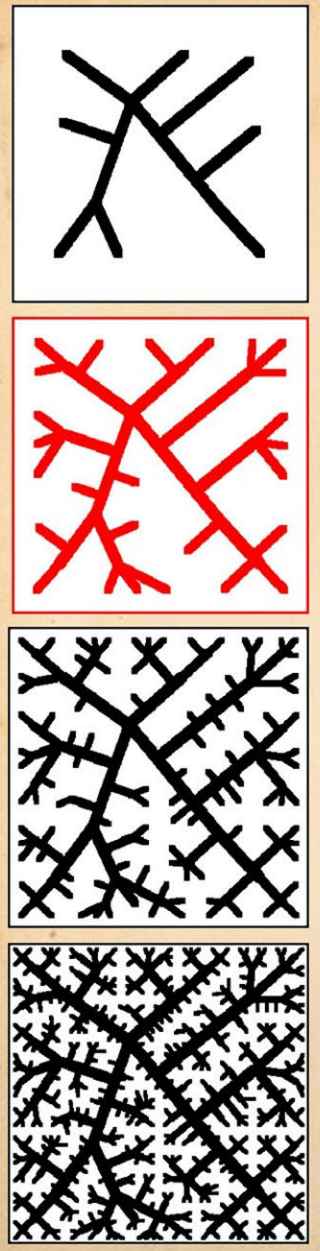
2D versus 3D



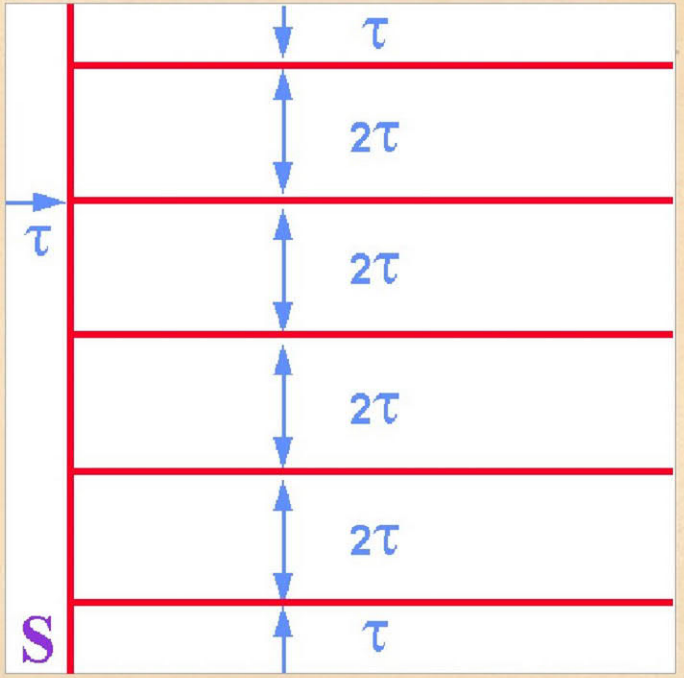


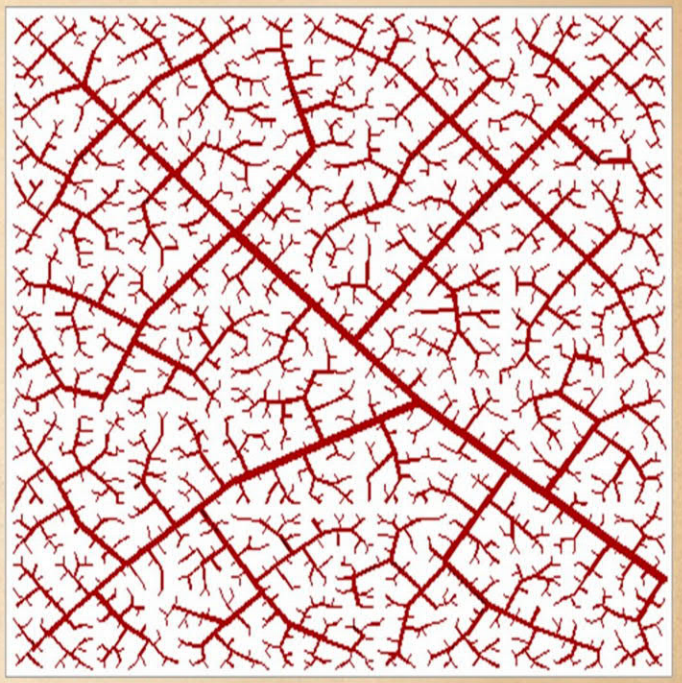
Realistic parameter choices closely match real cell-to-vessel distances.

VT = "Vascular neT" model

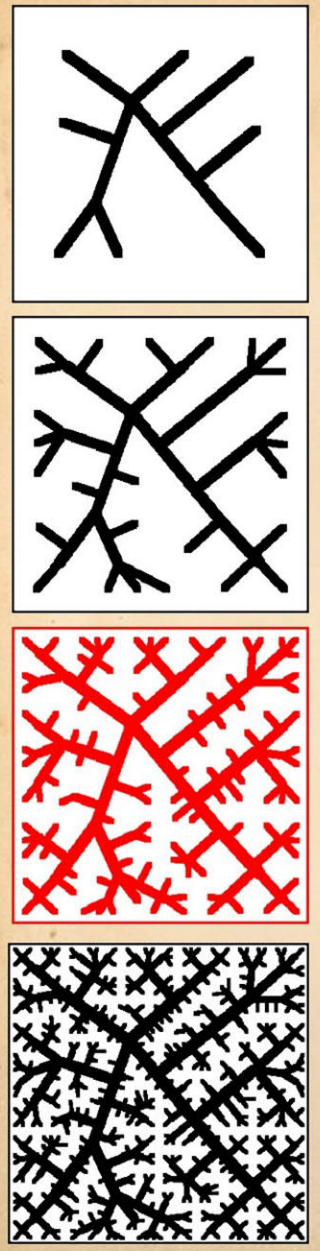


How little information is needed to engineer vascular networks, and how efficient is the process?

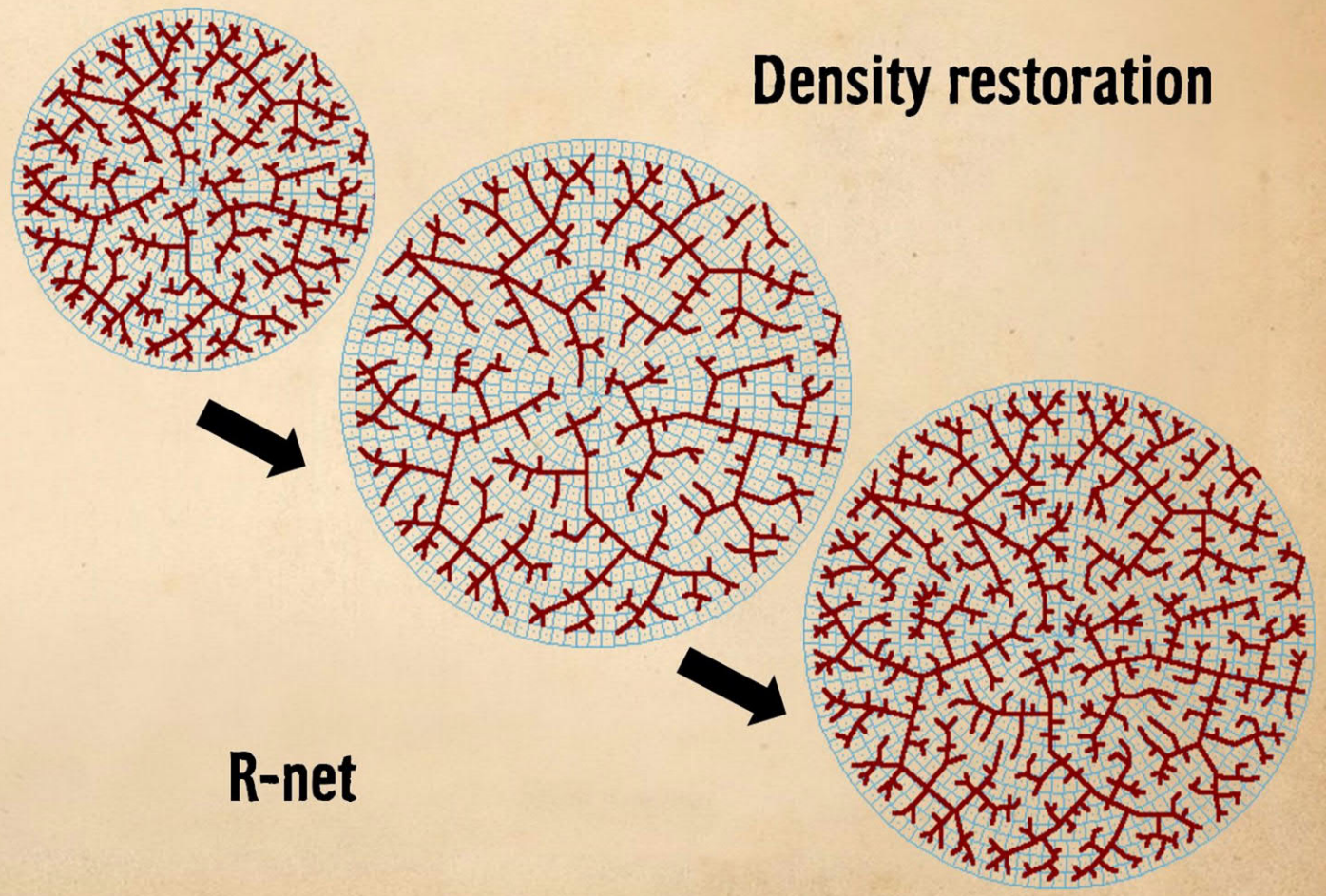


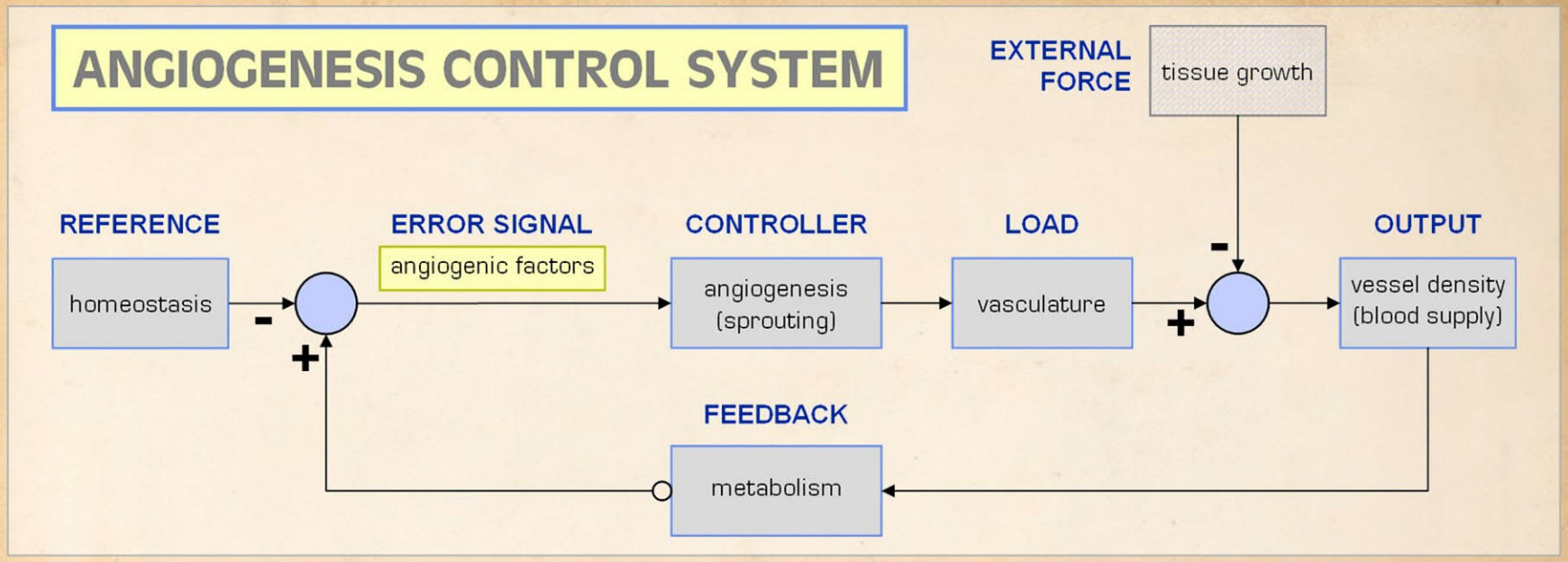


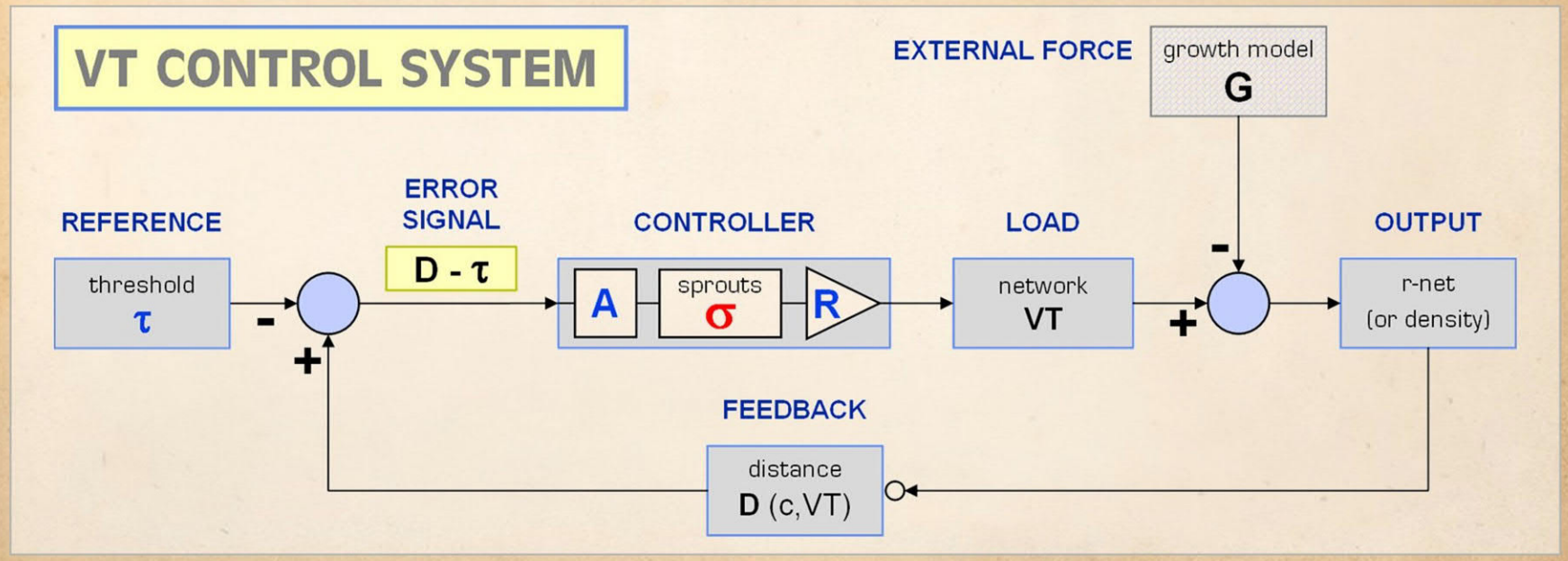
Length ratios $\approx$ 1

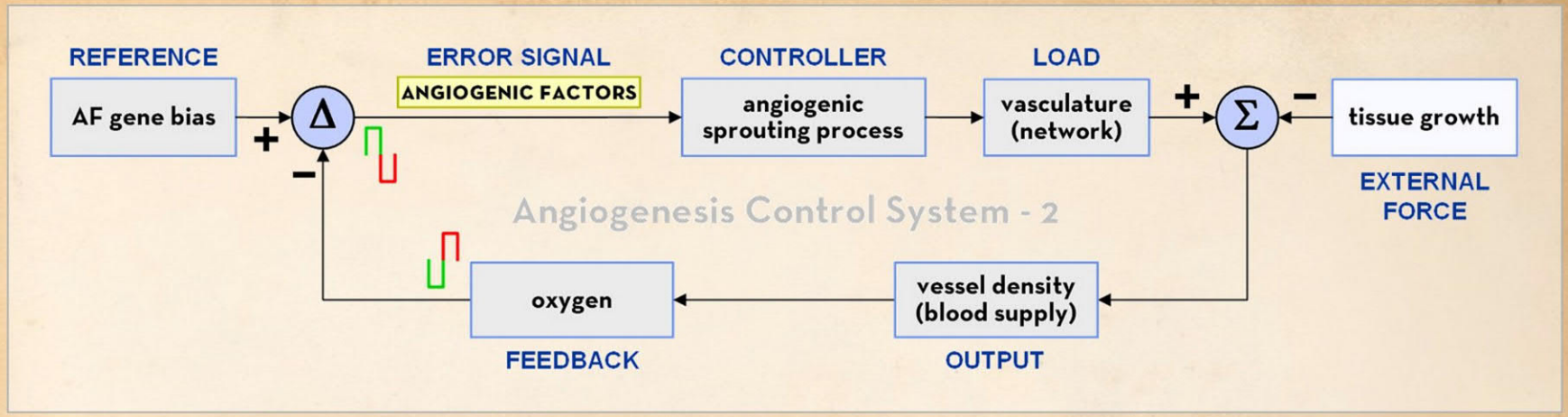


How does the system ensure that the life-and-death accuracy of the process is conserved?




ANGIOGENESIS CONTROL SYSTEM
EXTERNAL FORCE
tissue growth
REFERENCE
homeostasis
ERROR SIGNAL
angiogenic factors
CONTROLLER
angiogenesis (sprouting)
LOAD
vasculature
OUTPUT
vessel density (blood supply)
FEEDBACK
metabolism


VT CONTROL SYSTEM
EXTERNAL FORCE
growth model
G
REFERENCE
threshold
τ
ERROR SIGNAL
D - τ
CONTROLLER
A
sprouts
σ
R
LOAD
network
VT
OUTPUT
r-net
(or density)
FEEDBACK
distance
D (c,VT)

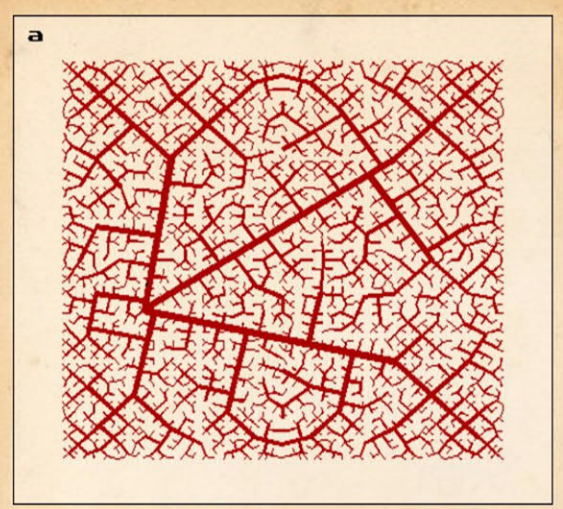


promoter = vegf

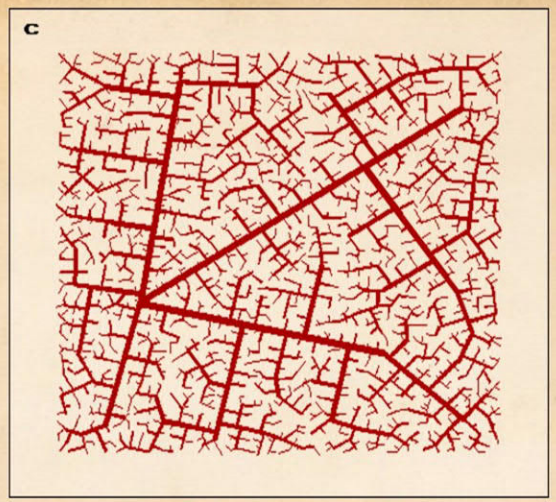
inhibitor = oxygen

Elements of the Control Systems

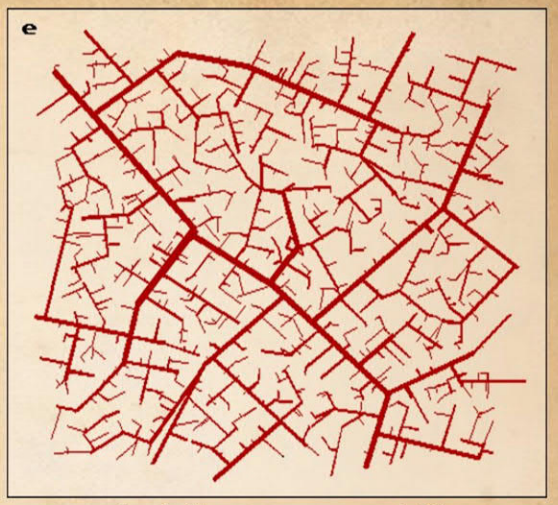
ANGIOGENESIS	GENERAL	VT
oxygen	feedback	distance D(c,VT)
correct oxygen (vegf gene bias)	system reference	threshold τ
angiogenic factors	error signal	D - τ
sprouting process	controller	sprouting, A, R
vascular network	load	VT network
r-net, blood supply	output	r-net, vessel density
tissue growth	external perturbation	growth model



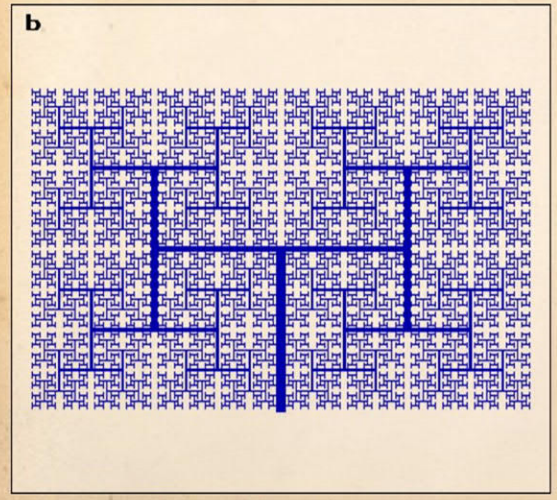
threshold $\tau = 0.7$
reach $R = 1.0$
sprout $P = 1.0$



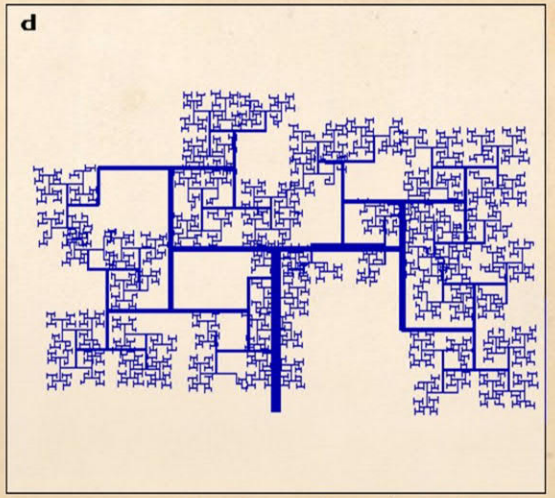
reach $R = 1 \pm 0.5$ *(efd)*
sprout $P = 0.5$



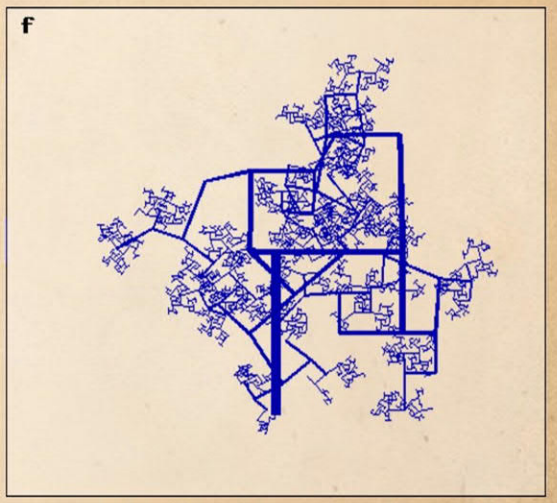
threshold $\tau = 0.14$ *to* 2.10 *(efd)*
reach $R = 1 \pm 1.0$ *(efd)*
sprout $P = 0.25$



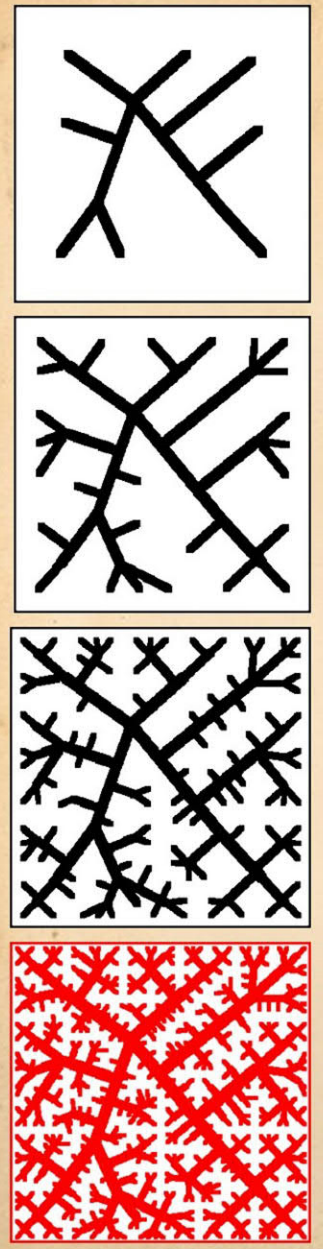
angles: left = right $= \pi/2$
scaling: left = right $= 1/\sqrt{2}$
sprout $P = 1.0$



scaling: left $= (1 \pm 0.5) \times 1/\sqrt{2}$ *(ngd)*
sprout $P = 0.95$

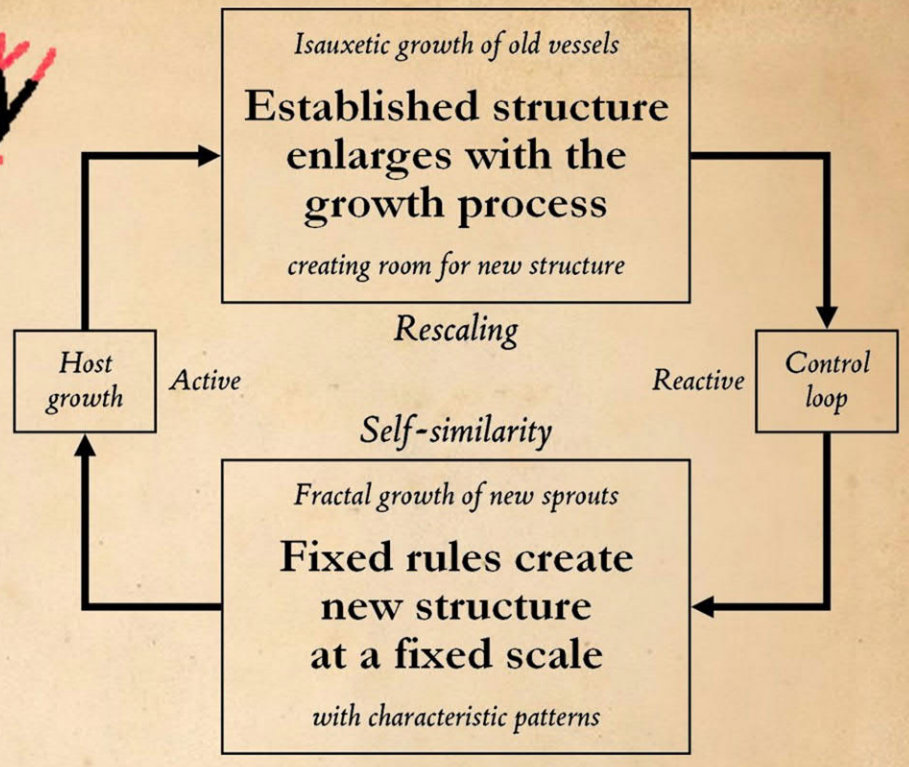


angles: left $= \pi/2 \pm \arctan(\sqrt{2})$ *(ngd)*
scaling: left $= 1/\sqrt{2} \pm 1/\sqrt{2}$ *(ngd)*
sprout $P = 0.90$



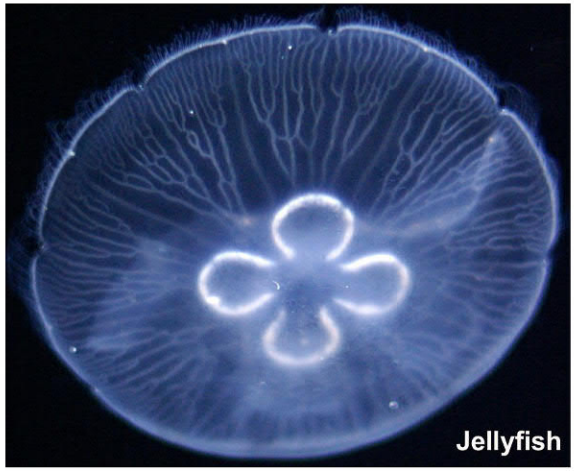
What are the geometries and topologies of vascular networks, and why do other structures share them?

Vascular networks are fractal r-nets

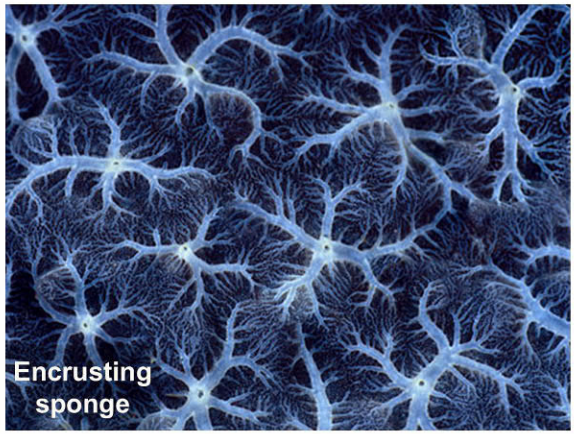


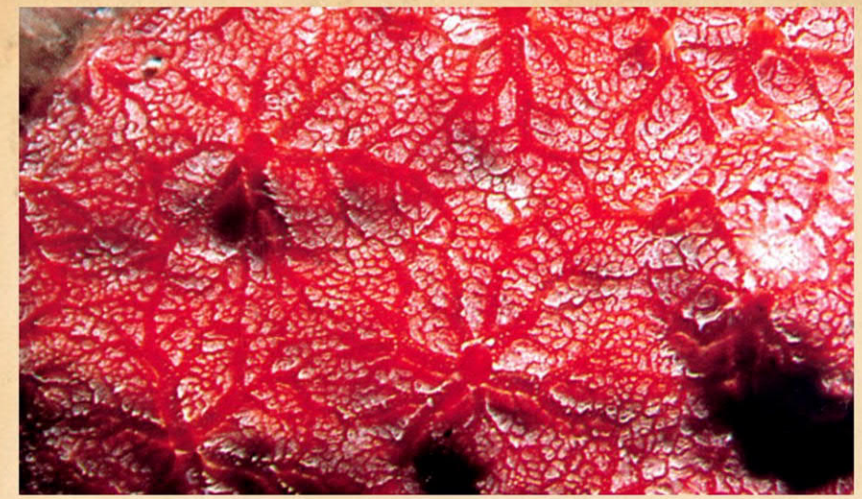
$$V_i \leftarrow g_i(V_{i-1}) \cup \{\sigma\}_i$$

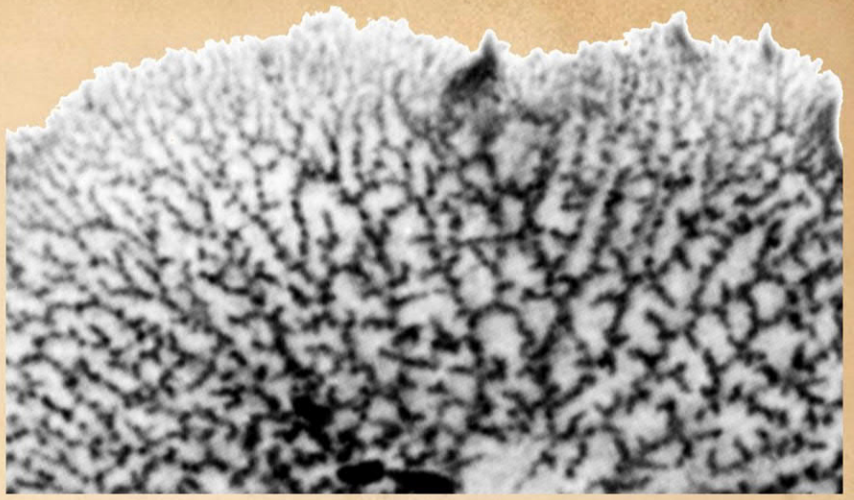
$$V_i = \{\Psi_{1,\ldots,N(i)}\} = \bigcup_{k=0}^{i} g^{(i-k)}(\{\sigma\}_k)$$

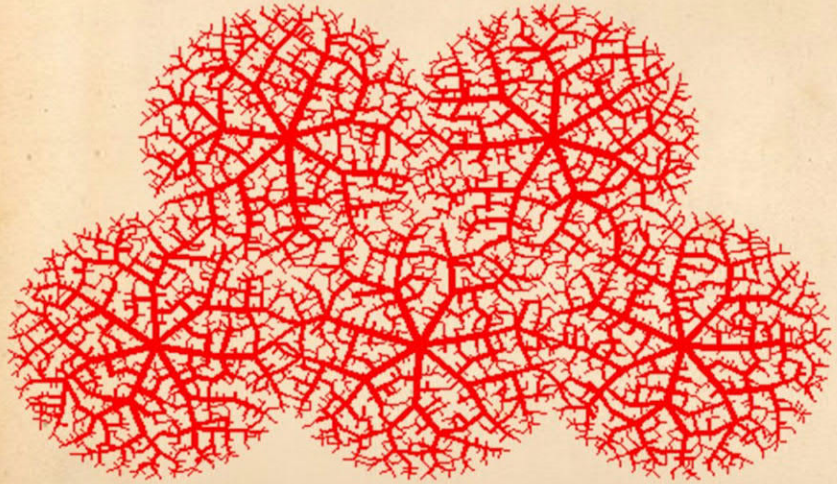

Jellyfish

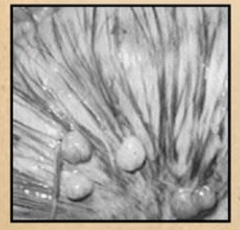

Jellyfish

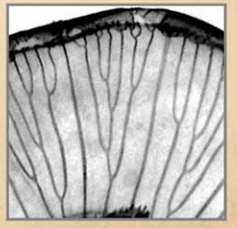

Encrusting
sponge

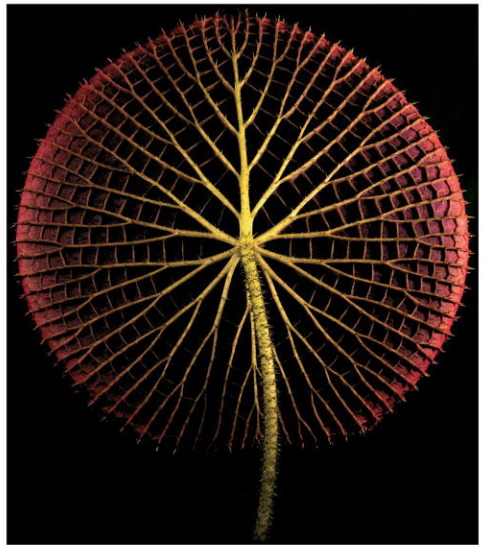


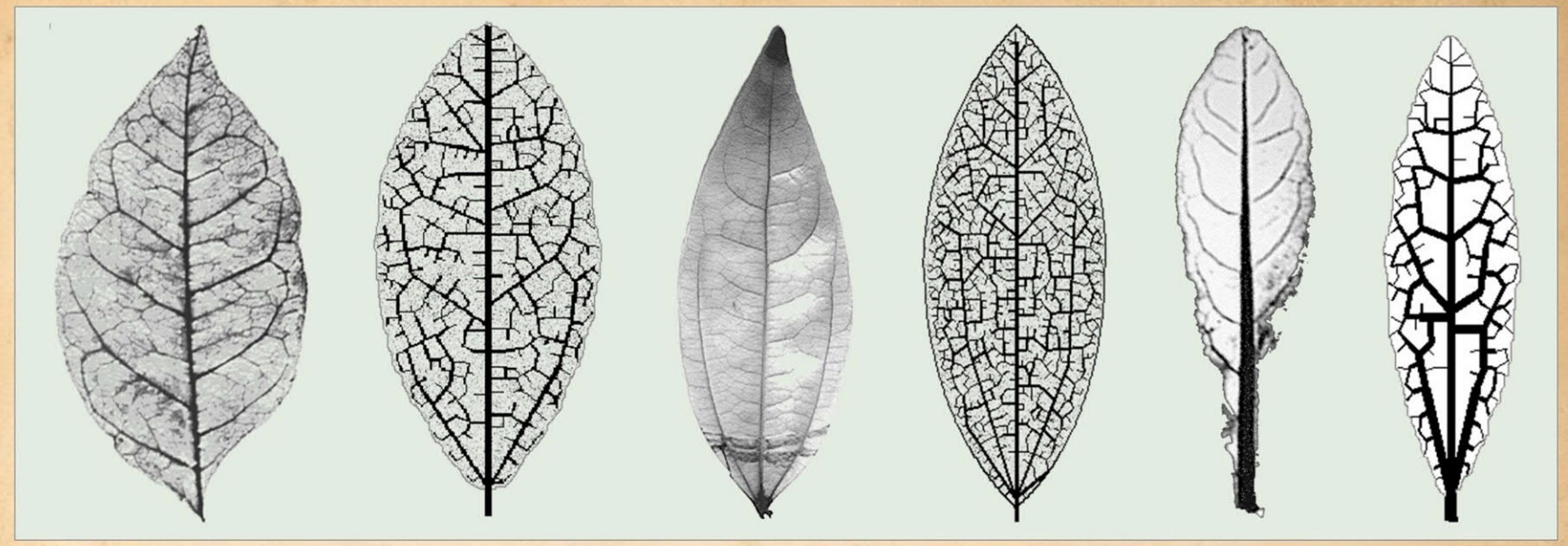


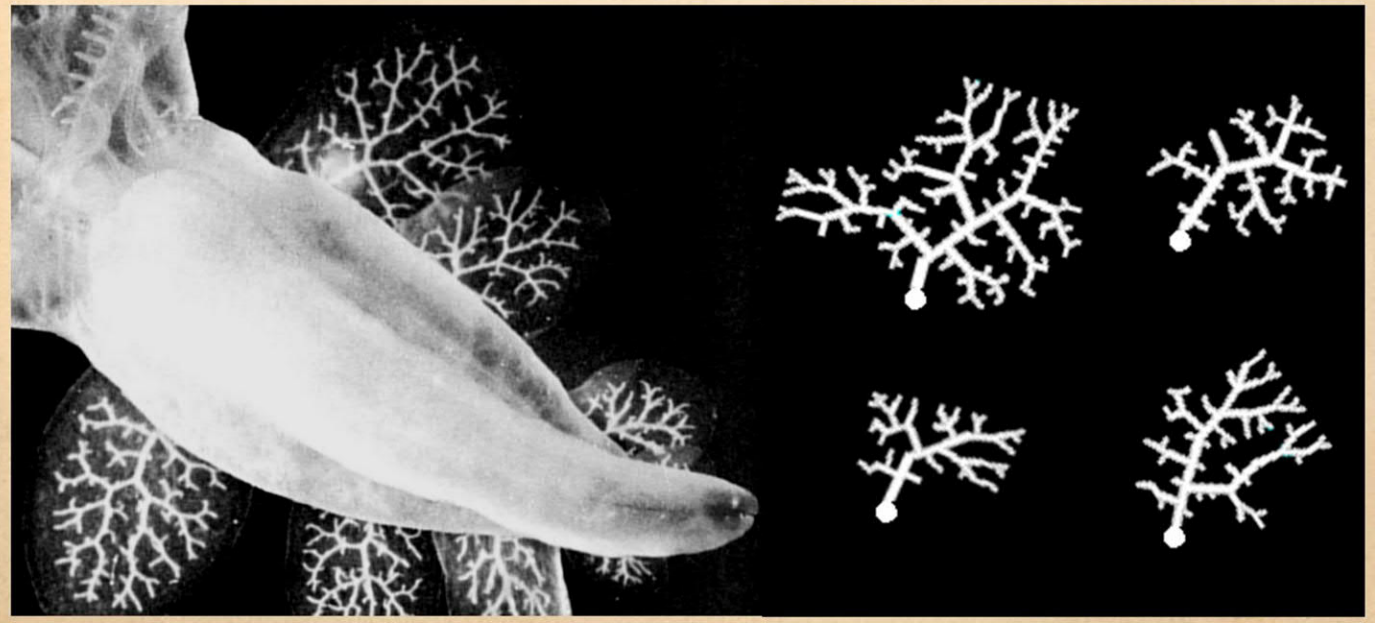


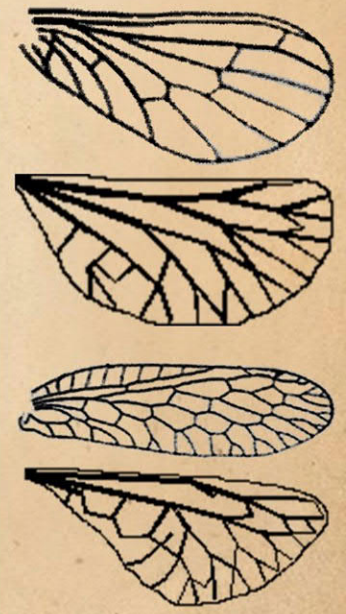


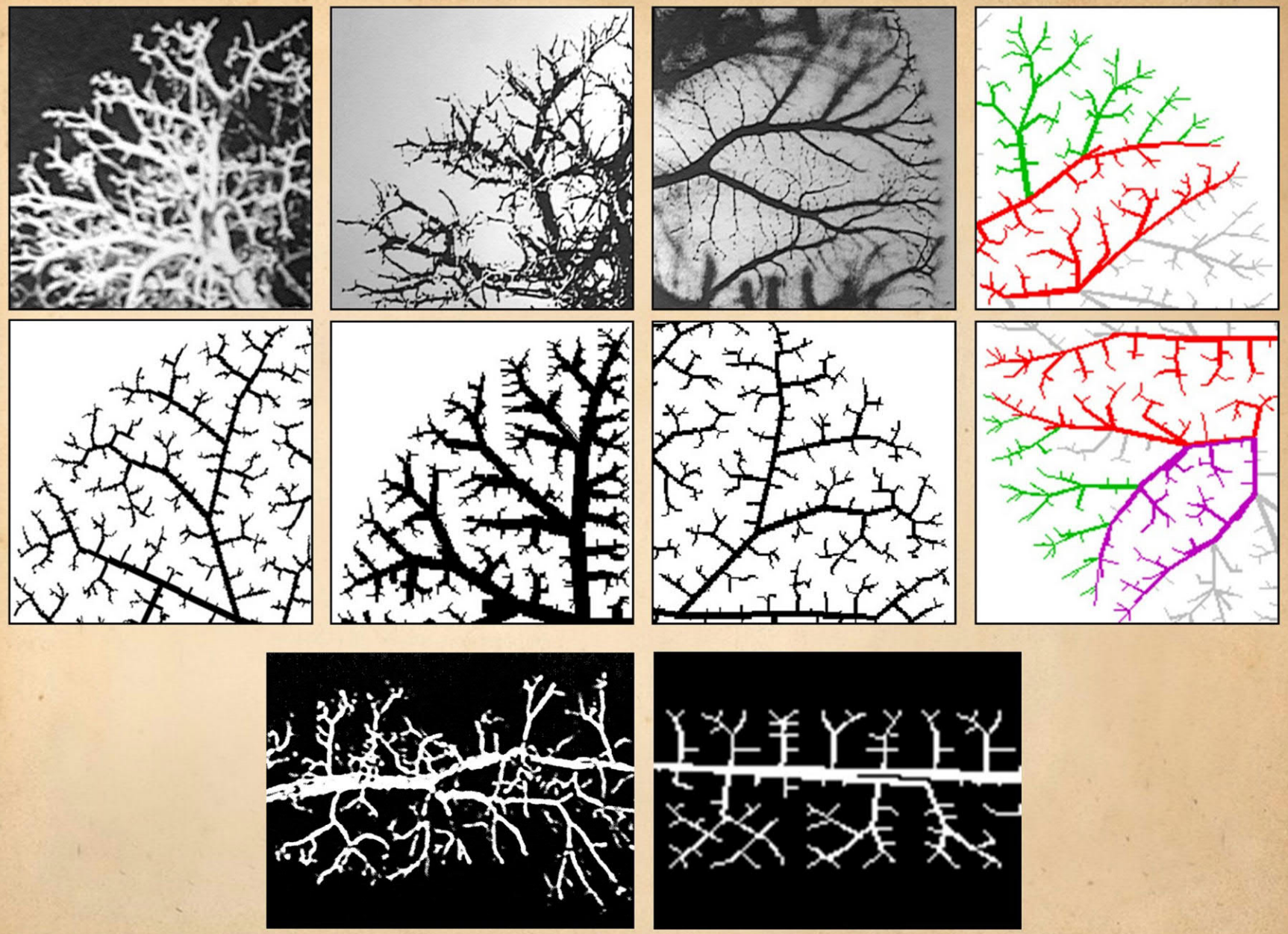


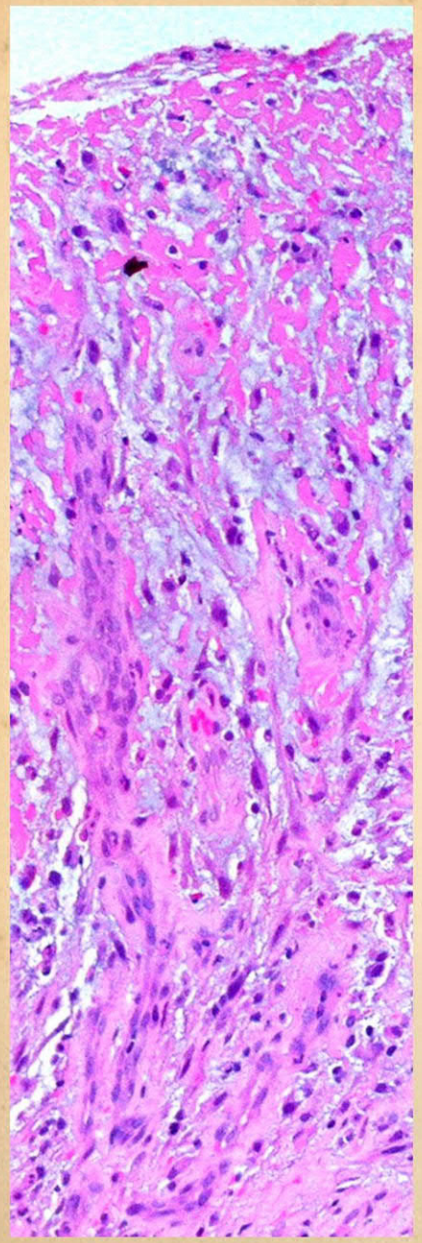


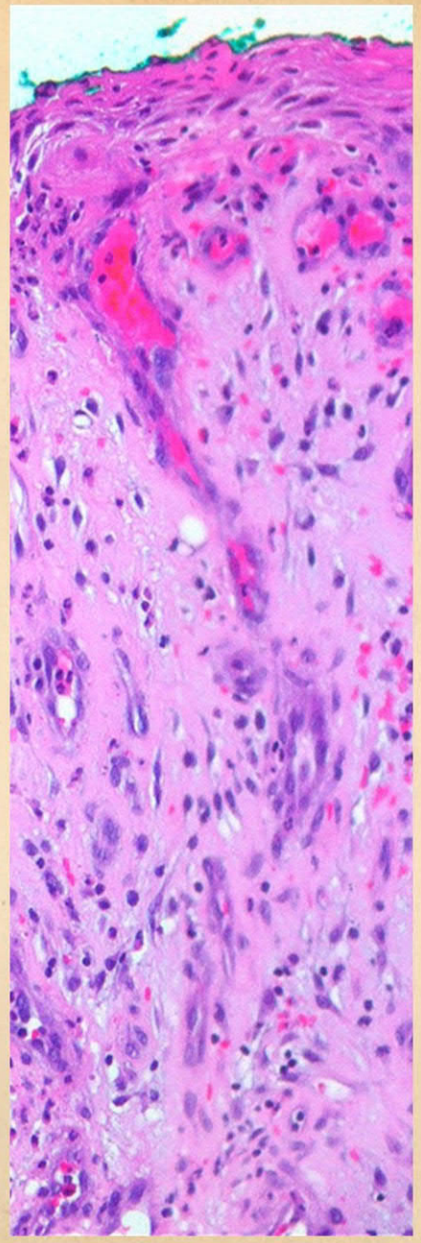


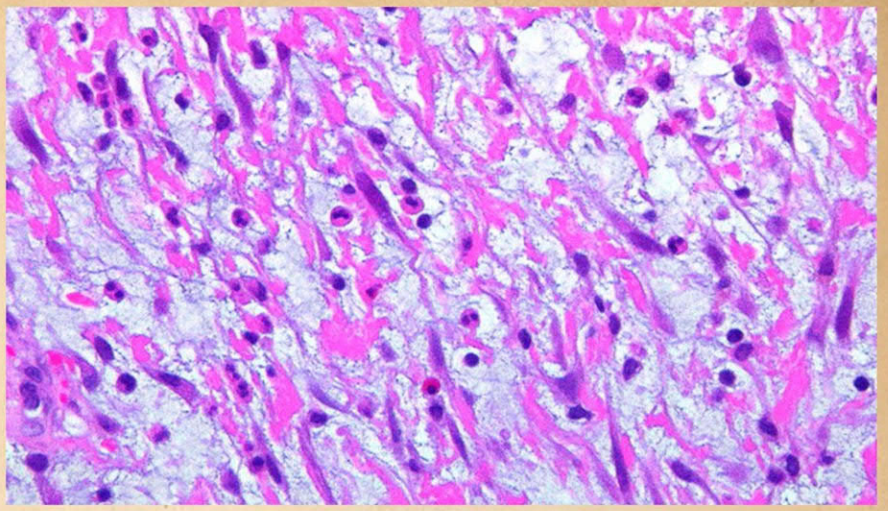




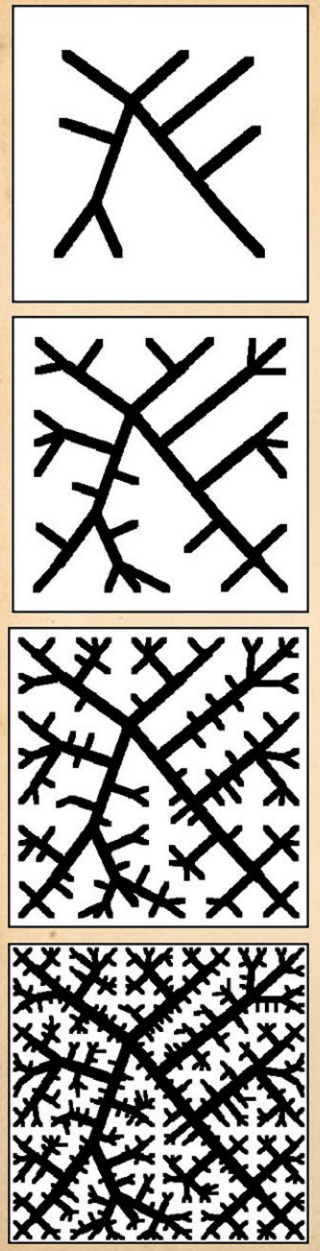








Field angiogenesis	Target angiogenesis
developmental	**incidental**
embryonic, growth & maturation	*wound, tumor, follicles, implants*
closed loop	**open loop**
controlled	**unregulated**
vessel restoration inhibits the controller	*vessel restoration does NOT inhibit the controller*
dispersed	**vector**



How do VEGF and angiogenesis operate to create a vascular network?

Simple physical system contingent on promoter-inhibitor diffusion.

How little information is needed; how efficient is the process?

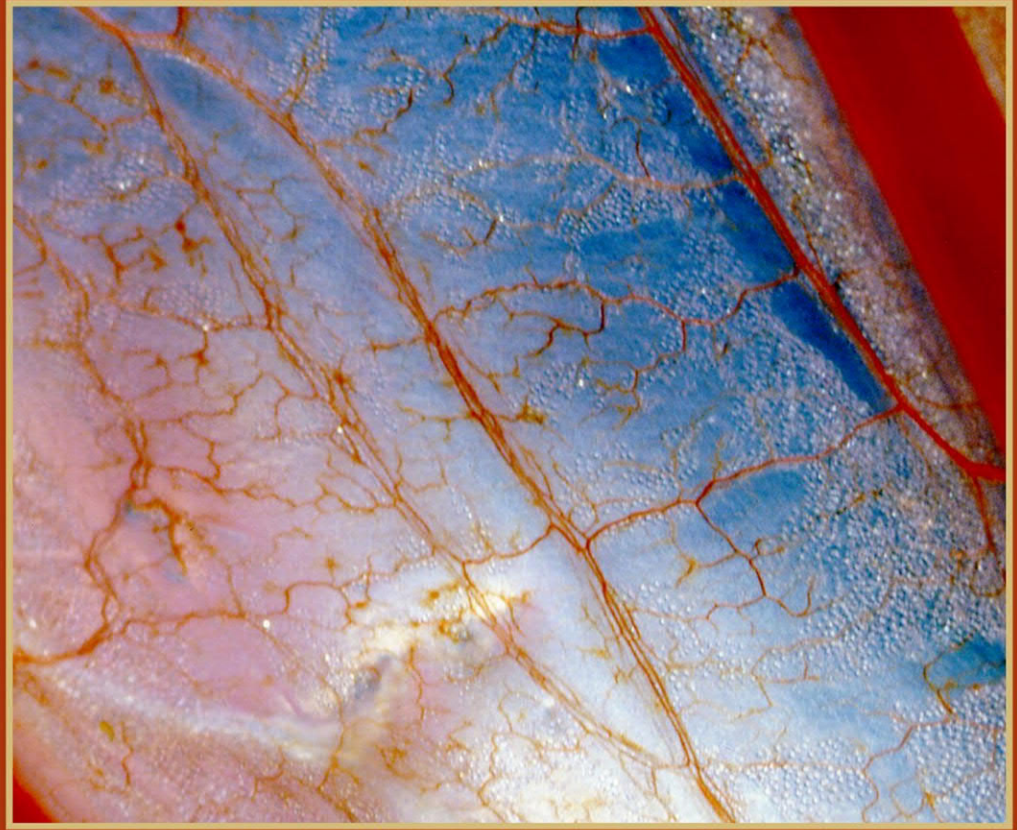
Very little. Very efficient. Parsimonious self-organization.

How is the life-and-death accuracy of the process conserved?

Process is a reactive, space-driven, density-restoring error-correcting closed-loop feedback control system.

What are the geometries and topologies; why in other structures?

Vascular networks are fractal r-nets, life-and-death crucial, highly conserved through evolution.



THE CENTURY OF THE SYSTEM

DEVELOPMENTAL ANGIOGENESIS

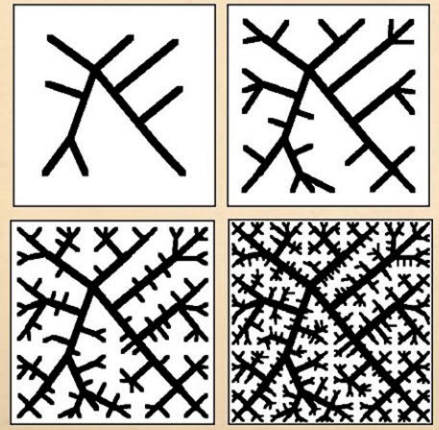
=

CLOSED LOOP CONTROL SYSTEM

The control loop ensures the correct development of the life-and-death critical vascular network. Multicellular life cannot exist without it.

THE VT MODEL OF ANGIOGENESIS

The Vascular neT Model of the Formation of Blood Vessels and Vascular Networks



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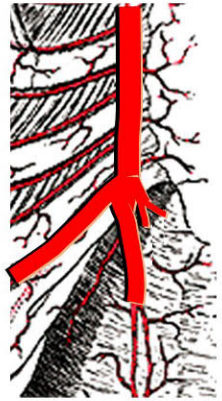
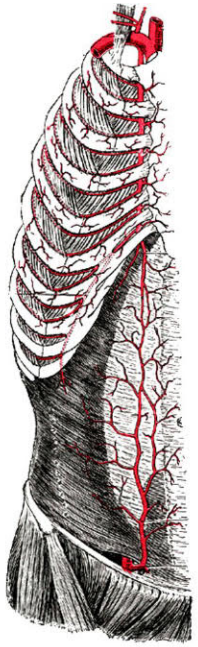
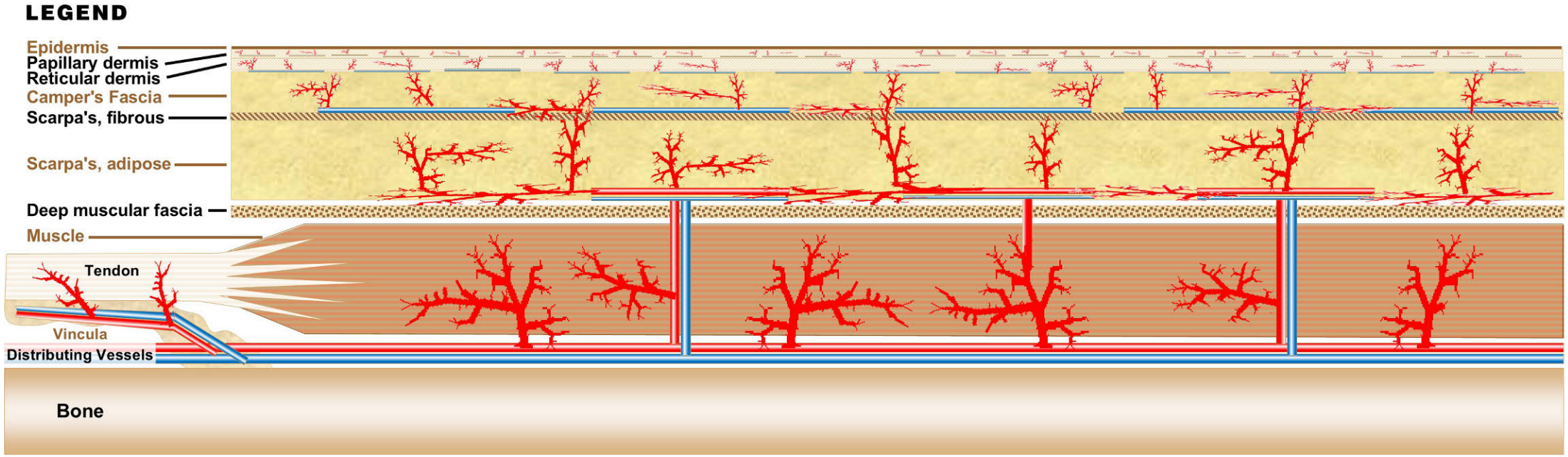
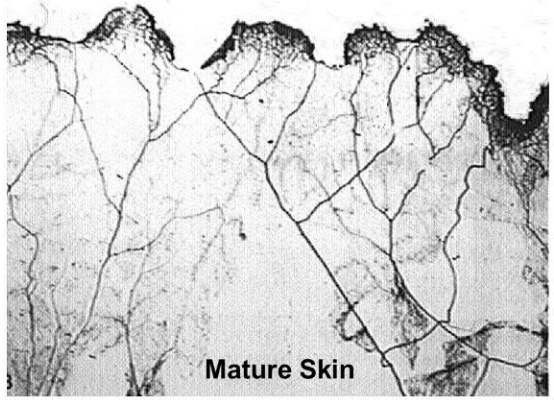
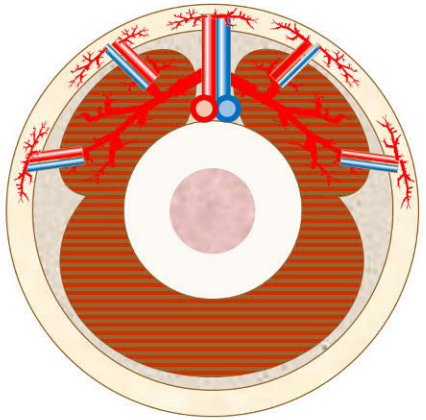
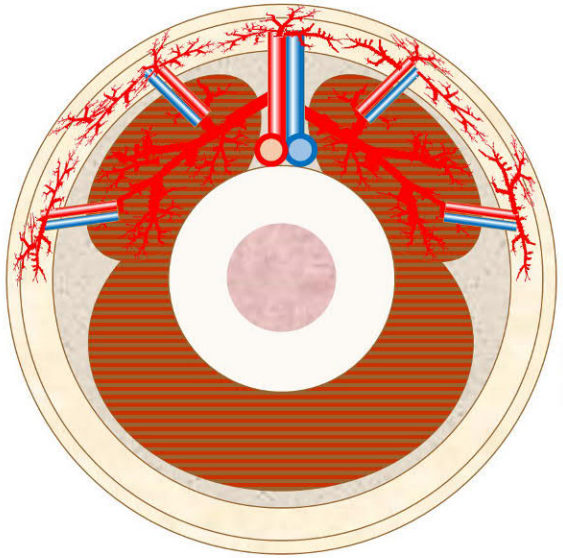


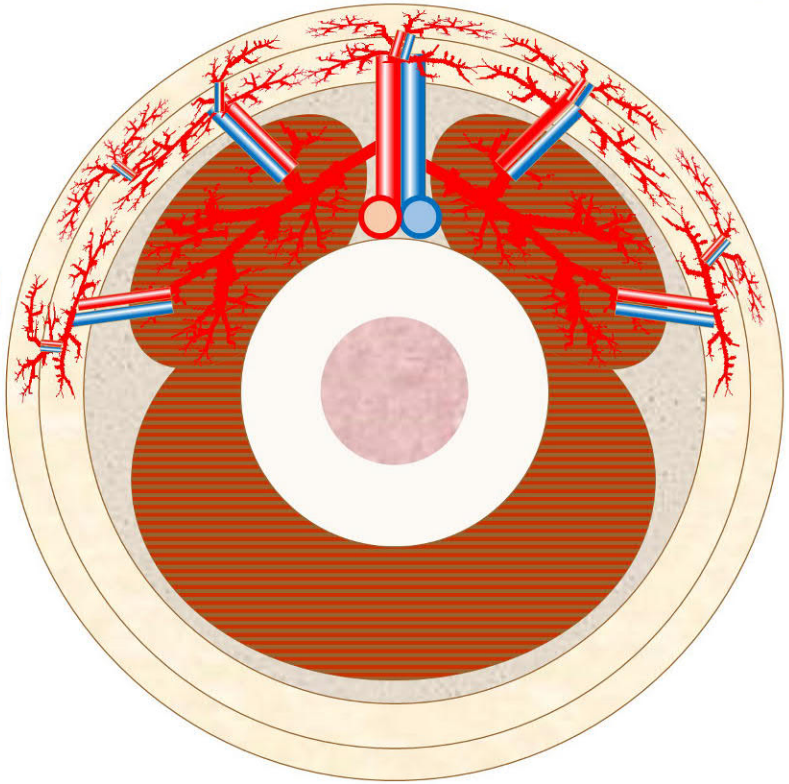




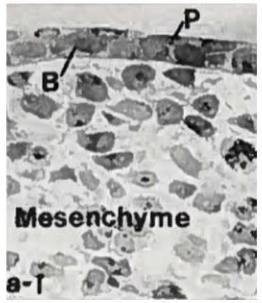


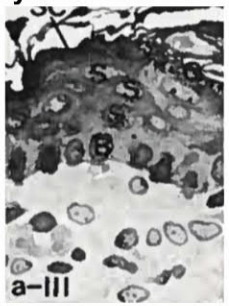


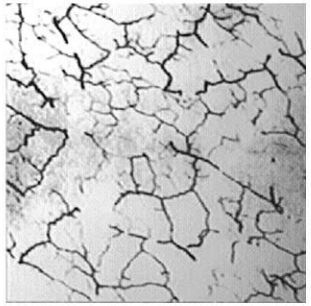




Embryonic-Fetal Skin







Subcutaneous fascia, tangential

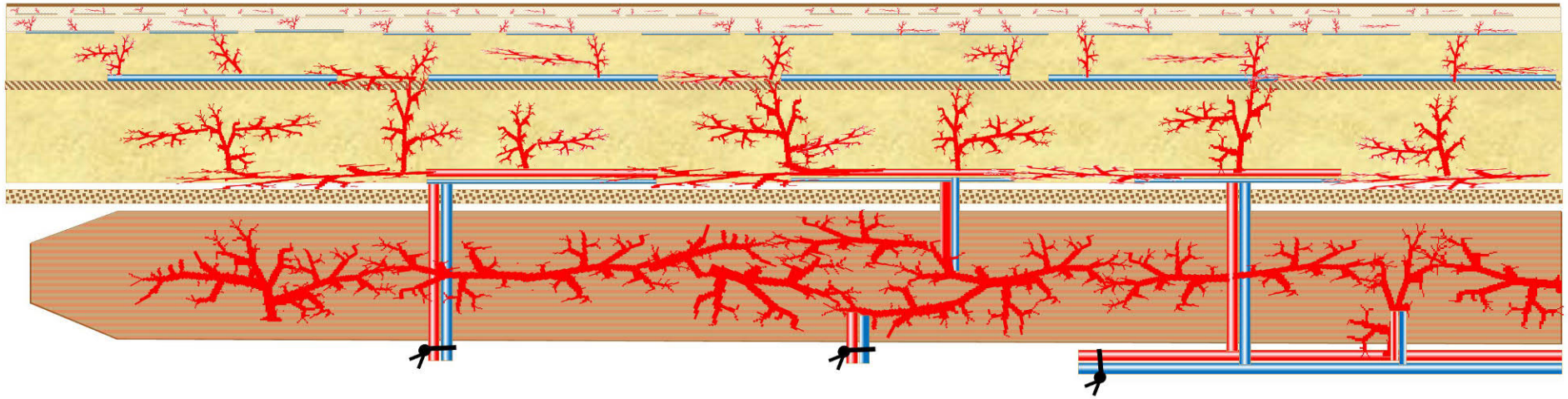
Musculocutaneous flaps

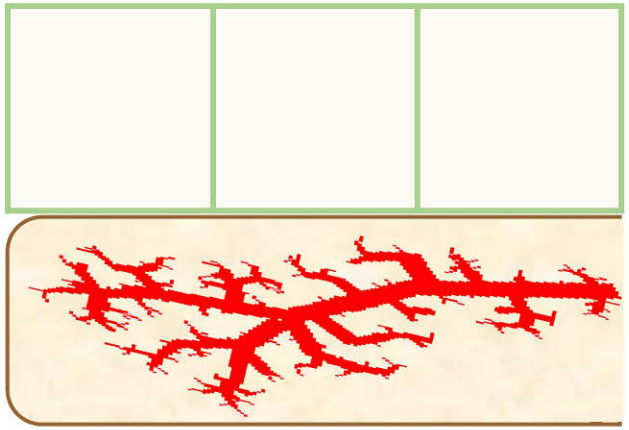
- versus -

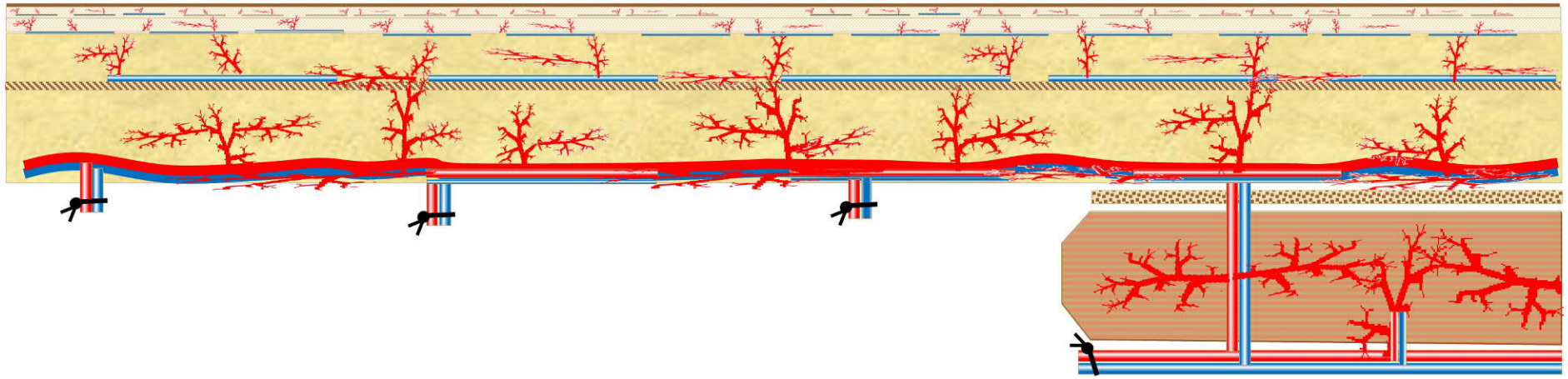
Axial - angiosomal flaps

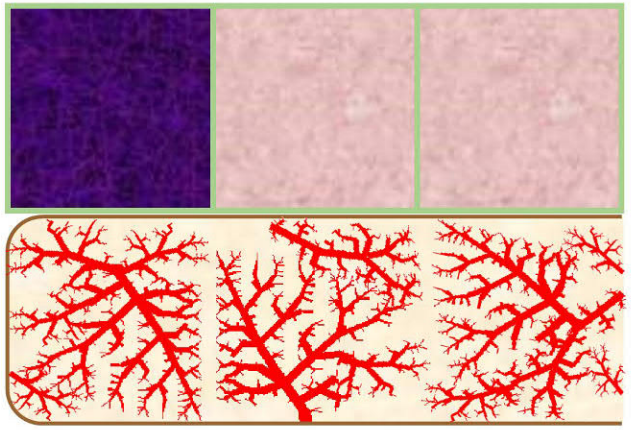
- versus -

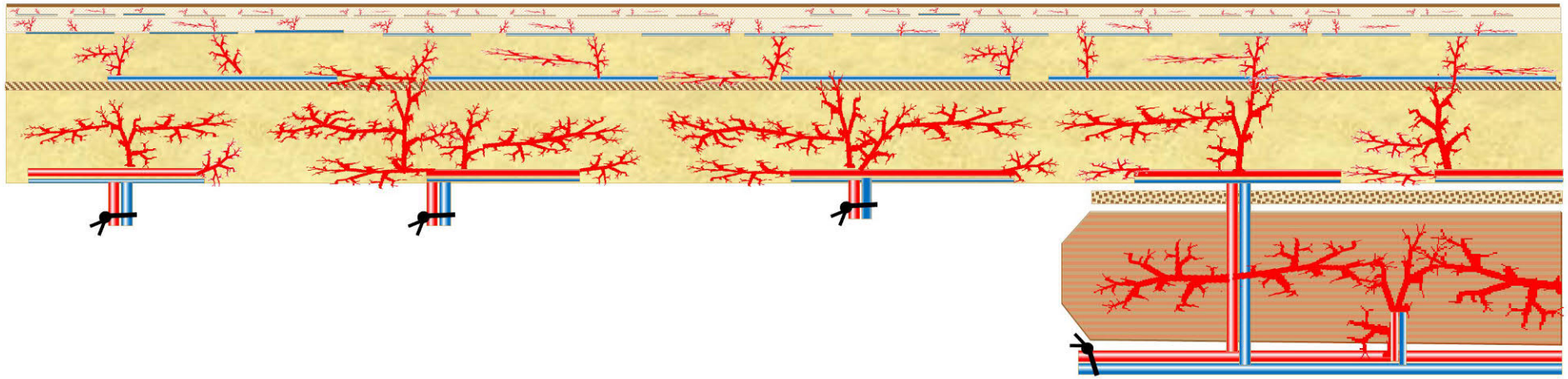
Random flaps

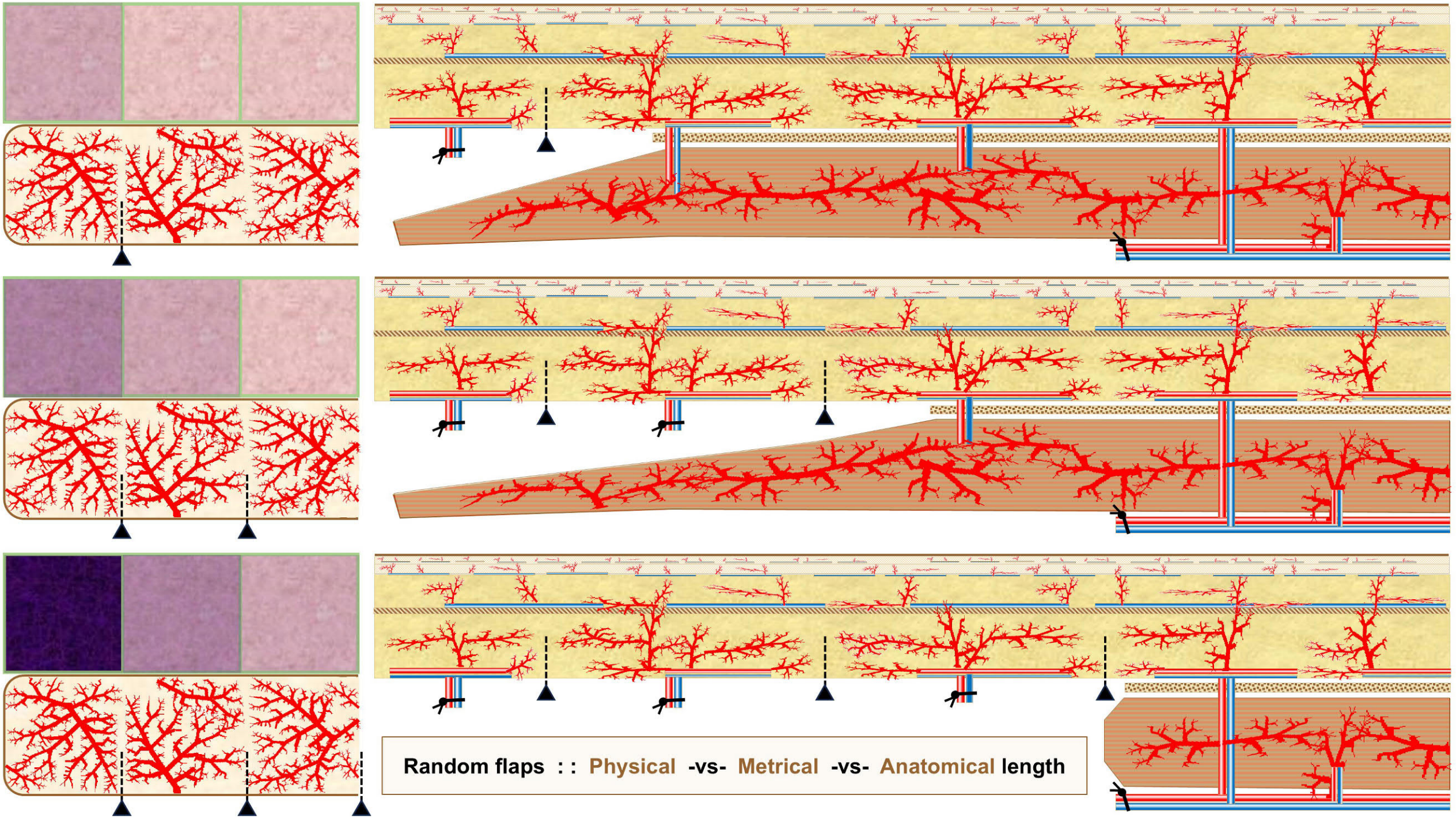


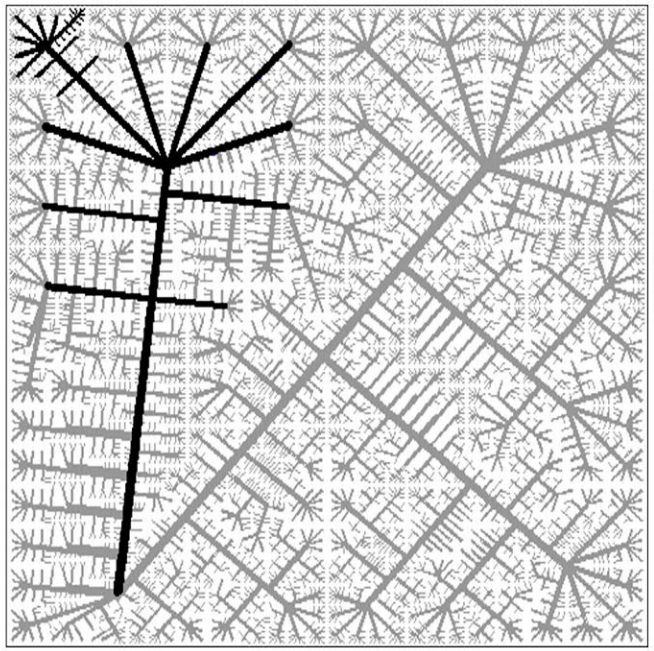


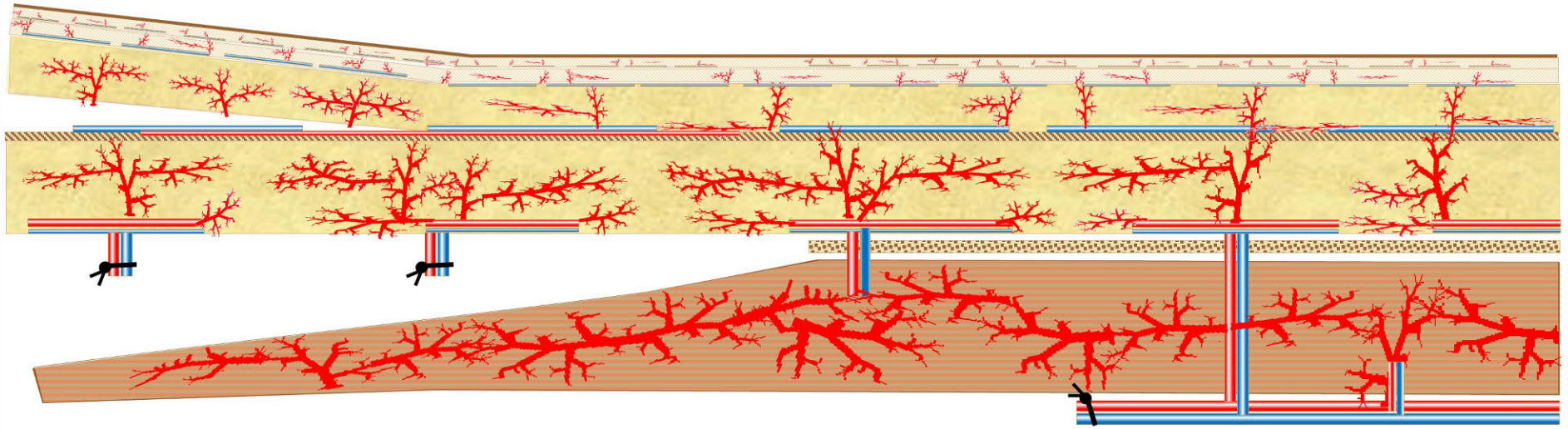


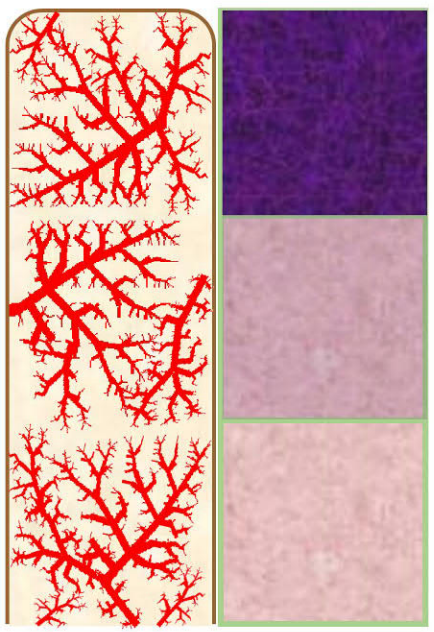




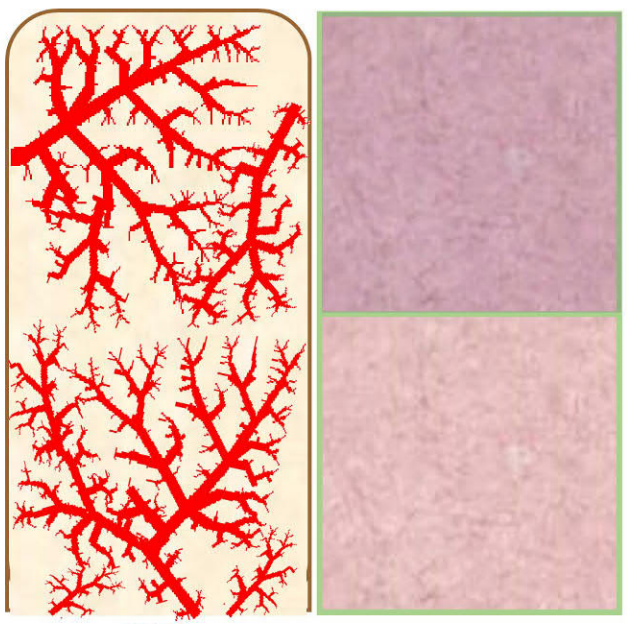

Random flaps : : Physical -vs- Metrical -vs- Anatomical length





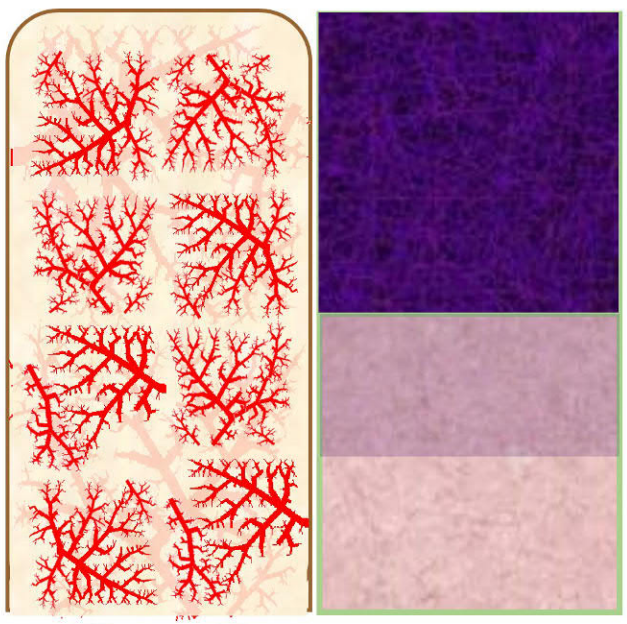


2 - layer : Camper - Scarpa
Aspect = 3 : 1



perforator
radius = R

2 - layer : Camper - Scarpa
Aspect = 2 : 1



perforator
radius = R / 2

1 - layer : Camper only
Aspect = 2 : 1 , area = 4

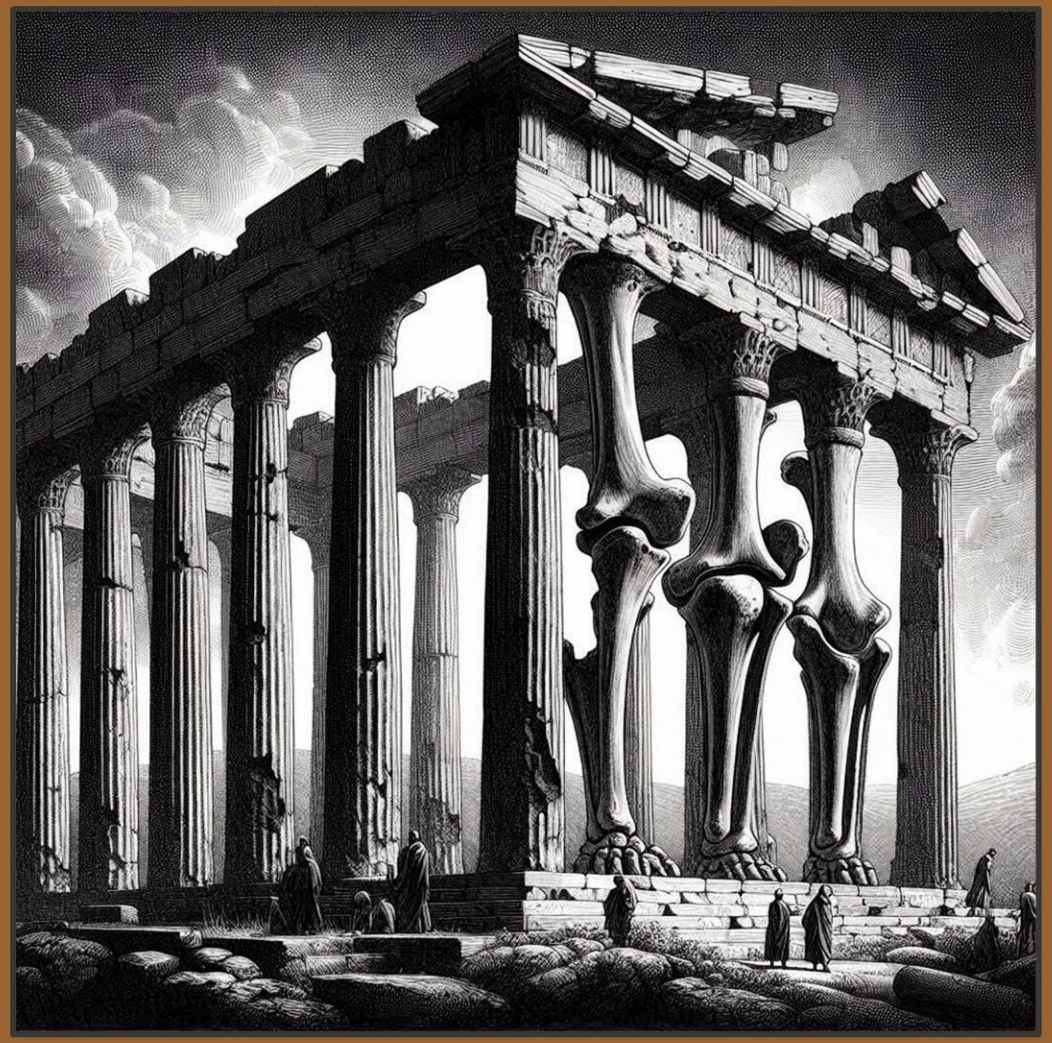
2-layer –vs- 1-layer flap

Flow = [coeff]
x flow per perforator F
x # perforators
x inflow pressure P

Consider effects of
tissue load,
perforator density,
perforator diameter
(Poiseuille, flow = f (r^4))
segmental pressures, inflow & drop

1-layer : Camper
Aspect = 2:1 , area = 1

Anatomy



Embryology

Segmental

Vasculature

Wolff's Law

Wolff's Law – or – Wolff-Davis Law

Julius Wolff
1836 – 1902
Poland & Germany
"Orthopedic" Surgeon

1870
Über die innere Architektur der Knochen und ihre Bedeutung für die Frage vom Knochenwachstum.

On the internal architecture of bones and its significance for the issue of bone growth.

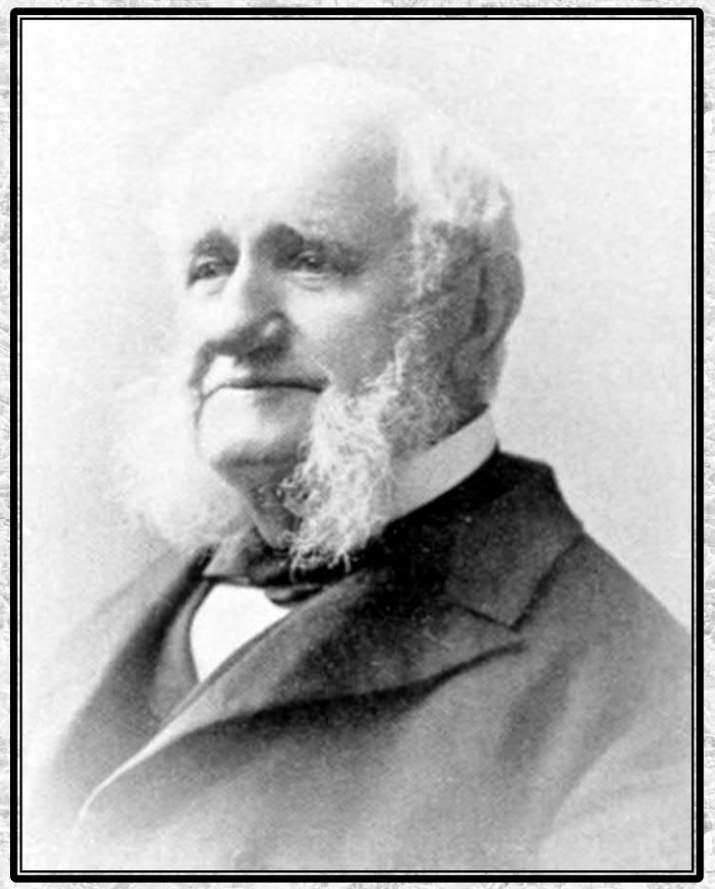
1892
Das Gesetz der Transformation der Knochen.
The Law of Bone Transformation.

Bone adapts to the loads applied, affecting internal trabecular architecture, bulk geometry, strength and properties.

Julius Wolff

1867
Book :: Conservative Surgery.

"Ligaments, or any soft tissue, when put under even a moderate degree of tension, if that tension is unremitting, will elongate by the addition of new material; on the contrary, when ligaments, or rather soft tissues, remain uninterruptedly in a loose or lax state, they will gradually shorten, as the effete material is removed, until they come to maintain the same relation to the bony structures with which they are united that they did before their shortening. Nature never wastes her time and material in maintaining a muscle or ligament at its original length when the distance between their points of origin and insertion is for any considerable time, without interruption, shortened."



Henry Gassett Davis
1807 – 1896
Massachusetts
"Orthopedic" surgeon

ANATOMY : **Wolff - Davis Law**

Basic Materials and Mechanics ::
- Stress-strain, compliance
- Elasticity
- Plasticity, creep, stress relaxation

Bioplasticity ::
- Mesoderm - mesenchyme
- Transduction off force
  - tension-compression-shear
- Response to force Wolff-Davis
- **Wolff-Davis – comprehensive :**
- Tissues subjected to sustained stress
  - *react to minimize resulting strain*
- Tissues subjected to sustained strain
  - *react to minimize resulting stress*

Relevance ::
- **Embryo- & organogenesis**
  - Serosas and bursas
  - Musculoskeletal system
  - Heart
- **Physiology & pathology :**
  - Bone mineralization - demineralization
  - Scar spectrum: mechano-reactive
    - -vs- injury-reactive -vs- pathological
  - Effects more susceptible during or after
    - injury – inflammation – wound-healing
- **Wounds & healing :**
  - fracture healing and repair
  - bone remodeling
  - heterotopic ossification at joints
  - passive joint contractures
  - tendon-ligament repair – solid vs mush
  - tendonization of flexor scar
  - relaxation of extensor scar
  - edsmi – motion
  - serosal metaplasia and bursa formation
  - pseudarthroses
  - non-adherent repairs and flaps
  - vent induced pulmonary fibrosis
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  - Therapeutic loading -vs- shielding
  - Intramedullary nails
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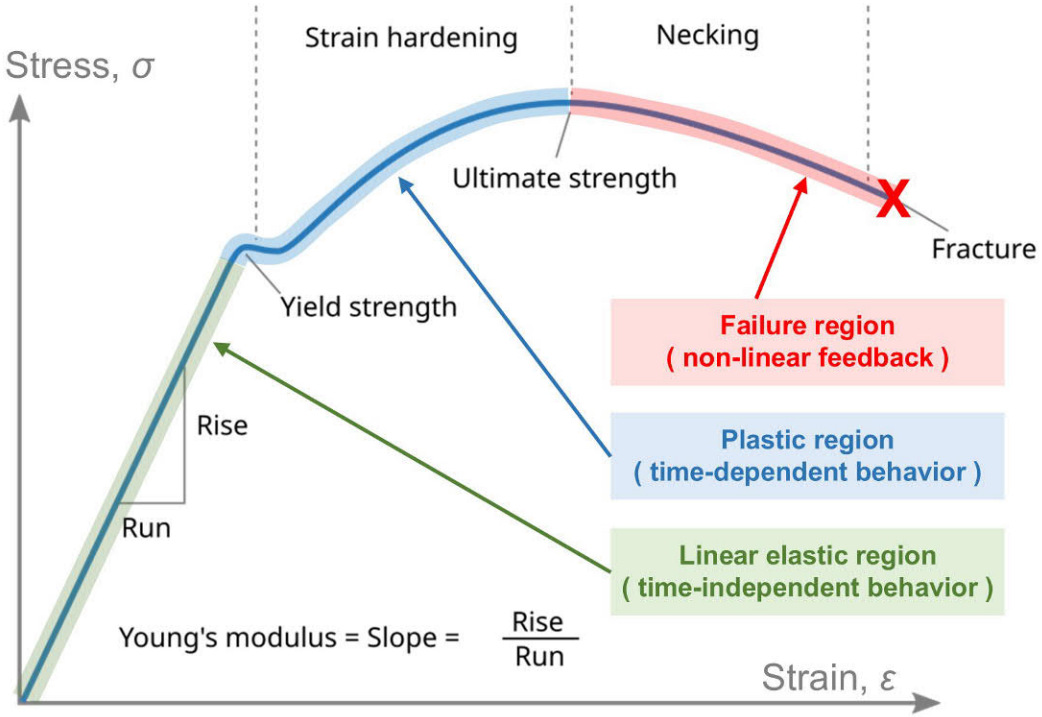
  - Z-plasties & interposition flaps



MATERIALS PROPERTIES

Deformation physical change due to an applied force
Strain deformation normalized (new ÷ original length = $(\ell - \ell_0) / \ell_0$)

Force applied load (tension, compression, shear)
Stress load normalized (force ÷ applied area = force per unit area)

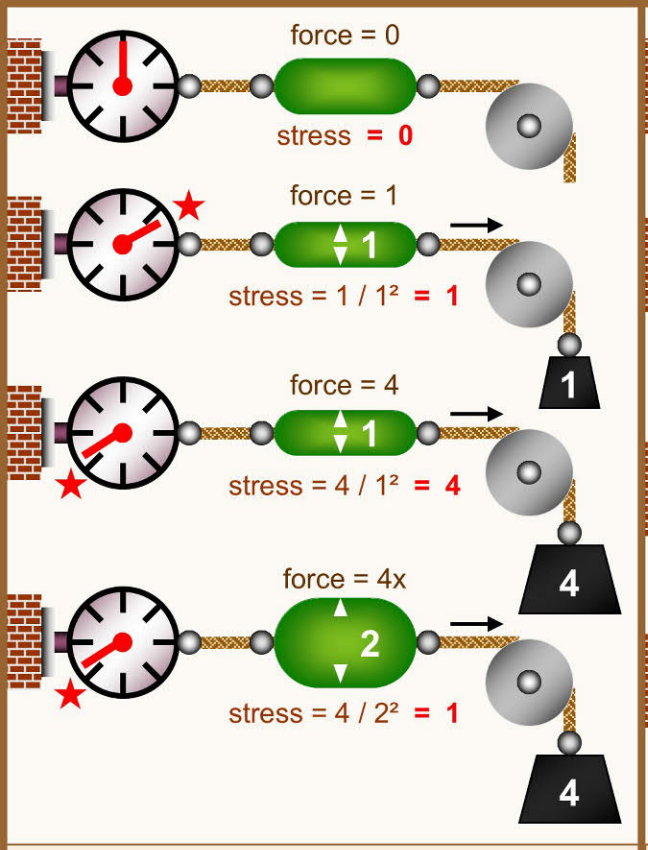
Elasticity repetitive loading has same profile without internal alterations (time-independent = same profile every time, in elastic zone)
Plasticity sustained-repetitive load causes internal alterations and flows (time-dependent = material evolves in time, in plastic zone)
Bioplasticity properties in biological tissues not present in ordinary materials (time-dependent adaptive self-annealing-healing-repair, or accommodative addition-subtraction of material substance)

Load applied stress or strain (momentary, sustained, cyclical)
Creep plastic response to repetitive, sustained, or constant stress
Stress relaxation plastic response to repetitive, sustained, or constant strain (plastic behaviors due to internal adaptations)

MESENCHYMAL AND MUSCULOSKELETAL TISSUES DERIVED FROM THE EMBRYONIC MESODERM

transduce and respond to mechanical force – tension, compression, shear.

This has a profound influence on developmental biology, pathology, response to injury and repair, and clinical care of multiple problems.

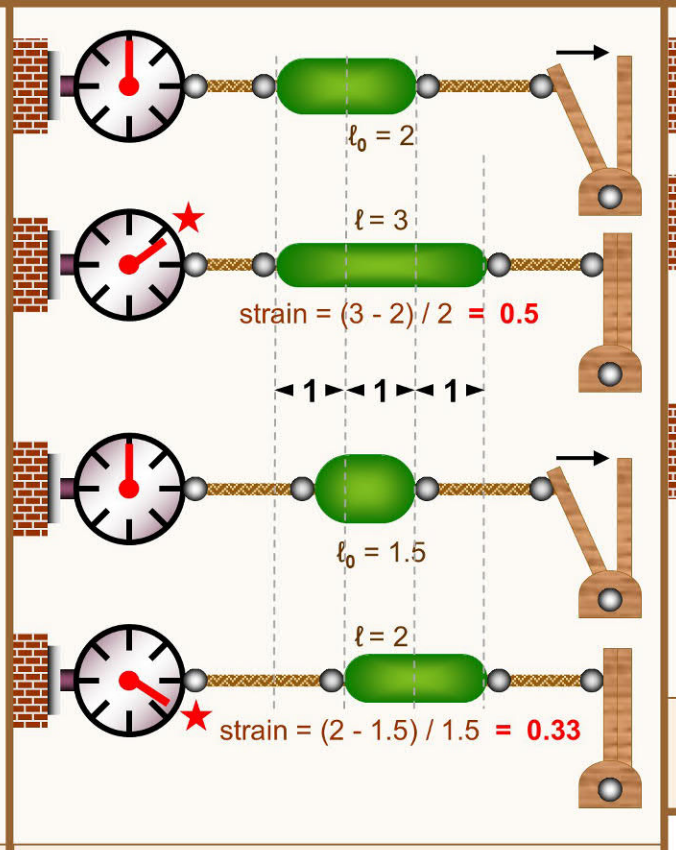


force of applied load
stress = force normalized by area

tensile (normal) stress
= tensile force / area

compressive (normal) stress
= compressive force / area = pressure

shear (tangential) stress
= shear force / area

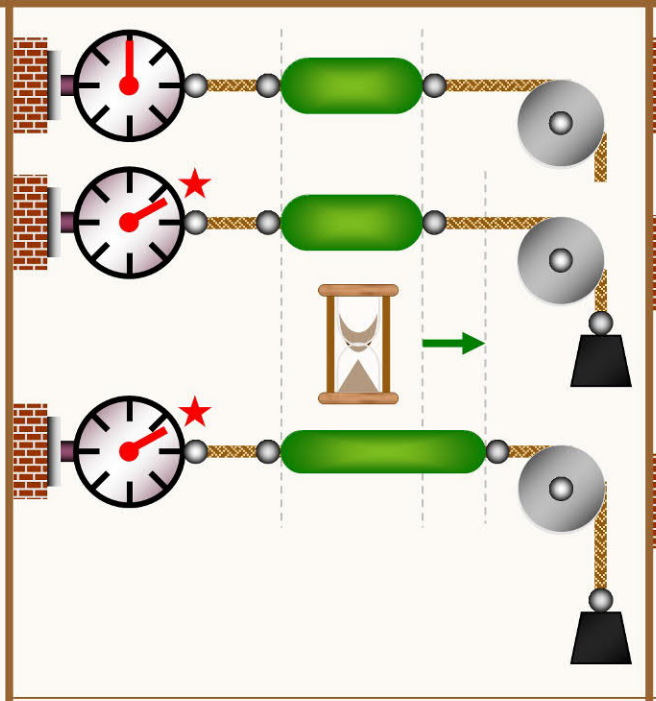


deformation due to applied load
strain = deformation normalized by original size

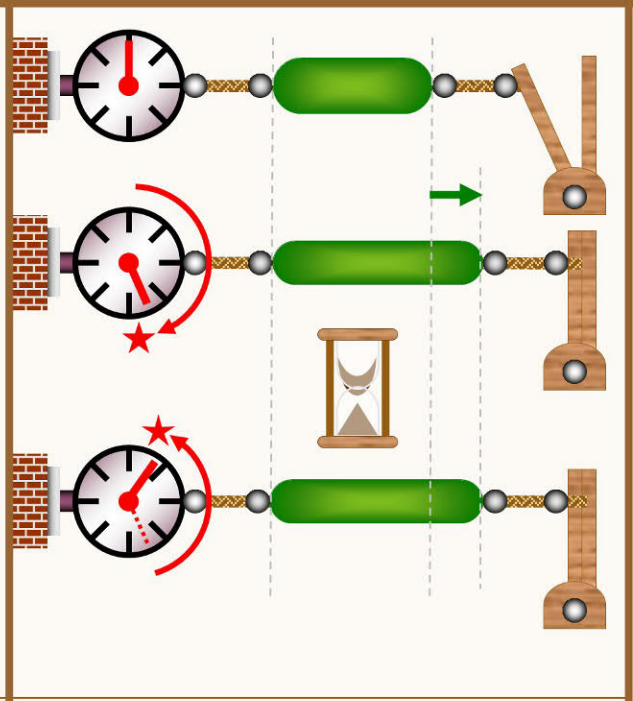
tensile (normal) strain (elongation)
= tensile deformation / length (0)

compressive (normal) strain
= compressive deformation / length (0)

shear (tangential) strain
= shear deformation / area



plasticity :: sustained stress
response = creep



plasticity :: fixed strain
response = stress relaxation

BIOPLASTICITY

Ordinary materials mostly cannot anneal or heal themselves. Even for the few that can, they cannot passively add or subtract substance from themselves. The ability to add or subtract then remodel tissue or substance into multiple complex functionally correct new material is unique to biology. This is the basis of Wolff's Law.

THE EFFECTS OF SUSTAINED LOAD

Time-dependent non-linearity = viscous behavior = plasticity.

Wolff - Davis Law

"Compression begets bone."

"The Law" as Wolff and Davis appreciated it :

Bone in compression or dynamic use heals, hypertrophies, remodels to normal.

Tendons and ligaments in use, disuse, stretch, or relaxation will strengthen, weaken, shorten, elongate.

Wolff and Davis were correct but incomplete.

Wolff-Davis Law Generalized

0

Tissues derived from the embryonic mesoderm transduce and react to mechanical force.

1

Subjected to chronic, sustained, repetitive-cyclical stress, the tissues will react or adapt to oppose or minimize any strain due to that stress.

2

Subjected to chronic, sustained, fixed or repetitive strain, the tissues will react or adapt to oppose or minimize any stress due to that strain.

This sounds simple and innocuous, but the implications are profound.

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Embryo- & organogenesis
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- Musculoskeletal system
- Heart

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- Bone mineralization - demineralization
- Scar spectrum: mechano-reactive
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- fracture healing and repair
- bone remodeling
- heterotopic ossification at joints
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Clinical care :
- Therapeutic loading -vs- shielding
- Intramedullary nails
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- Serial casting
- Distraction & coaptation devices
- Orthodontia
- Tissue expansion
- Z-plasties & interposition flaps

Wolff-Davis Law Generalized

0	1	2
Tissues derived from the embryonic mesoderm transduce and react to mechanical force.	Subjected to chronic, sustained, repetitive-cyclical stress, the tissues will react or adapt to oppose or minimize any strain due to that stress.	Subjected to chronic, sustained, fixed or repetitive strain, the tissues will react or adapt to oppose or minimize any stress due to that strain.

. . . meaning . . .

a1	b1	c1
Tissues subjected to chronic compressive stress resist compression by becoming bone (osseous metaplasia).	Tissues subjected to chronic tensile stress resist elongation by becoming tendon - ligament (tendinous metaplasia).	Tissues subjected to chronic shear stress resist tangential deformation by becoming bursa - arthrosis (serosal - synovial metaplasia).

a2	b2	c2
Tissues subjected to chronic-incremental compressive strain react against compression by tissue involution (atrophy).	Tissues subjected to chronic-incremental tensile strain react against elongation by tissue relaxation – augmentation (hypertrophy). (Includes negative strain with atrophy.)	Tissues subjected to chronic-incremental shear strain react against tangential stretch by tissue remodeling (vincular – areolar metaplasia).

Adaptive responses are non-linear, self-organizing.

For soft tissues, the system reference that the process controls on (by fibroblasts et al) is tissue tension.

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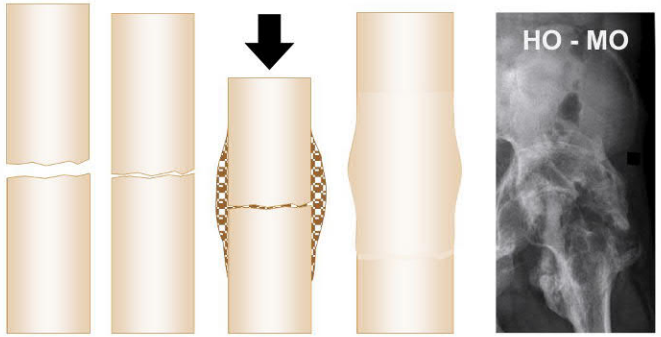
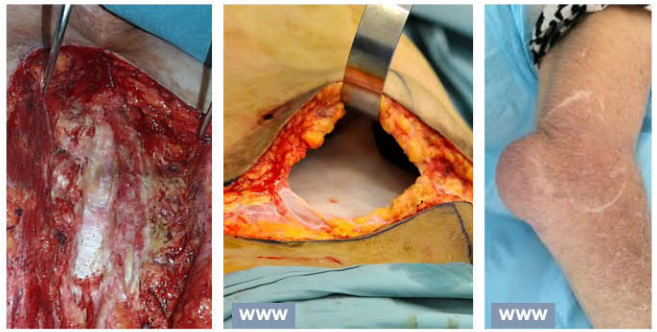
0	1	2
Tissues derived from embryonic mesoderm transduce and react to mechanical force.	**Subjected to chronic or repetitive stress, they react to minimize strain due to that stress.**	**Subjected to chronic or repetitive strain, they react to minimize stress due to that strain.**

a1	b1	c1
Tissues subjected to chronic compressive stress resist compression by becoming bone (osseous metaplasia).	**Tissues subjected to chronic tensile stress resist elongation by becoming tendon - ligament (tendinous metaplasia).**	**Tissues subjected to chronic shear stress resist tangential deformation by bursa - arthrosis (serosal - synovial metaplasia).**





fracture healing ♦ heterotopic ossification / myositis ossificans — *burn scar and other contractures* — *sternal non-union pseudarthrosis ♦ abd sub-flap bursa ♦ olecranon bursa*

a2	b2	c2
Tissues subjected to chronic compressive strain react against compression by tissue involution (atrophy).	**Tissues subjected to chronic tensile strain react against elongation by relaxation – elongation (hypertrophy).**	**Tissues subjected to chronic shear strain react against tangential stretch by remodeling (vincular – areolar metaplasia).**

pending

lymphedema compression ♦ burn scar compression — *contracture serial casting (pos.) ♦ ligament atrophy (neg) ♦ skin reduction*

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b 1
Tissues subjected to chronic tensile STRESS resist elongation by becoming tendon - ligament (tendinous metaplasia).

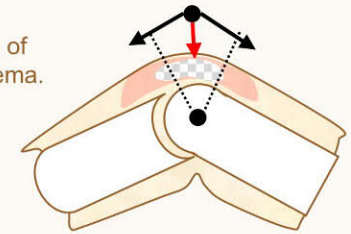
c 1
Tissues subjected to chronic shear STRESS resist tangential deformation by bursa - arthrosis (serosal - synovial metaplasia).

+ **Positive compression** - relevance & examples.

Induce osteogenesis and bone healing.
Promote fracture healing by nature or surgery.
Bone remodeling ; correct malunion.
Dynamic compression plates.

Ancillary effects:
Mechanical stability, control of motion – deadspace - edema.

Induce heterotopic bone :
contracted joints
hernia ossicles
arthritis osteophytes



+ **Positive tension** - relevance & examples.

Formation of musculoskeletal tendons, joint ligaments.
Other restraining tethers, e.g. chordae tendineae, falciform ligament.
Preserve tendon - ligament length and architecture.

Tendinous scars-contractures :
aggravated across joints
tethered scars on muscle
by gravity,
e.g. peritoneal tendons

+ **Positive shear** - relevance & examples.

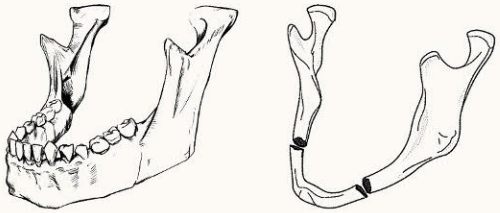
Embryogenesis of visceral serosas & coeloms.
Embryogenesis and maintenance of musculoskeletal, joints, bursas, tendons.
Maintenance of motion and gliding function after injury, inflammation.

Shear and motion – the good (physiological, constrained) -vs- the bad (edsmi, unconstrained).

Non-unions, pseudarthroses.
Rupture of tangential repairs.
Failed adhesion of flaps and repaired surfaces.
Seromas, effusions, wound bursitis.

− **Lack of compression** - relevance & examples.

Impaired osteogenesis.
Osteoclasis.
Uncertain or failed fracture healing.
Plastic bone subject to deformation.
Osteopenia, atrophy, fracture risk.



− **Lack of tension** - relevance & examples.

(Or lack of length.)
Weak scar and maturation.

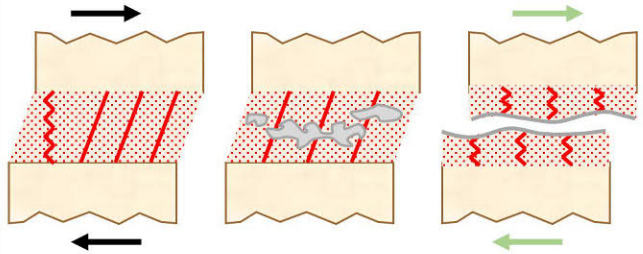
Weak scar & attrition with rupture or loss of repair,
e.g. post-op hernia, tendon rupture.
Loss of tendon-ligament architecture, weakness.
Tendon-ligament shortening,
with joint contractures-stiffness.
Impaired organ structure generation,
e.g. gastroschisis, acp dwarfism.

- *Cf. baseline body tissue tension.*
- *Quintessential role of fibroblasts.*

− **Lack of shear** - relevance & examples.

Protects tangential repairs.

Promotes tendon and joint adhesions - stiffness.



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2

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a2

Tissues subjected to chronic compressive STRAIN correct compaction by tissue involution (atrophy to tension).

Positive compression - relevance & examples.

Bone is not subject to elastic or ordinary plastic strains.

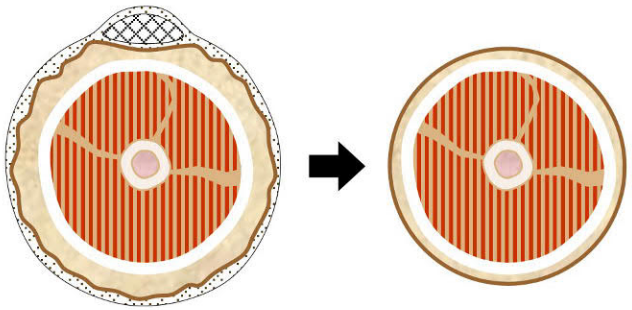
Acute strains such as compression bandaging results from fluid shifts, not bio-plastic cell-matrix adaptations.

Chronic and brawny edema reduction.

Scar reduction.

Lack of compression - relevance & examples.

N/A, baseline (unlike lack of compressive stress).



b2

Tissues subjected to chronic tensile STRAIN correct elongation by relaxation – augmentation (positive strain: hypertrophy, negative strain: atrophy).

Positive tension - relevance & examples.

Incremental strains
(15-20 days apart for optimized soft tissue effect).

Serial casting.

Tissue expansion, skin approximation.

Orthodontia, cleft palate care, limb lengthening.

* * Distinguish between short term incremental strains achieving effect through fluid shifts, elastic deformations, yield-point micro-damage, and masquerading as sustained stress risking opposing reaction to limit strain - versus - longer term adaptive bioplasticity.

Laxity (negative) tension - relevance & examples

Restore skin length-circumference and tensions after compression wrapping for edema.

Improved LV anatomy-dynamics in controlled CHF-DCM.

Correction of flap dog-ears.

Shortening - tightening of lax ligaments, joint contractures.

Atrophy of "unsatisfied" flaps.

Atrophy of soft tissue reconstructions lacking support.

c2

Tissues subjected to chronic shear STRAIN correct tangential stretch by tissue remodeling (vincular – areolar metaplasia).

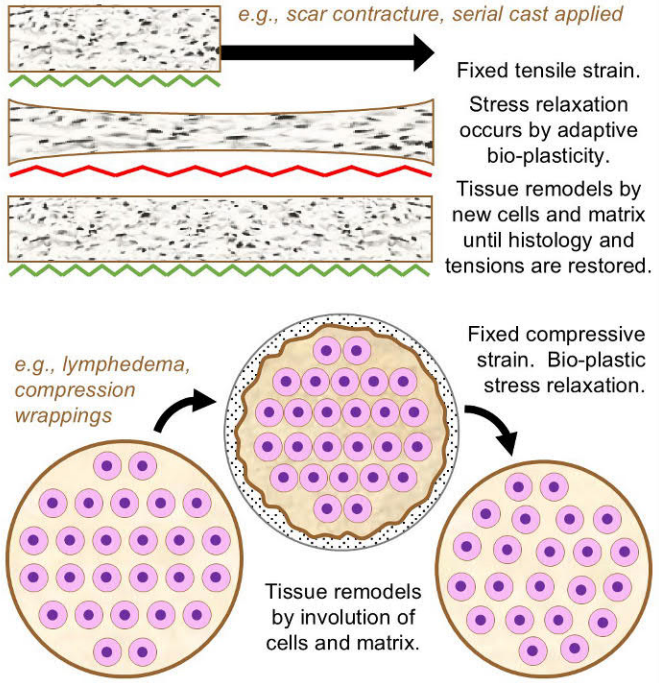
Positive shear - relevance & examples.

Not a common situation.

Lack of shear - relevance & examples.

Protects tangential repairs.

Promotes tendon and joint adhesions - stiffness.



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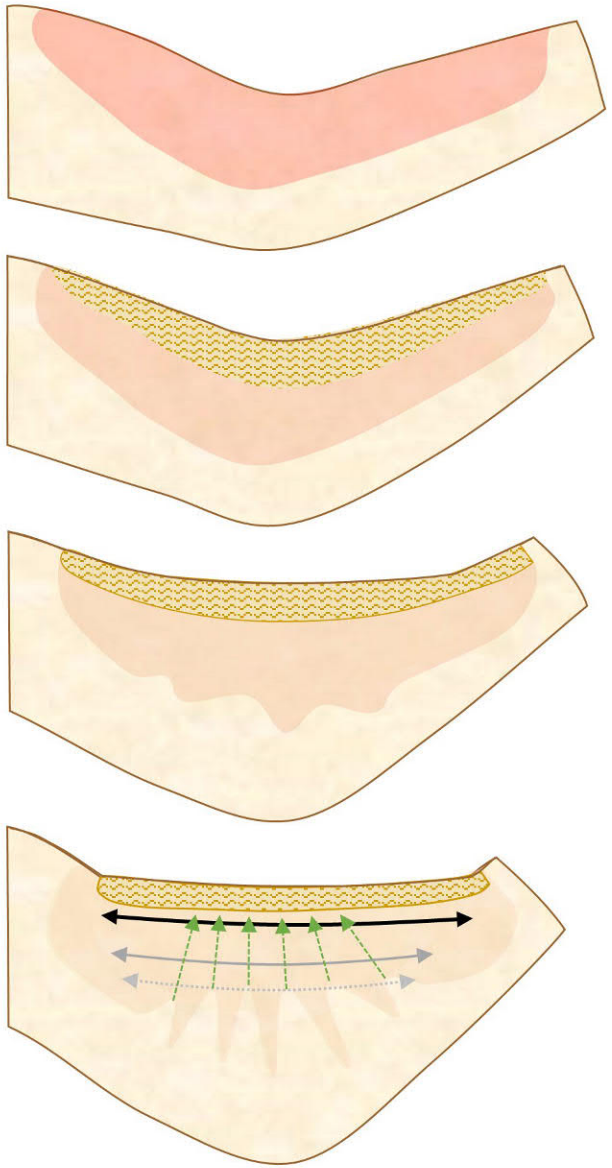
Physiology & pathology :
Bone mineralization - demineralization
Scar spectrum: mechano-reactive
-vs- injury-reactive -vs- pathological
Effects more susceptible during or after
injury – inflammation – wound-healing

Wounds & healing :
fracture healing and repair
bone remodeling
heterotopic ossification at joints
passive joint contractures
tendon-ligament repair – solid vs mush
tendonization of flexor scar
relaxation of extensor scar
edsmi – motion
serosal metaplasia and bursa formation
pseudarthroses
non-adherent repairs and flaps
vent induced pulmonary fibrosis

Clinical care :
Therapeutic loading -vs- shielding
Intramedullary nails
Compression plates
Dynamic splinting
Serial casting
Distraction & coaptation devices
Orthodontia
Z-plasties & interposition flaps

Embryonic tendon-ligament genesis
- and - post-injury, post-inflammatory
Tendinous metaplasia and joint contractures.

A non-linear self-organizing system, parsimonious, closed-loop reference driven.

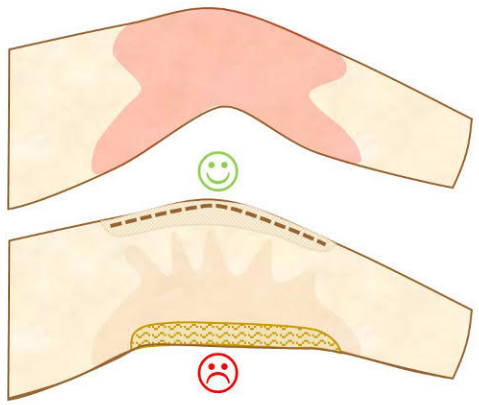


Hypertrophic scar. Discriminate:

Normal scar spectrum – fibroblasts functioning properly with closed-loop control in response to unusual circumstances or errant inputs.

- versus –

Pathological scar spectrum (e.g., keloid) – fibroblasts acting errantly, open-loop, uncontrolled, disregarding references.



Flexor surfaces = repetitive stress.
Process reacts to minimize strain = tendinous scar.

Extensor surfaces = sustained strain.
Process reacts to minimize stress = scar atrophy.

Incremental strain therapies

Serial splinting - casting (soft tissues)
Serial splinting - casting (skeletal)
Tissue expansion
Coaptation devices (soft tissues)
Distraction - coaptation devices (skeletal)
Orthodontia

Increments

Soft tissues : 15-20 days (2-3 weeks) intervals, optimizes biological effect (longer preferred) versus clinical efficiency (shorter preferred).

Bone-skeletal : 4-6 week increments typical, same cell-stroma timeline, but extra time needed for demineralization-mineralization to adapt or support loads.

cf. Flap delays (ischemia-vascular adaptation).

*** * * Distinguish between :**
rapid short-term incremental strains achieving effect through fluid shifts, elastic deformations, yield-point micro-damage (risk of premature failure), and perceived as sustained stress (inducing strain limiting response) **- versus -** longer increments for adaptive bioplasticity.

ANATOMY : **Wolff - Davis Law**

Basic Materials and Mechanics ::
- Stress-strain, compliance
- Elasticity
- Plasticity, creep, stress relaxation

Bioplasticity ::
- Mesoderm - mesenchyme
- Transduction off force
  - tension-compression-shear
- Response to force Wolff-Davis

Wolff-Davis – comprehensive :
- Tissues subjected to sustained stress
  - *react to minimize resulting strain*
- Tissues subjected to sustained strain
  - *react to minimize resulting stress*

Relevance ::

Embryo- & organogenesis
- Serosas and bursas
- Musculoskeletal system
- Heart

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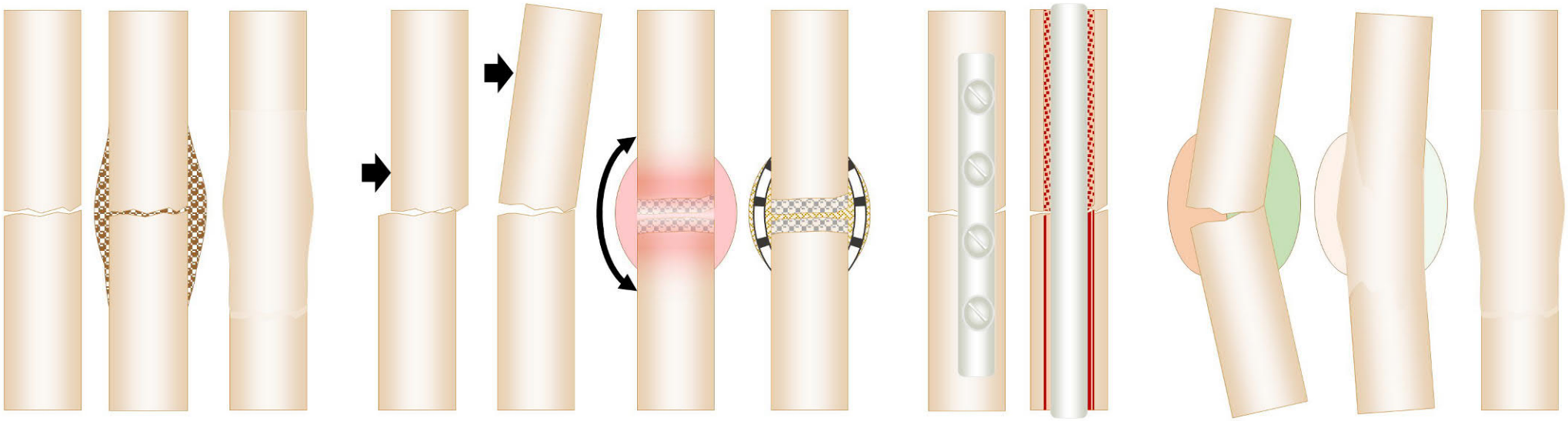
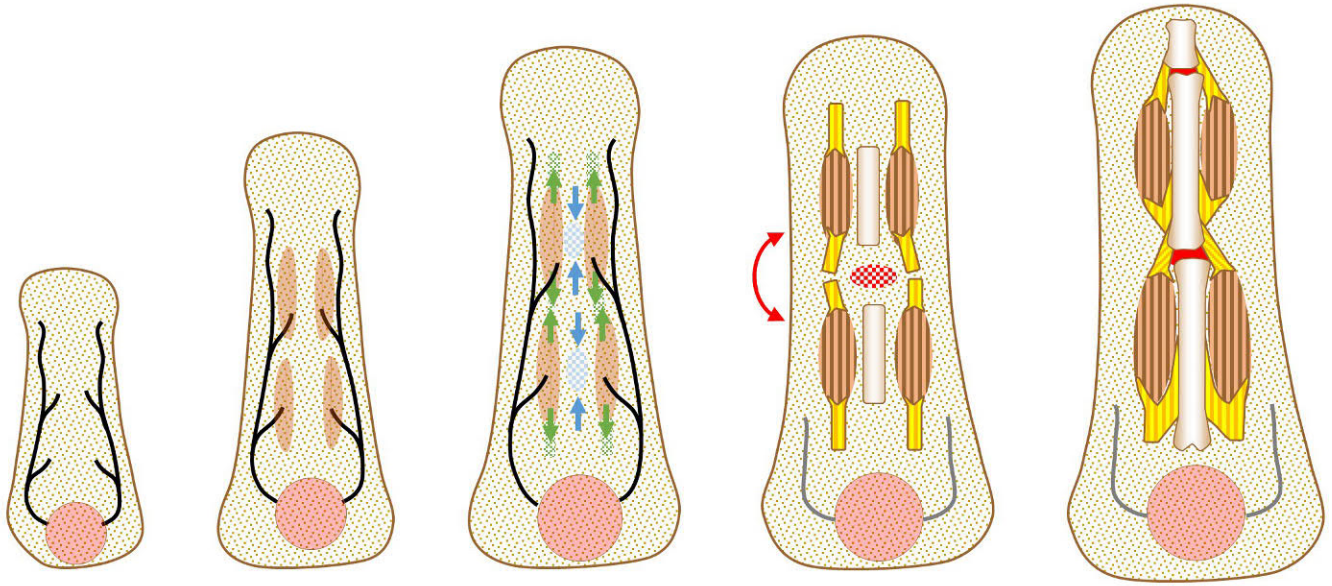


Sustained, chronic, repetitive, cyclical
Stresses induce cell - tissue Metaplasia.
Mesenchyme, wound module, scar become a tissue type – bone, cartilage, tendon ligament, bursa, serosa.

Central to these bioplastic processes are Fibroblasts.
They sense mechanical force, control on force, and they correct variances by remodeling scar - stroma – mesenchyme back to reference.

Sustained, chronic, repetitive, incremental
Strains cause tissue Hypertrophy - Atrophy.
Scar and mesenchymal structures retain their identity, but reduce - augment until proper tension - length are restored.



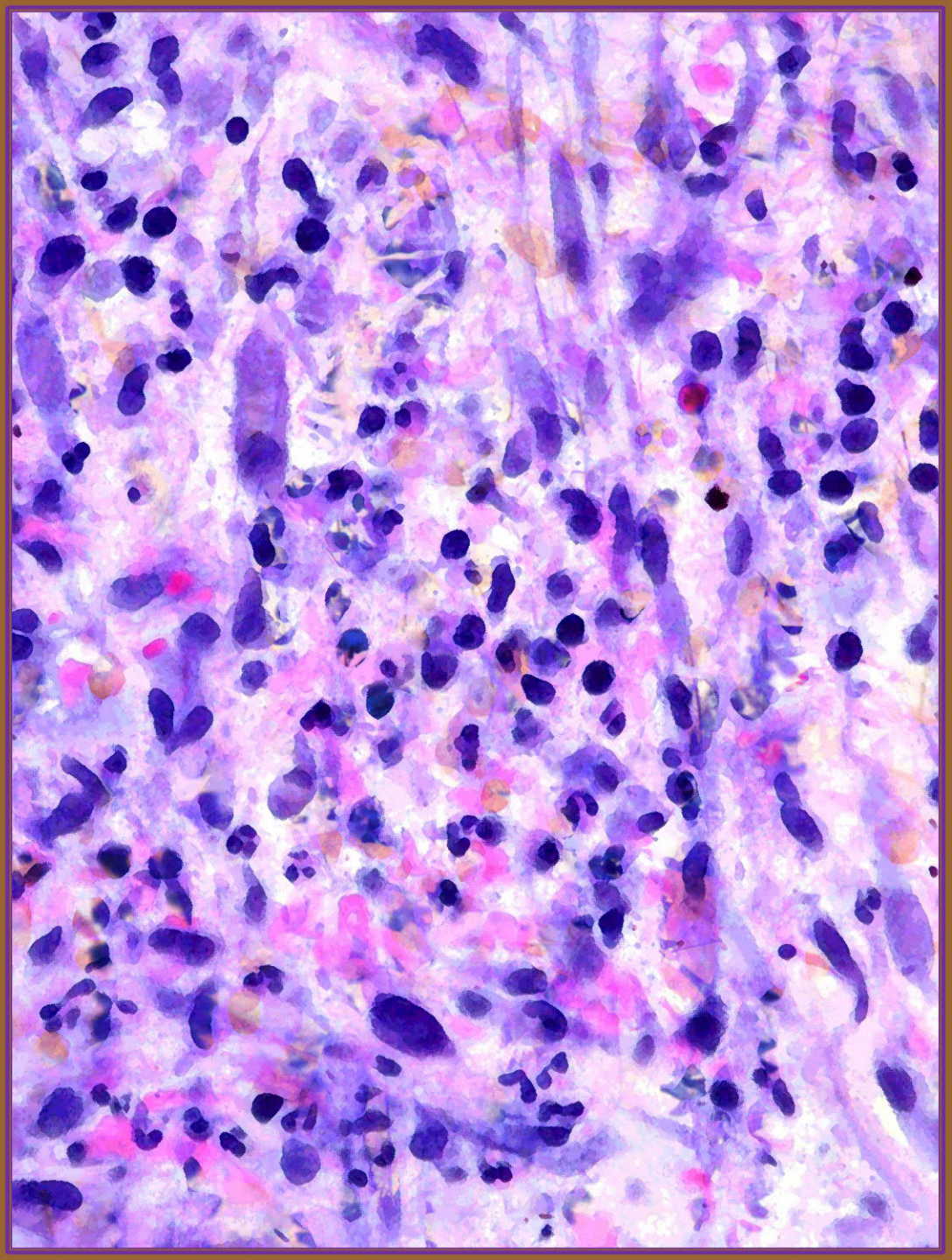
Wolff - Davis Law generalized

0 Tissues derived from embryonic mesoderm transduce and react to mechanical force.
1 Subjected to chronic or repetitive stress, they react to minimize strain due to that stress.
2 Subjected to chronic or repetitive strain, they react to minimize stress due to that strain.

Autoimmune & Hypercoagulable Disorders

Autoimmune, Chronic Inflammatory, CVD - CTD

Hypercoagulable, Micro-occlusive Disorders



Autoimmune Disorders

Why it is Important

Basics

Autoimmunopathies, CVD-CTD's.
Incidence, prevalence, etc.
Increasing awareness and appreciation.
Increasing richness of nomenclature.
Protean target tissues and presentations.
Syndromic versus unclassified presentations.
Organ pathology versus infrastructure pathology (cvd-ctd, etc.).
Diverse specialties seeing different facets.
More commonality than differences.
"Autoimmunity" is a single disease with multiple avatars and aliases.

How these diseases intersect with Plastic Surgery

Treating complications of these diseases.
(e.g. rheumatoid hand, chronic wounds, nose recon after gpa)
Consultant / co-surgeon for closing wounds & complications.
(e.g. ortho close joints & implants, general surgery fistulas)
Your patients who coincidentally have autoimmune or cvd-ctd dx.
(avoid disease flareup, avoid wound-surgery complications)
Your patients with established ai-cvd-ctd dx who have flareups.
(get control to protect patient and your surgery and wounds)
Your patients without prior ai-cvd-ctd dx,
who have unexpected complications of trauma or surgery.
(need evaluation, diagnosis, initial rx, planning & referrals)

Autoimmune Pathology

Acute versus chronic inflammation

Acute inflammation = neutrophilic.
PMN neutrophils.
Non-specific primary response to any injury.
Hot feverish inflammation.
Rubor – tumor – calor – dolor, & drainage, lysis, ulceration.
Reactive healthy –vs– autonomous-idiopathic pathological.
(pg, pan, lcv, mpa, sweet's, et al)

Reaginic inflammation = IgE.
Basophils, mast cells, eosinophils.
Allergy, etc.
Reactive healthy –vs– unbounded-idiopathic pathological.
(atopy, anaphylaxis, drug rxn, ev, egpa)

Chronic inflammation = lymphoplasmacytic.
Lymphocytes, plasmacytes (B-cells), eosinophils.
"Quiet" inflammation, standby –vs– active phases.
Mediators and markers of auto-immunity.
Breeder disorders.
(allergy, infection, hypercoag, drugs, chronic trauma, et al)
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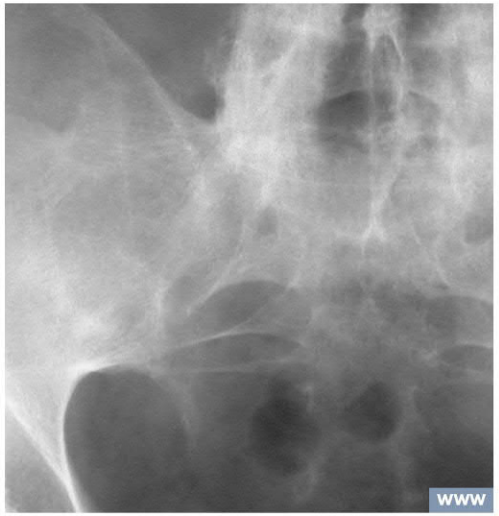

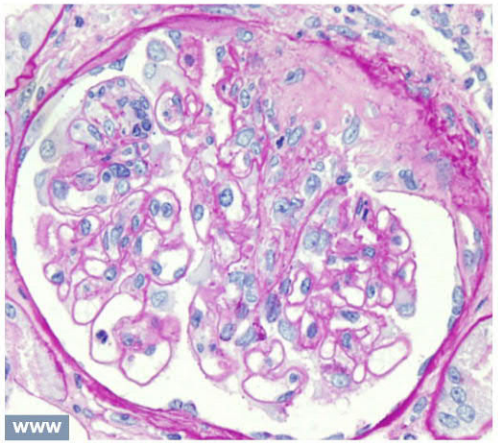

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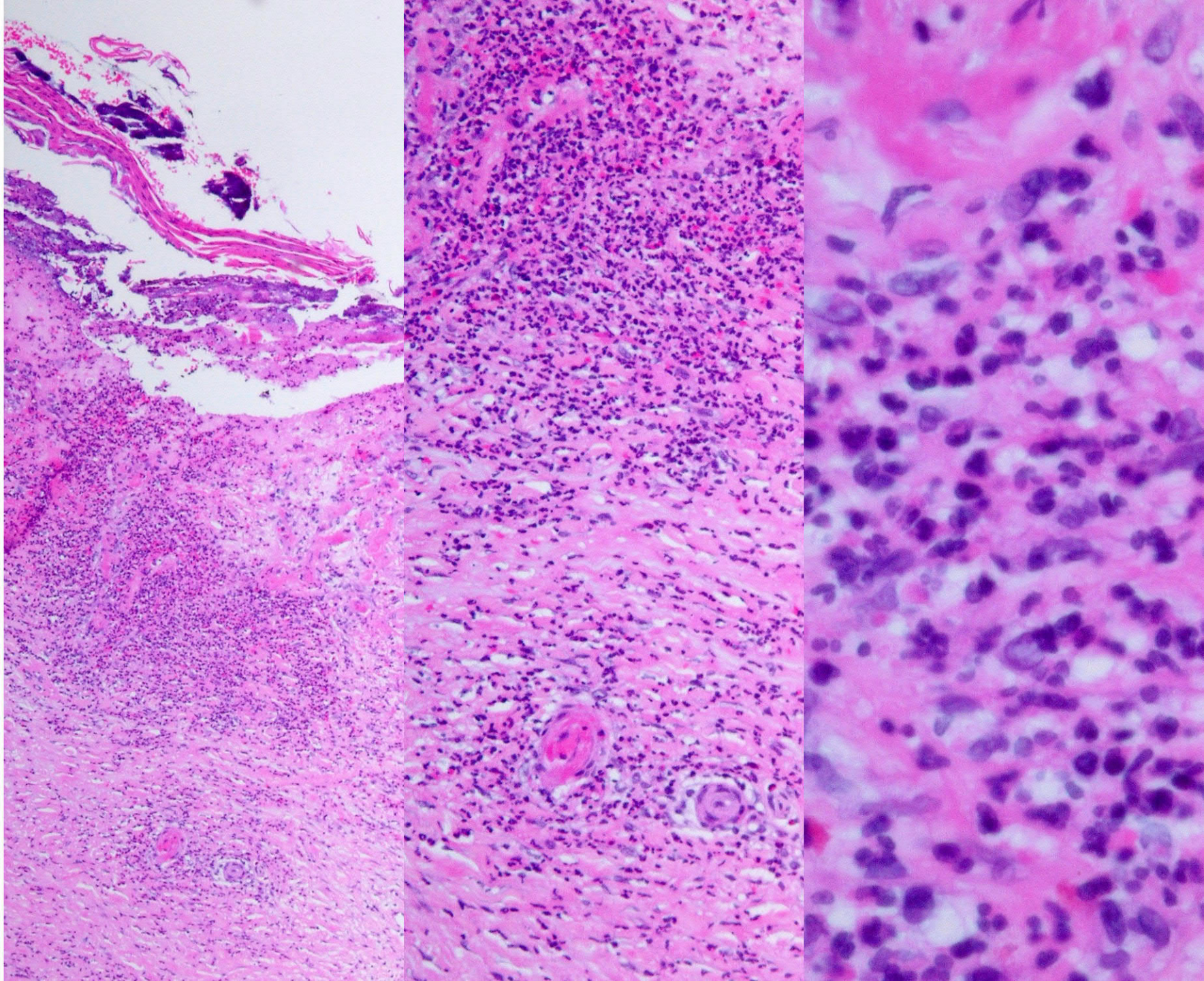

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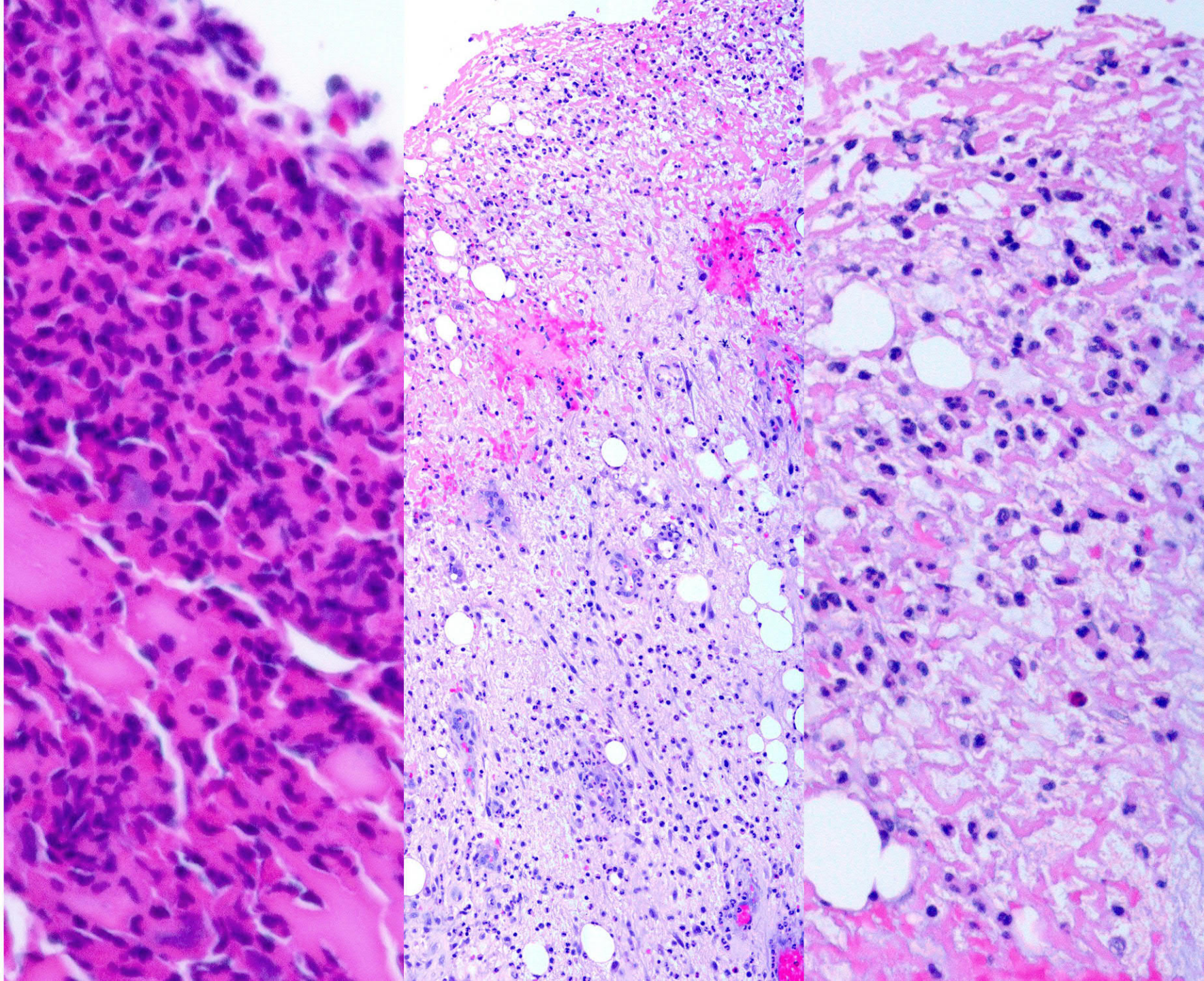

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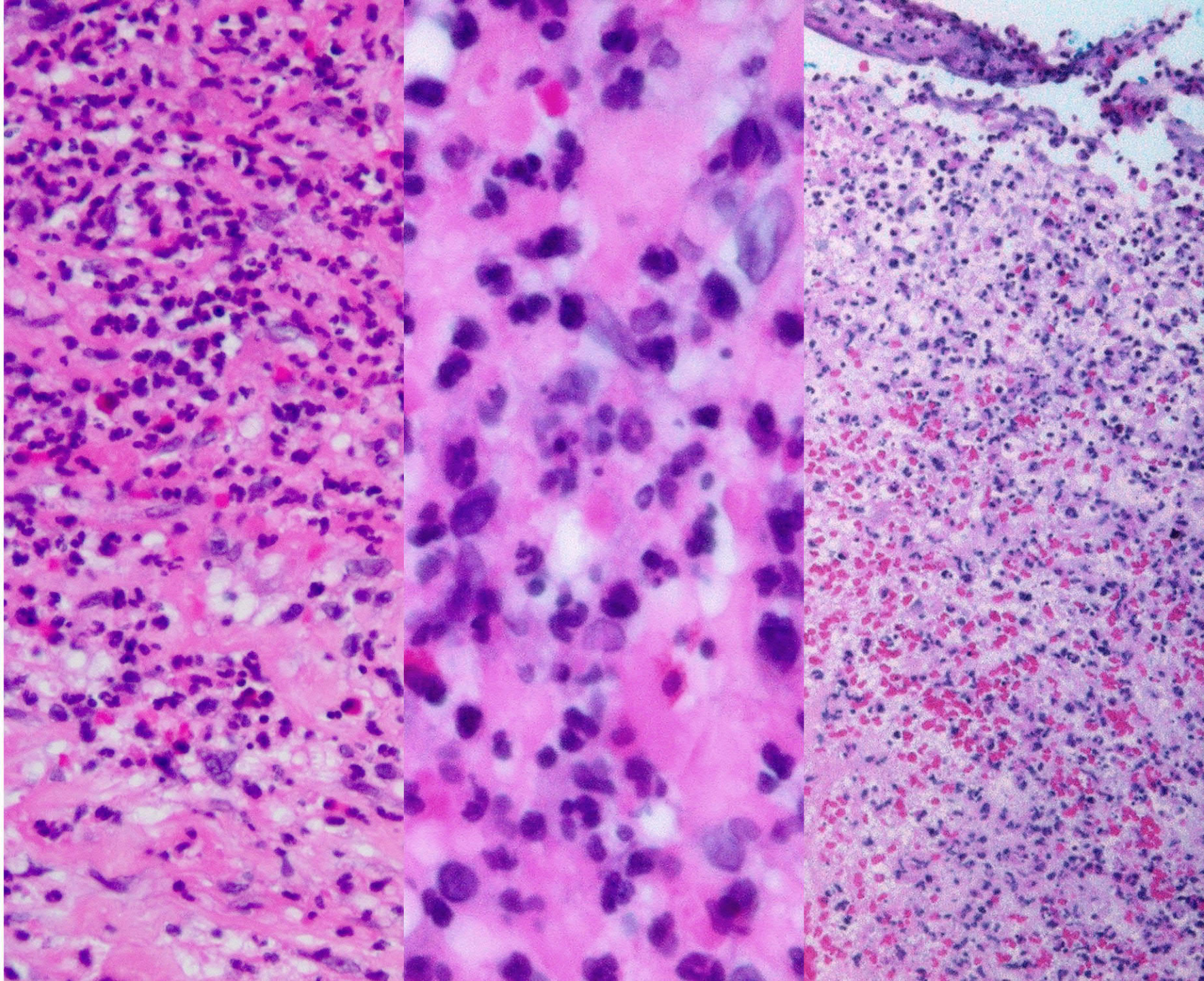

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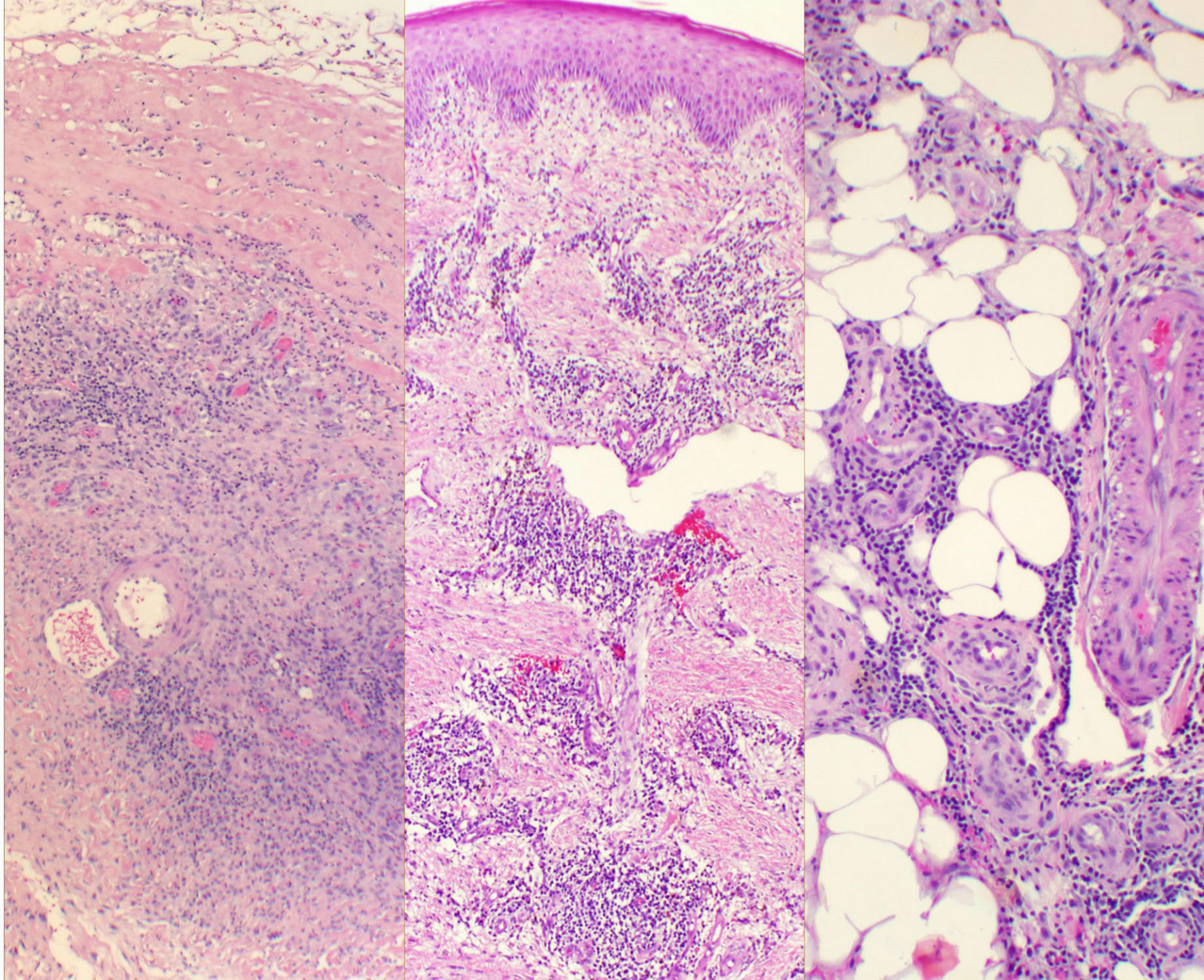

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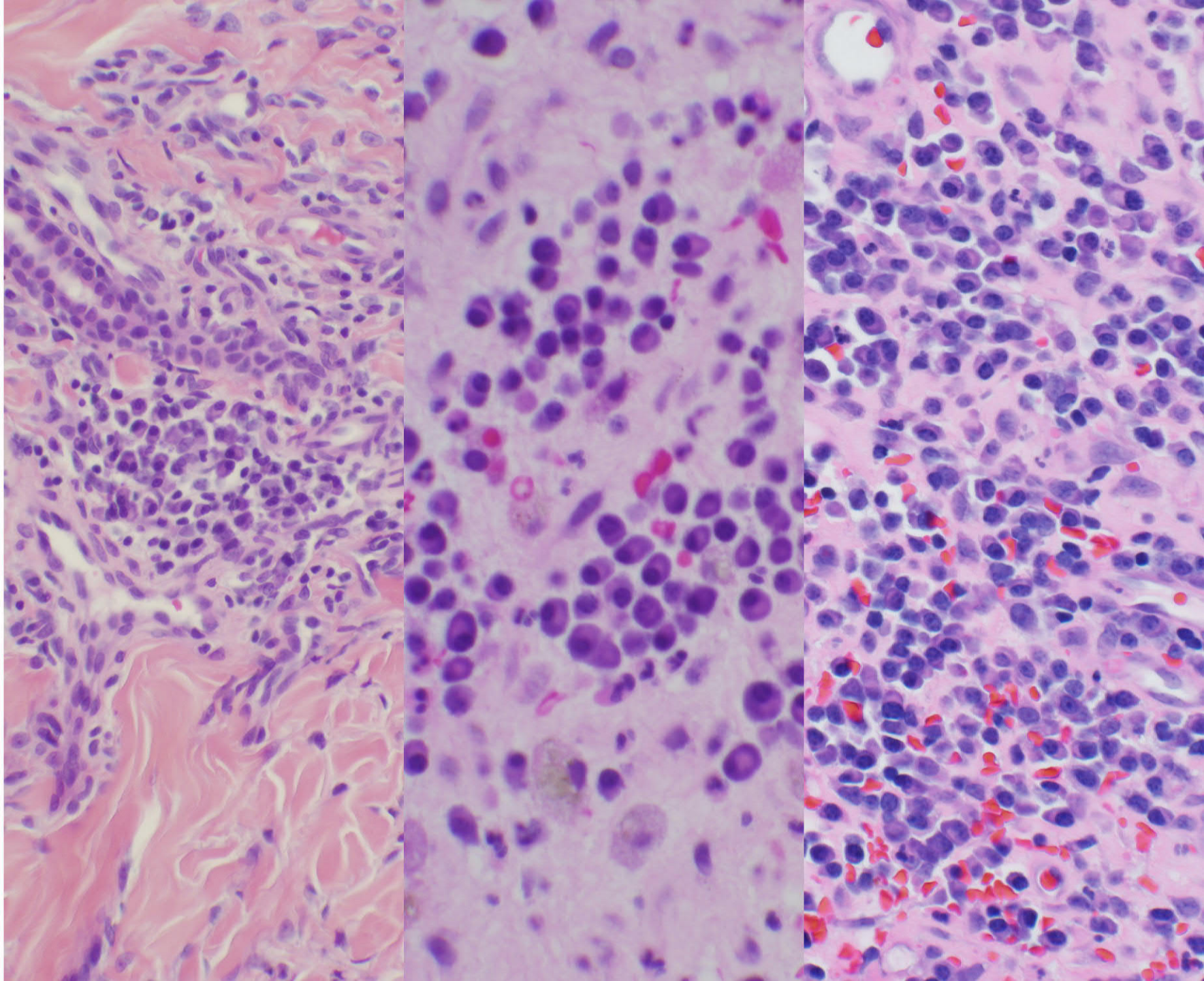

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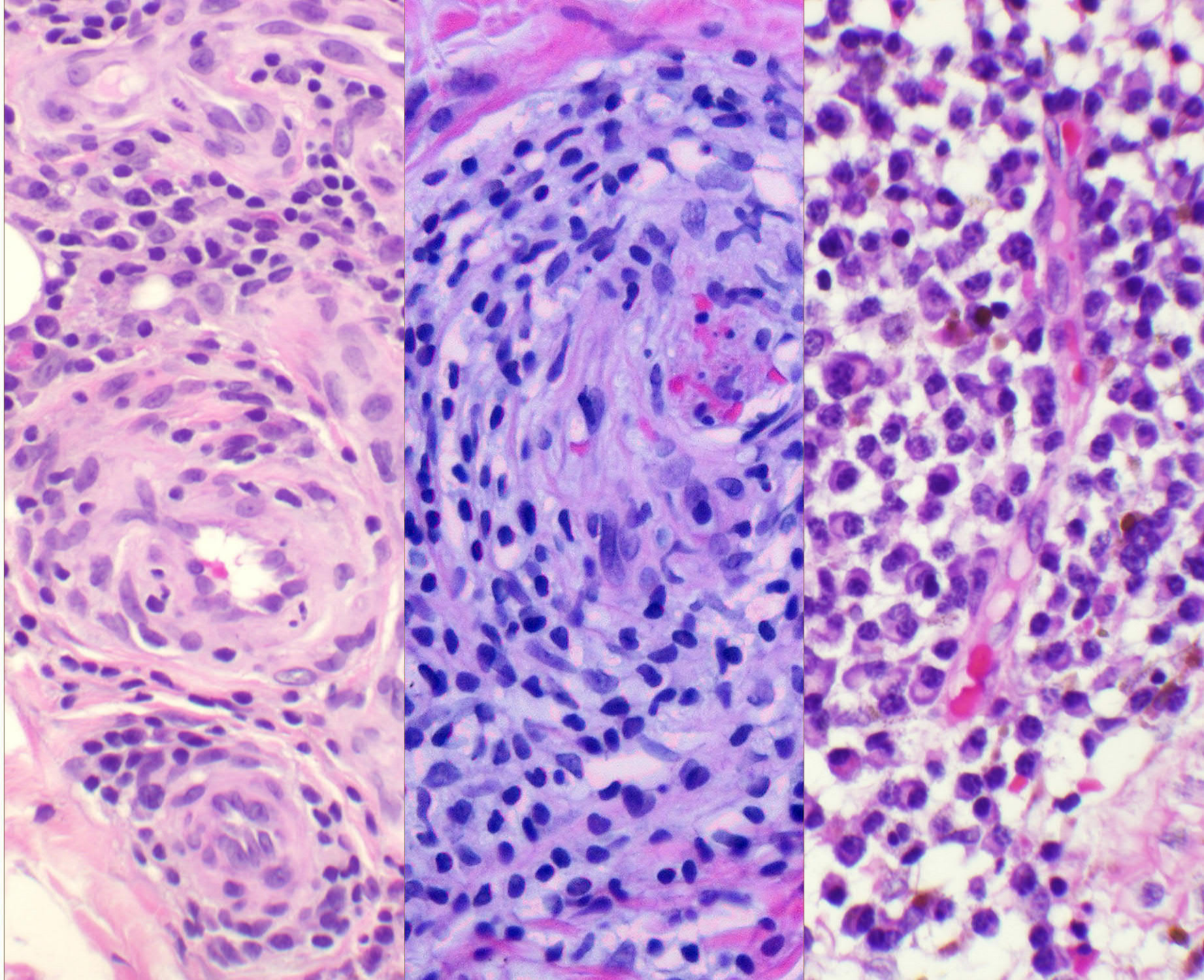
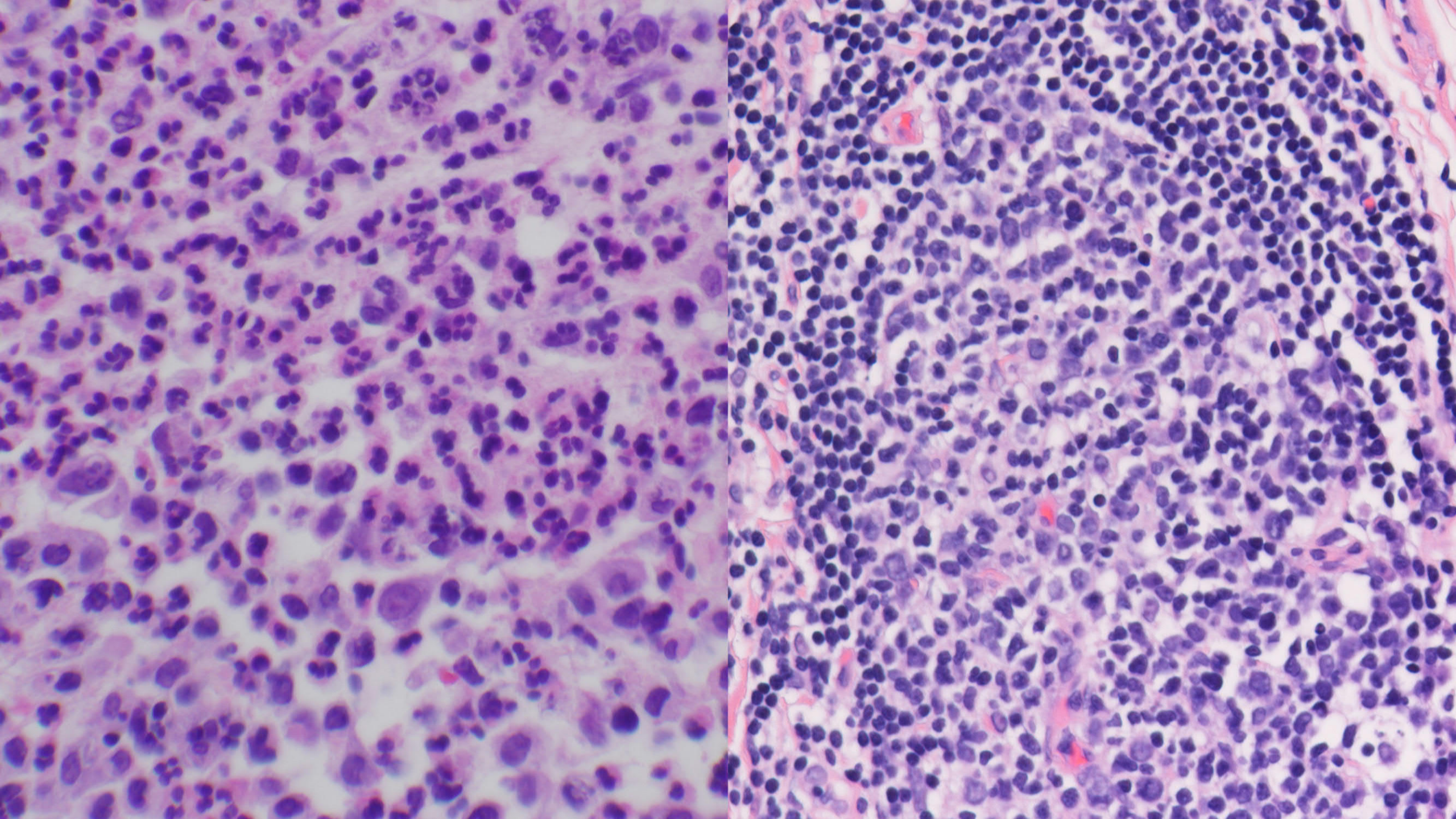
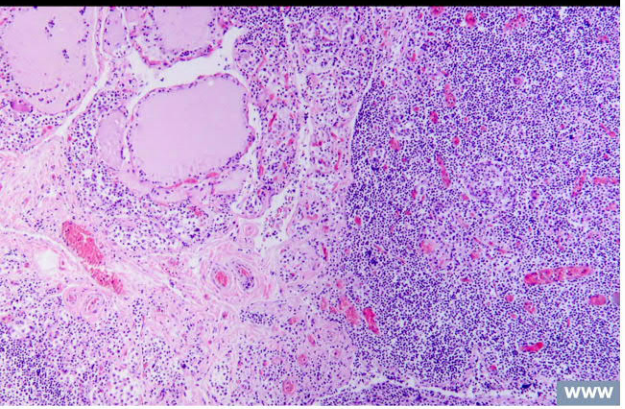
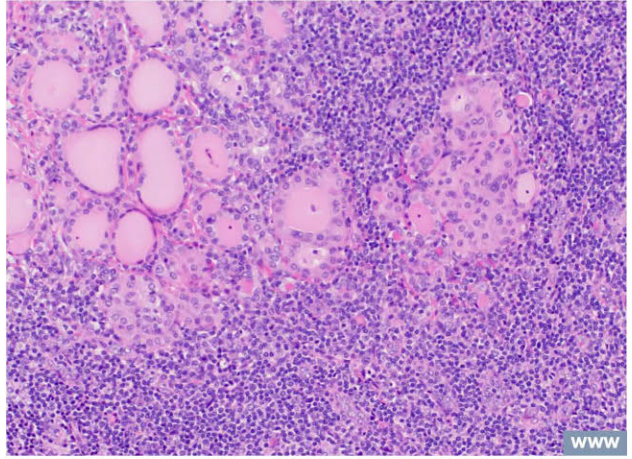
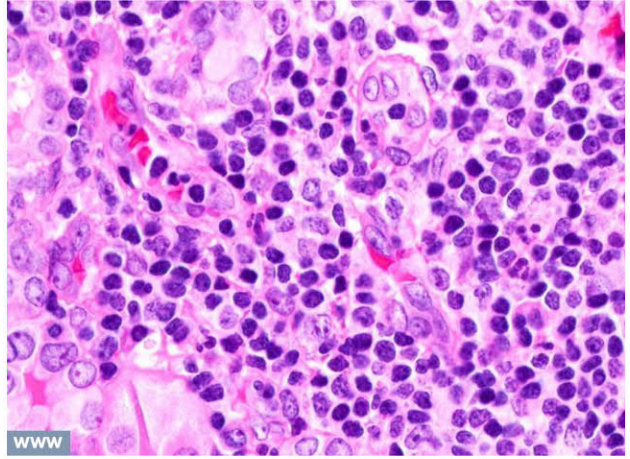


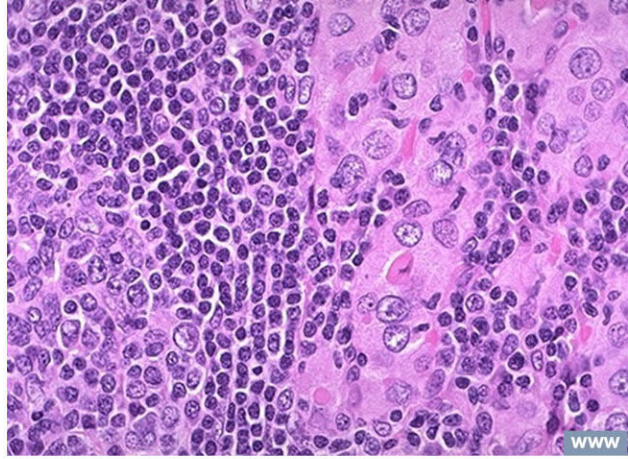


Autoimmune Thyroiditis - Hashimoto's

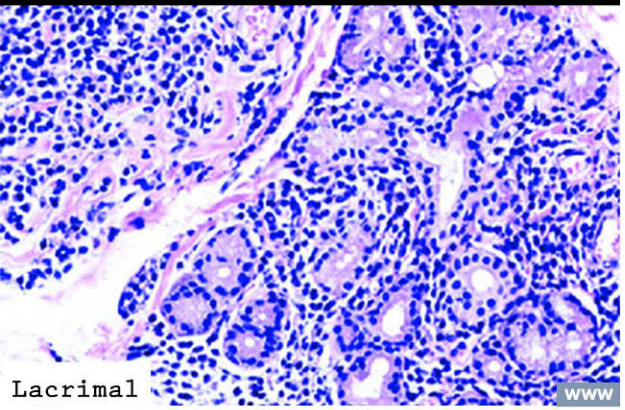


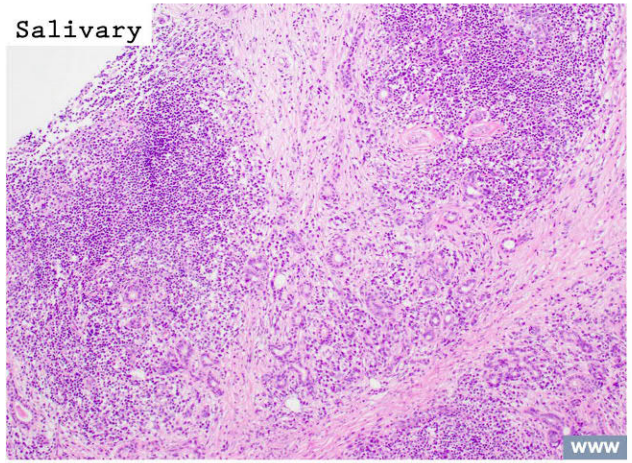


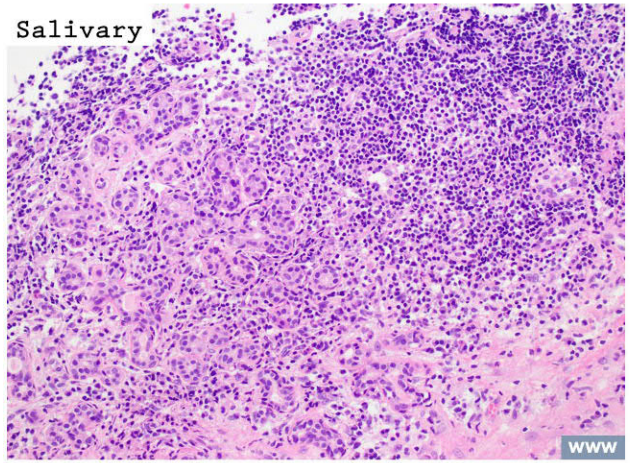


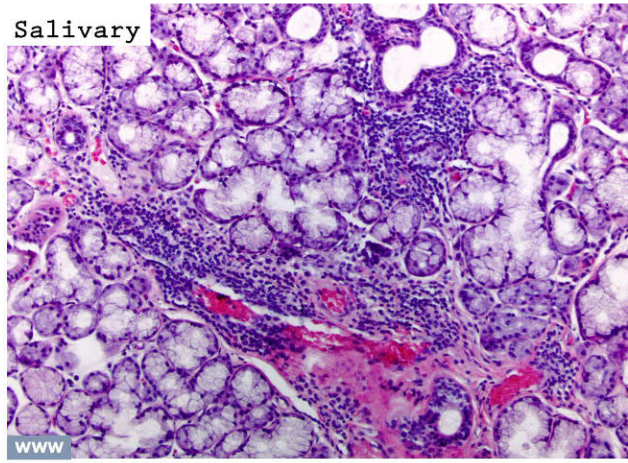


Sjögren's Syndrome

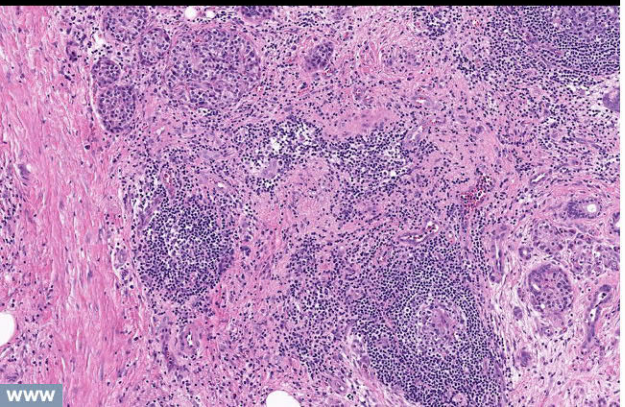


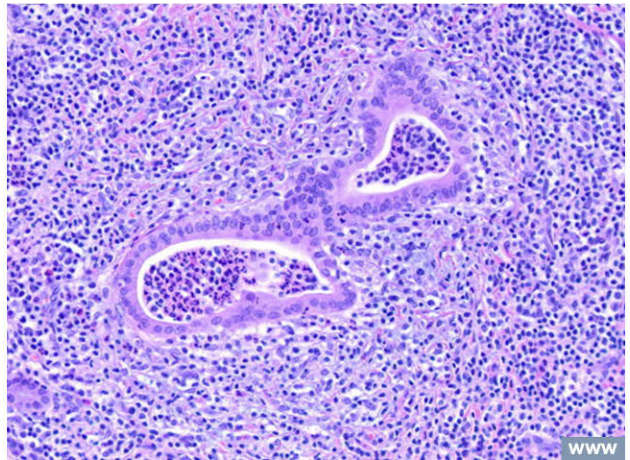


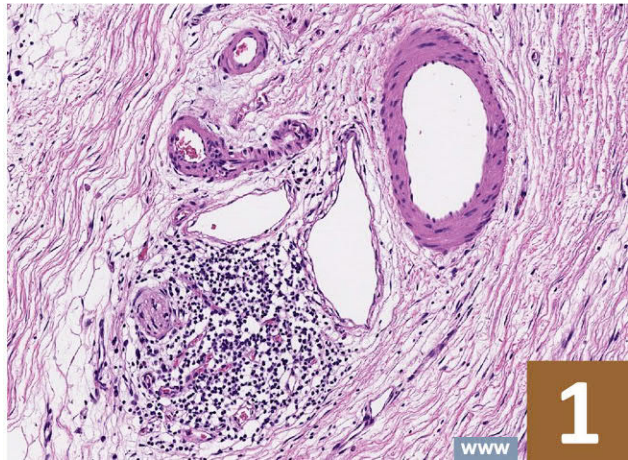




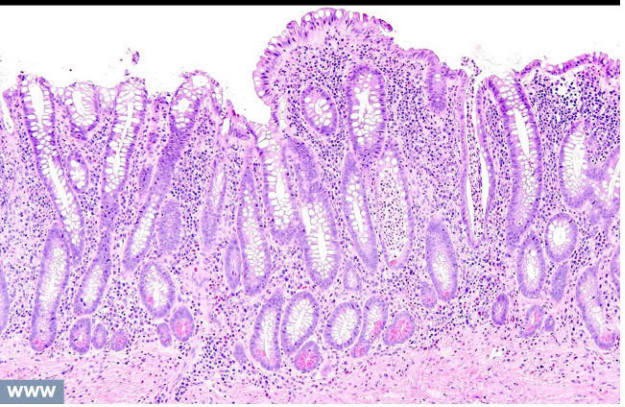
Autoimmune Pancreatitis - AIP

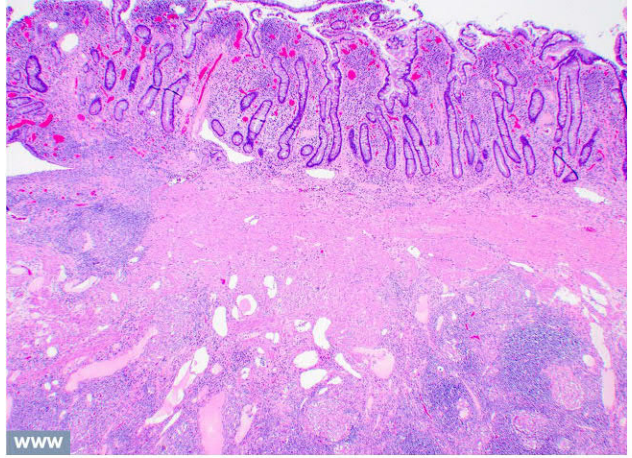


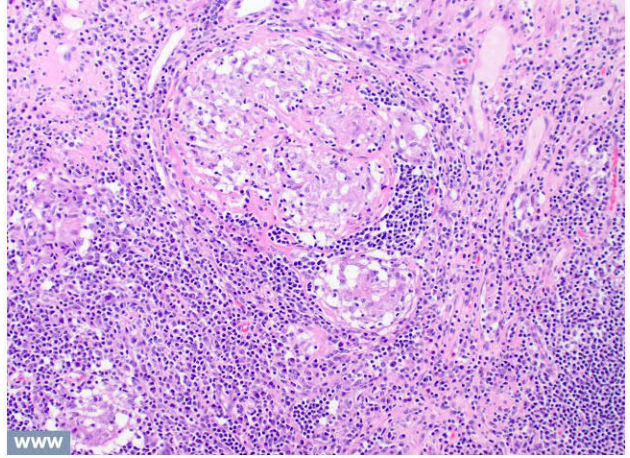


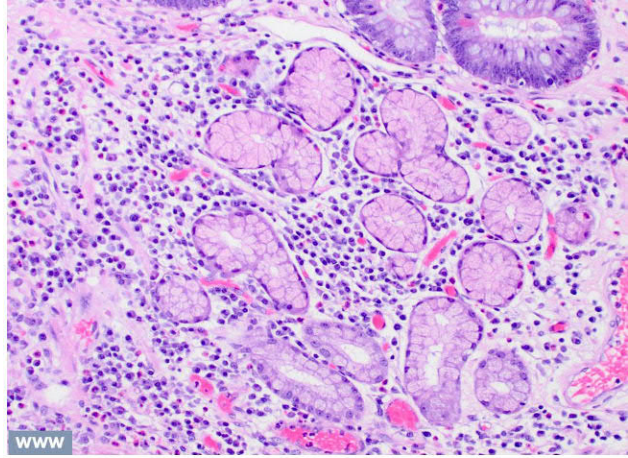


IBD – Crohn's

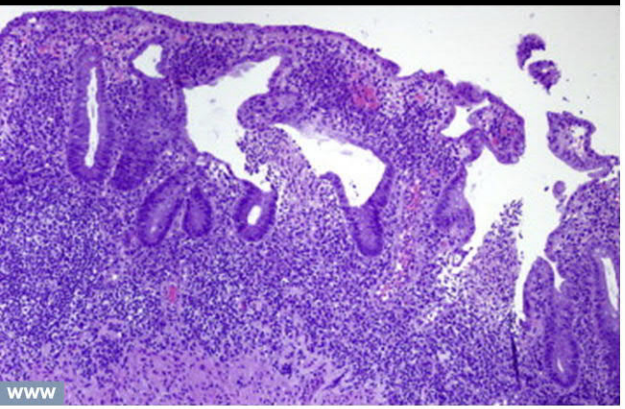


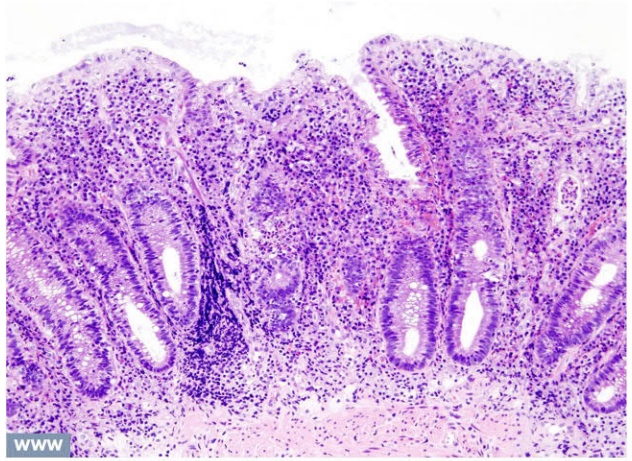


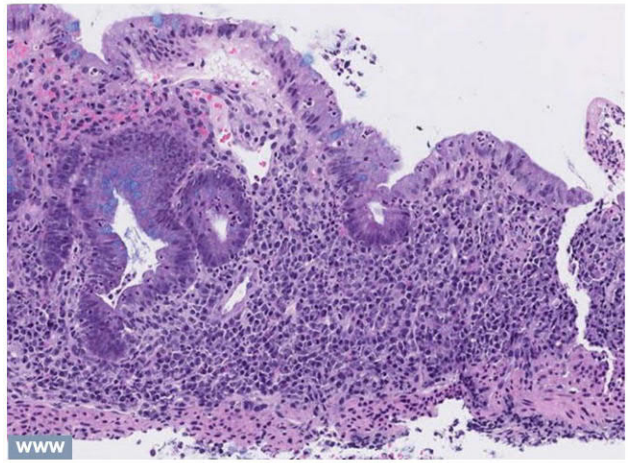


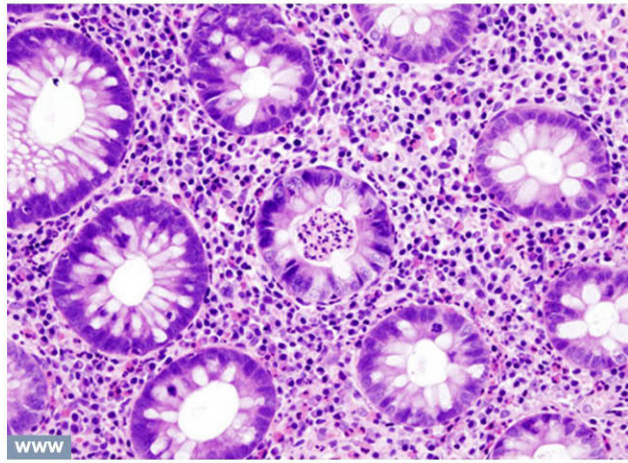


IBD – Ulcerative Colitis

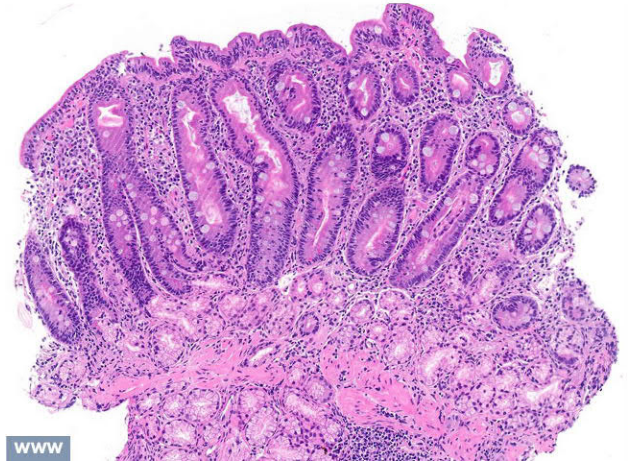




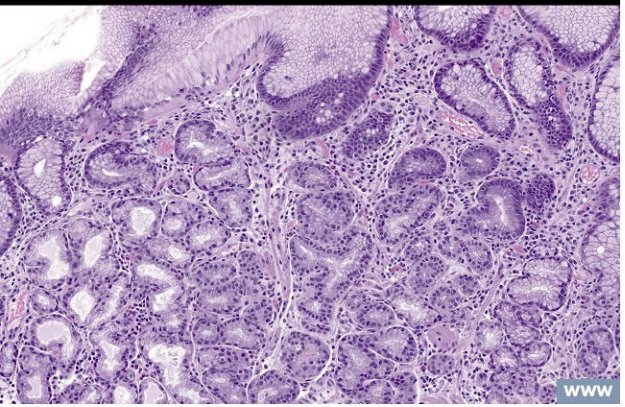


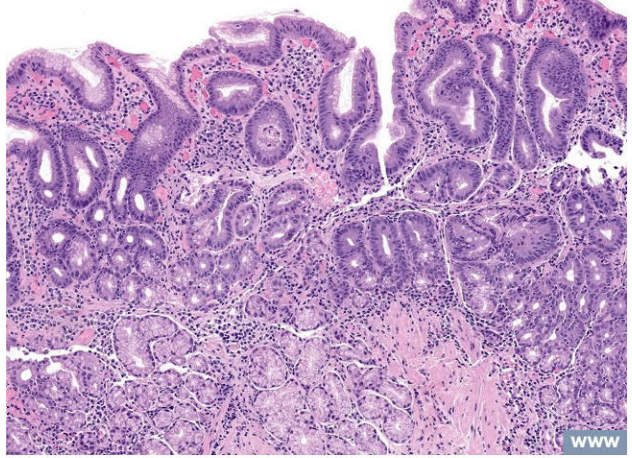


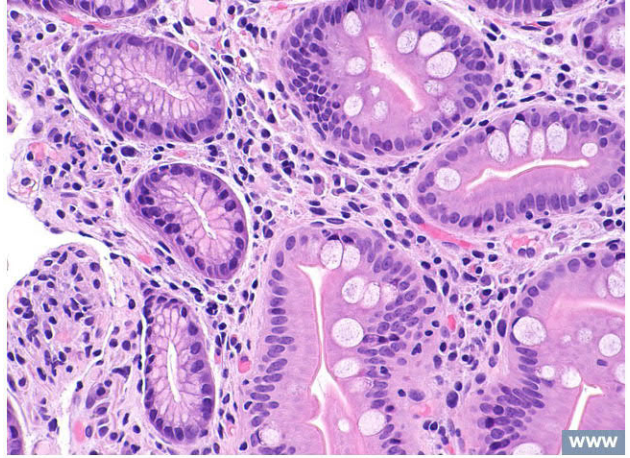
IBD – Lymphocytic Colitis

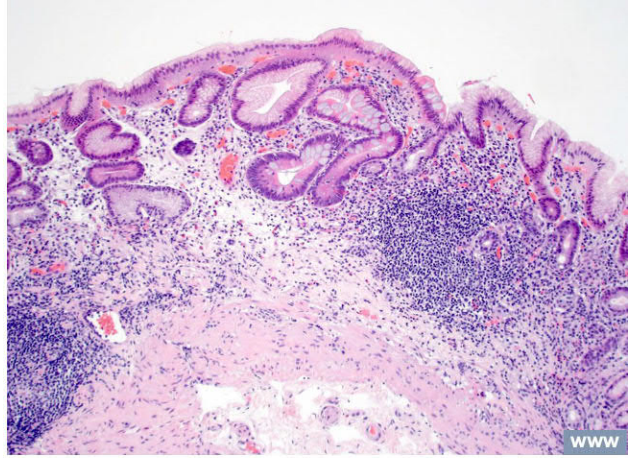


Autoimmune Gastritis

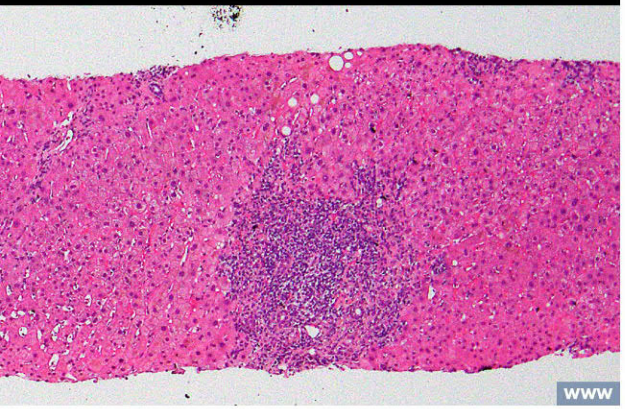


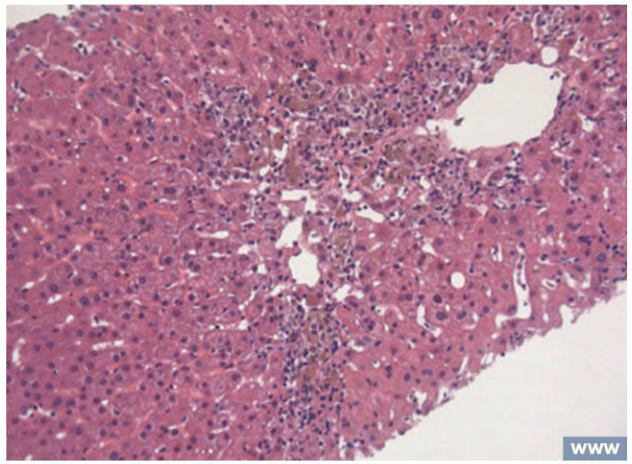


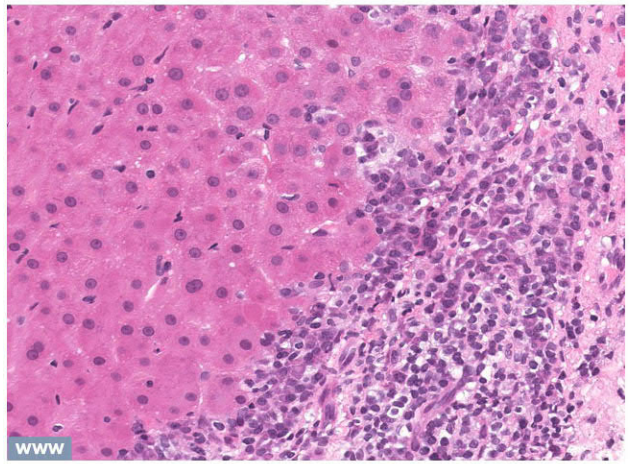


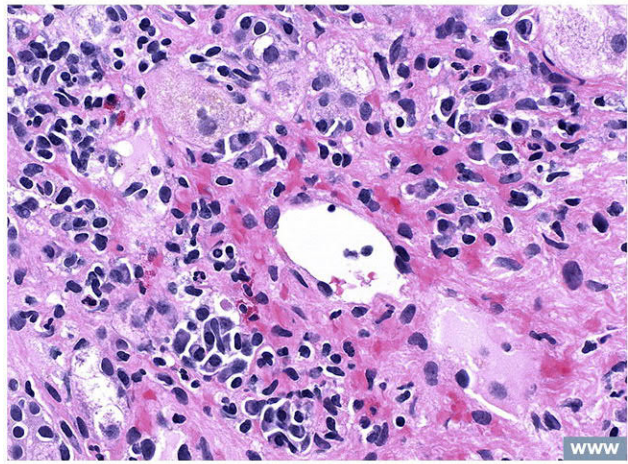


Autoimmune Hepatitis

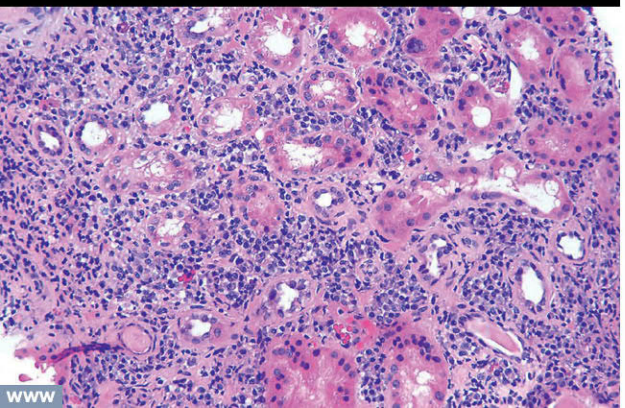


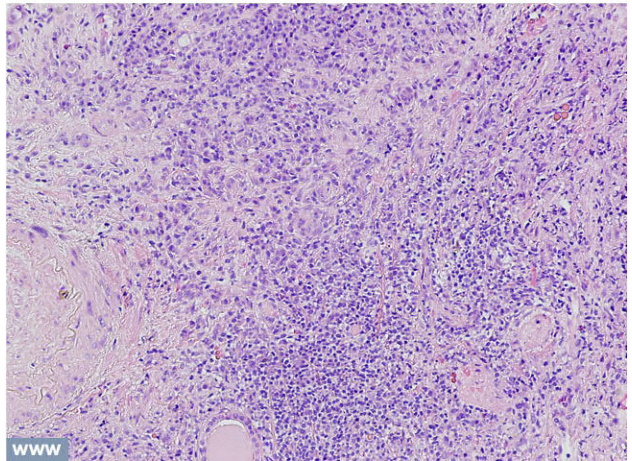


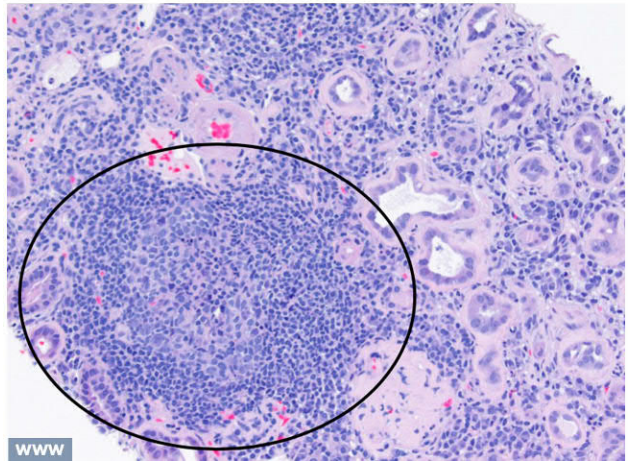


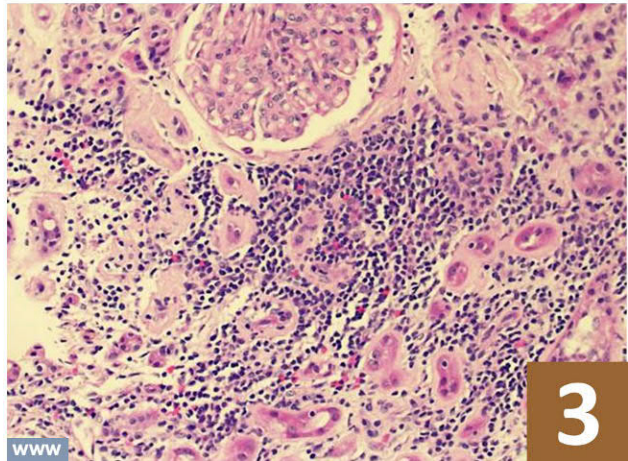


Autoimmune Nephritis

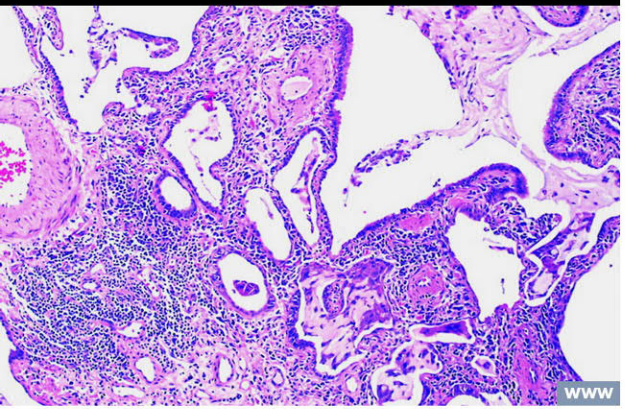
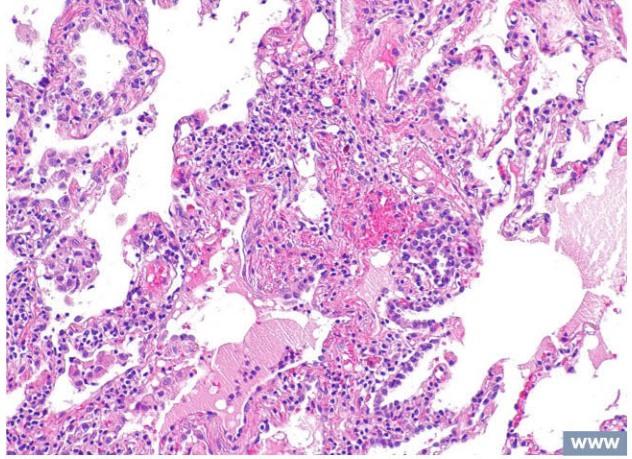
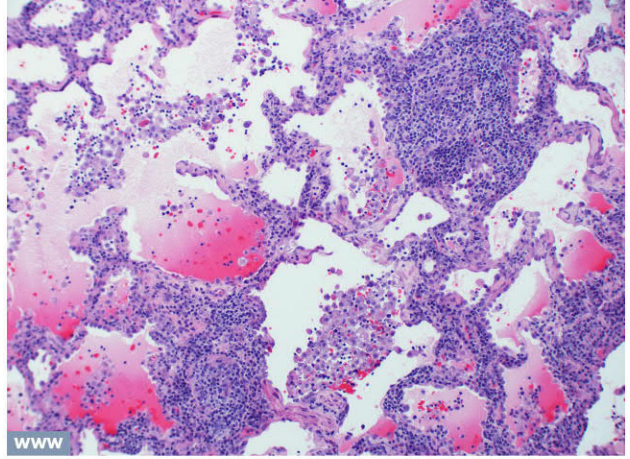
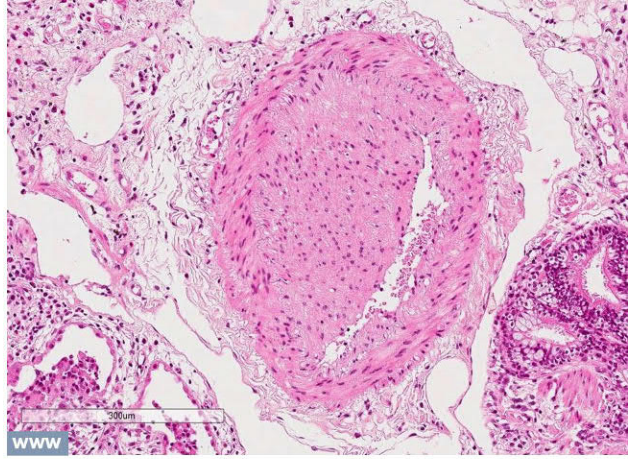




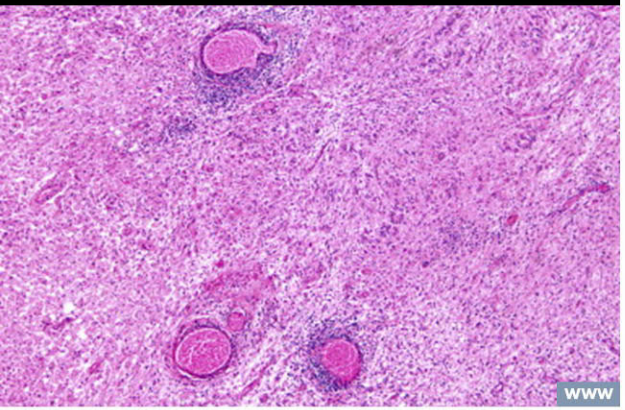
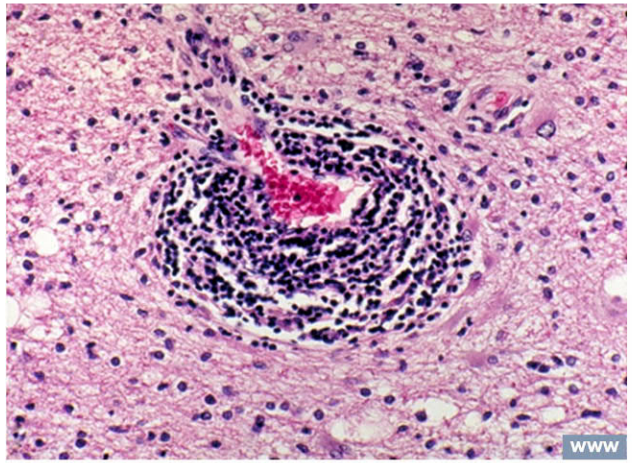
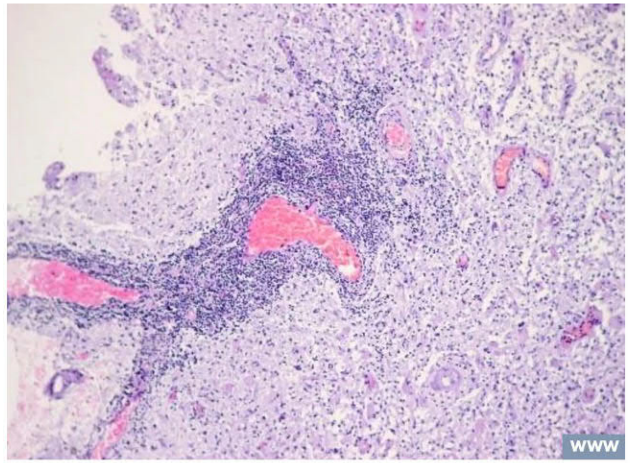
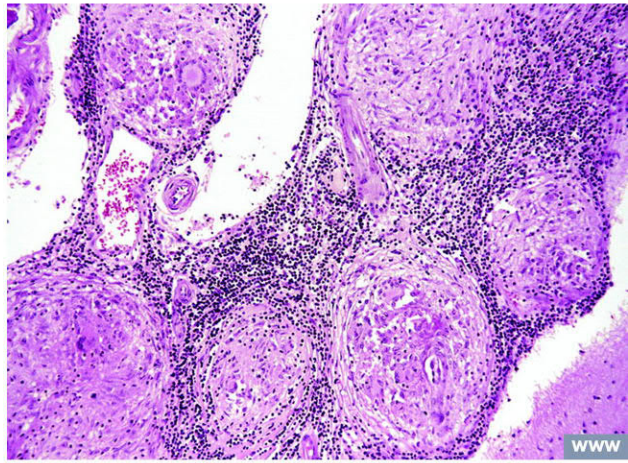




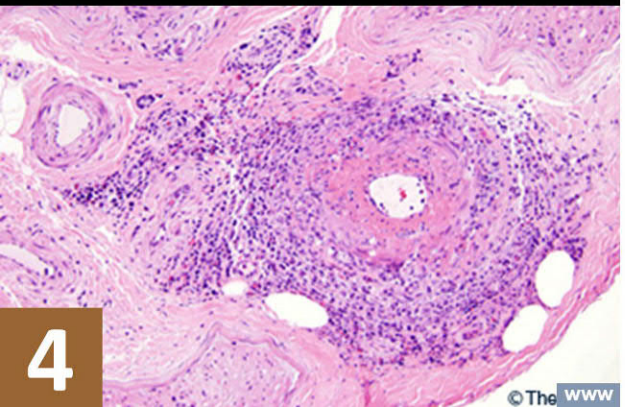
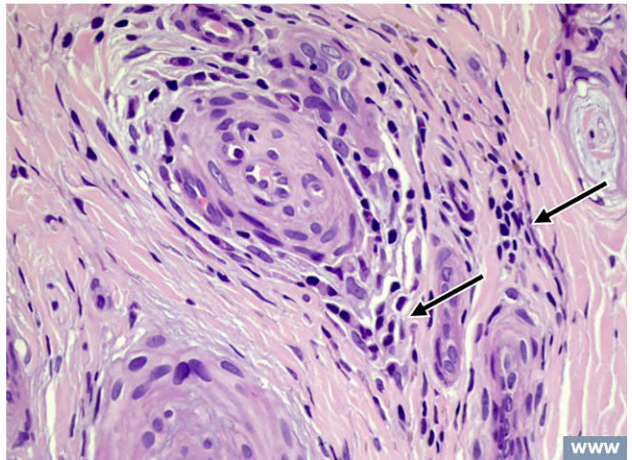
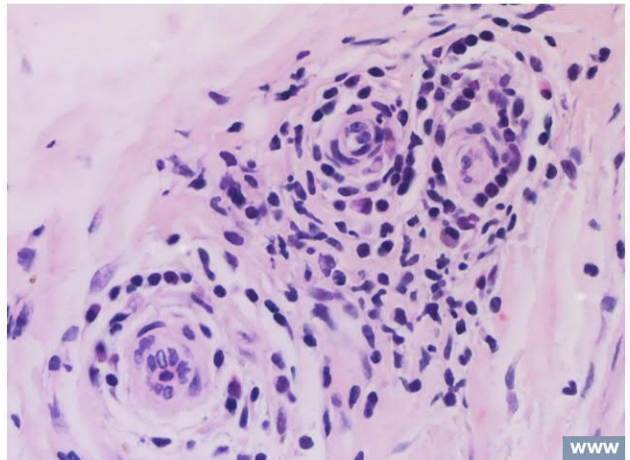
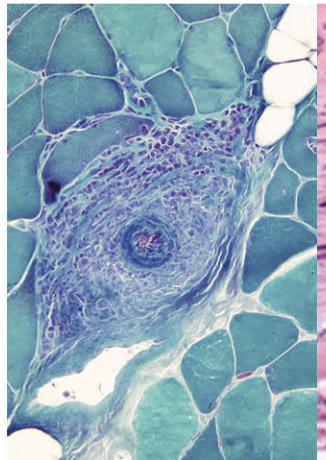
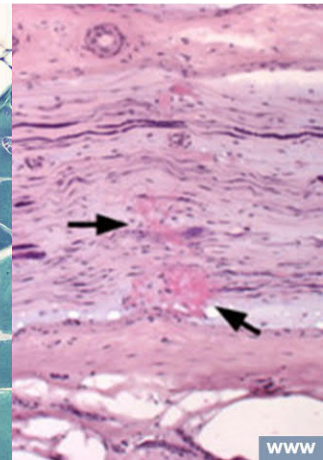
ILD-LIP – Lymphocytic Interstitial Pneumonia

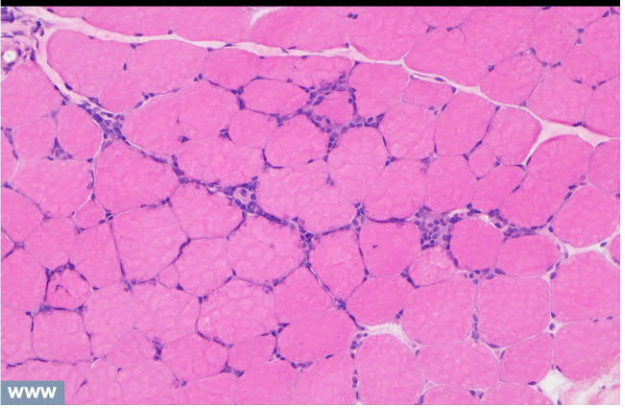
Multiple Sclerosis & Demyelinating Disorders, &al

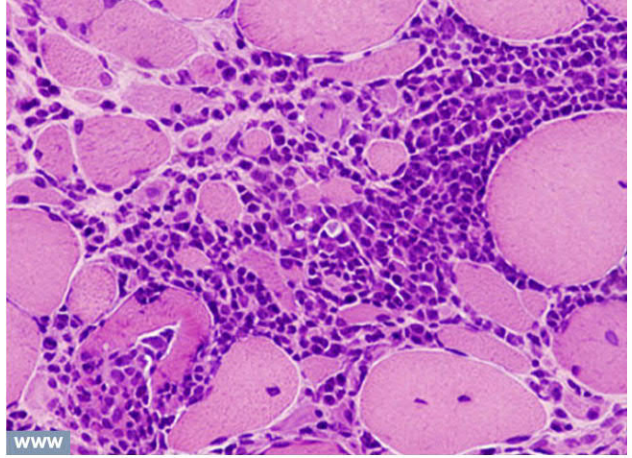





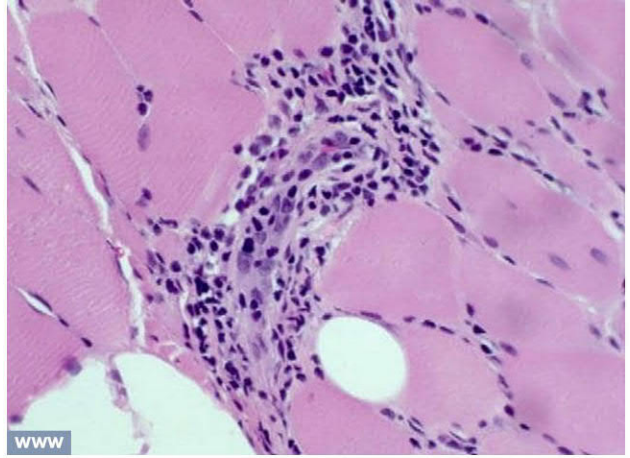
Vasculitic and Immune Neuropathy

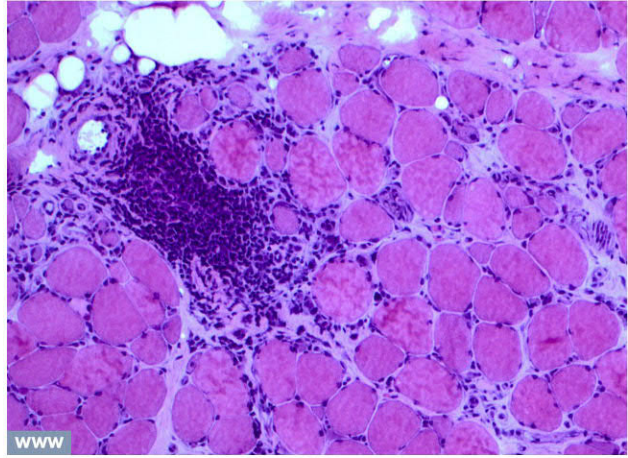






Polymyositis

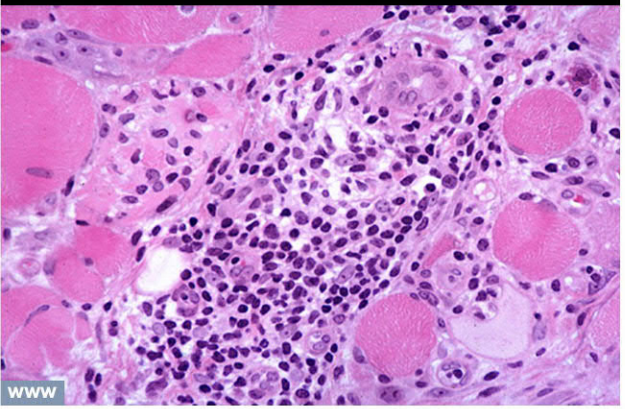


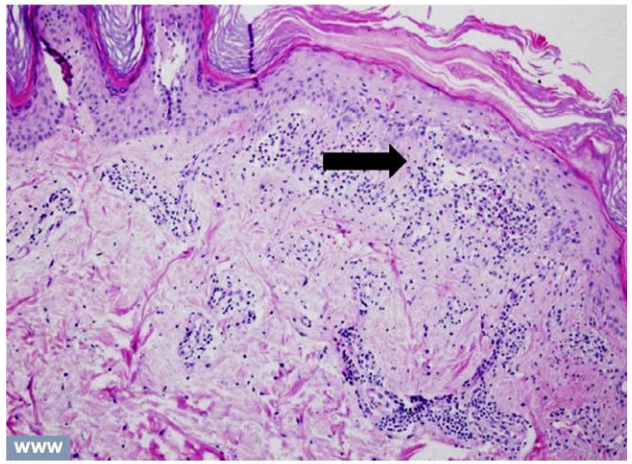


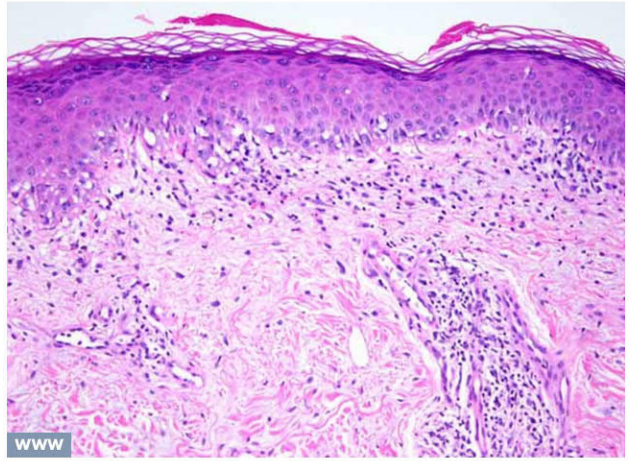


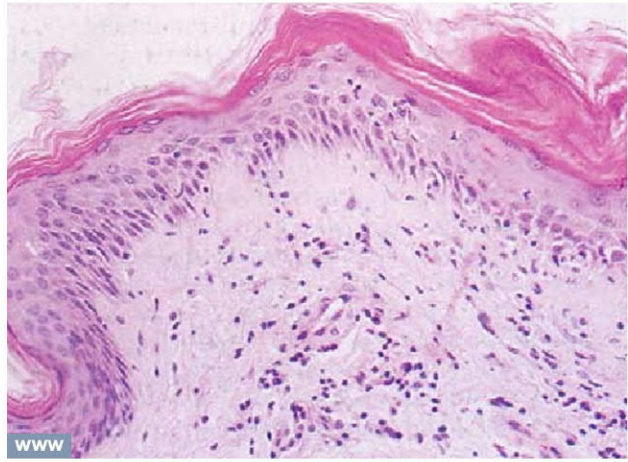


Dermatomyositis

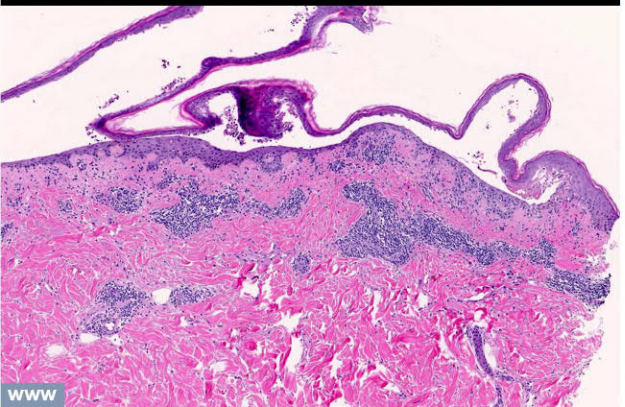


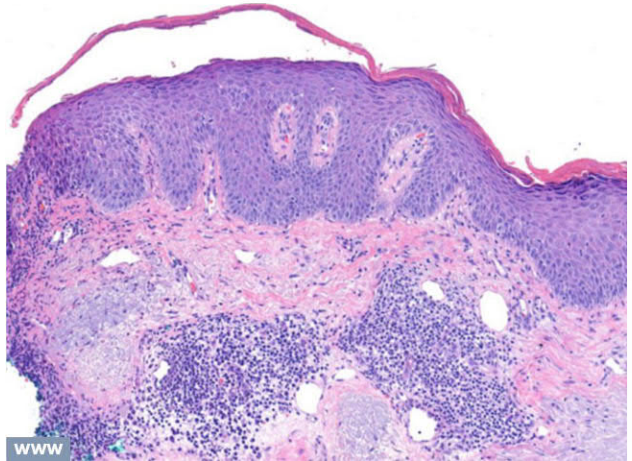


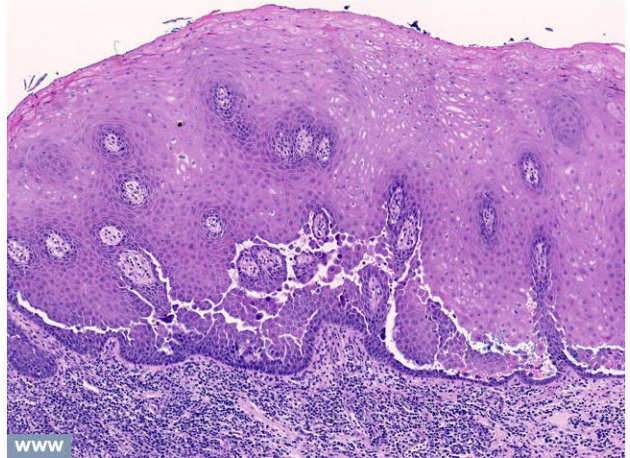


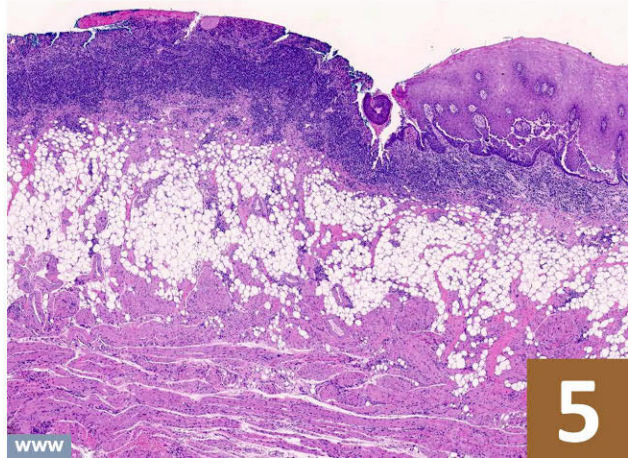


Pemphigus

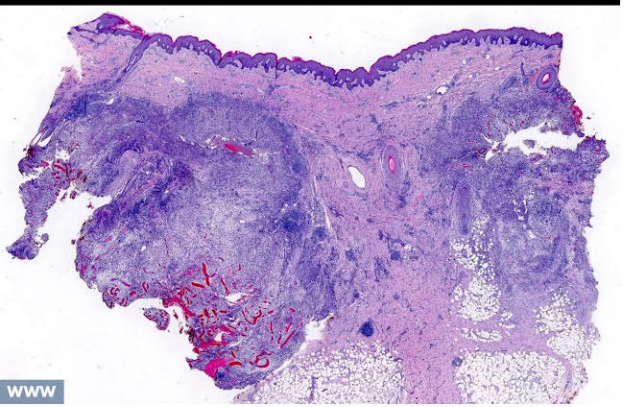


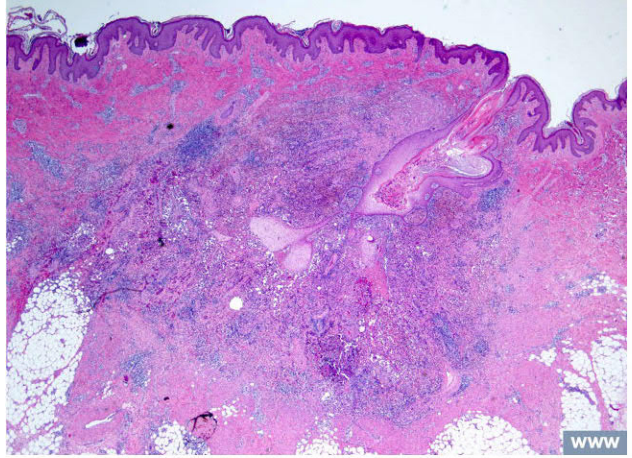


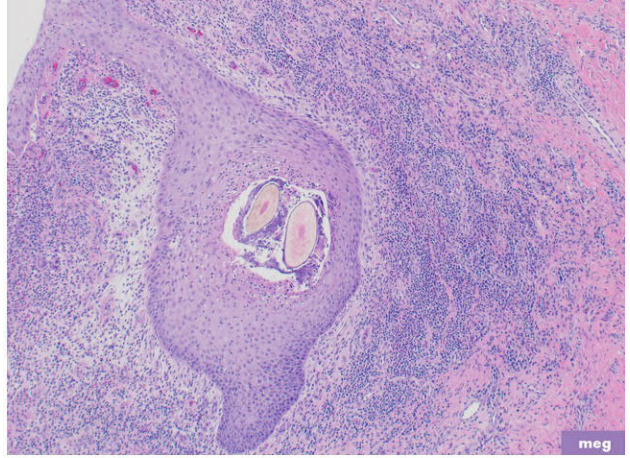


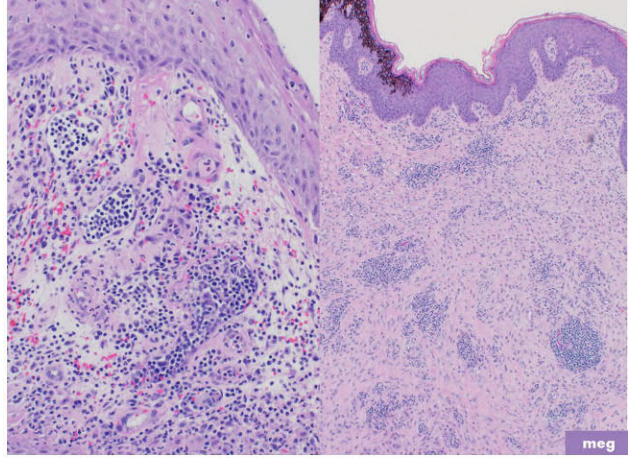


Hidradenitis / Acne Inversa

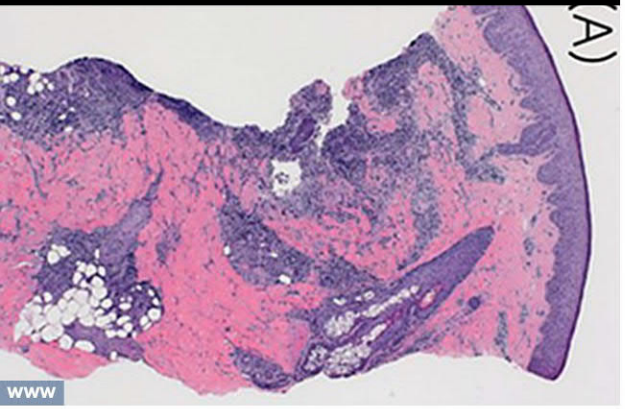


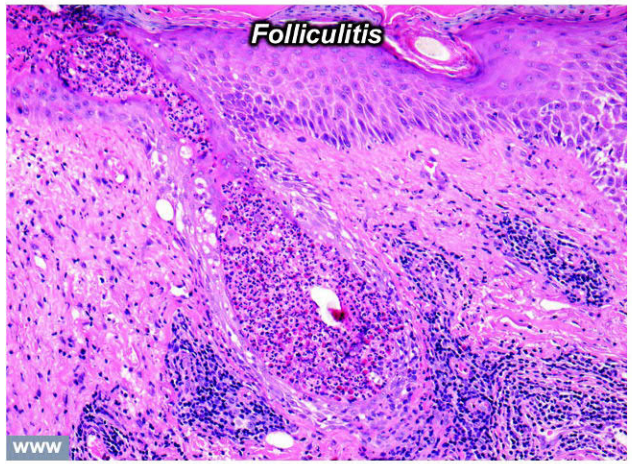


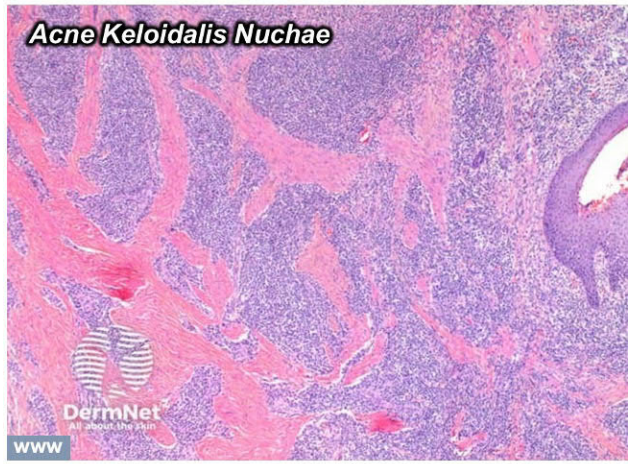




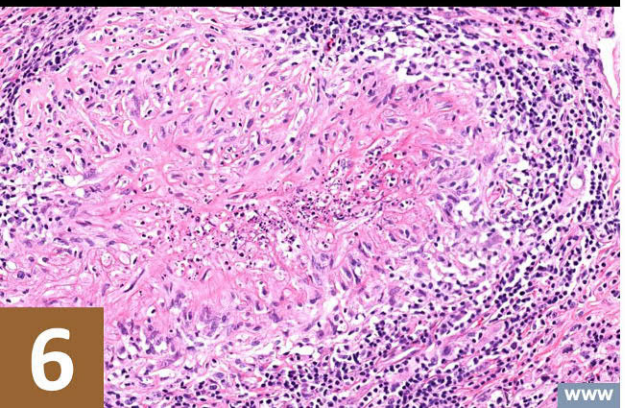
Acnes & Skin Appendages - Vulgaris / Cystic

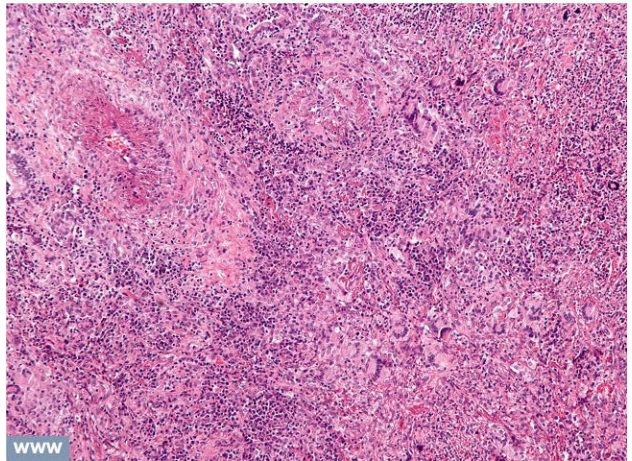


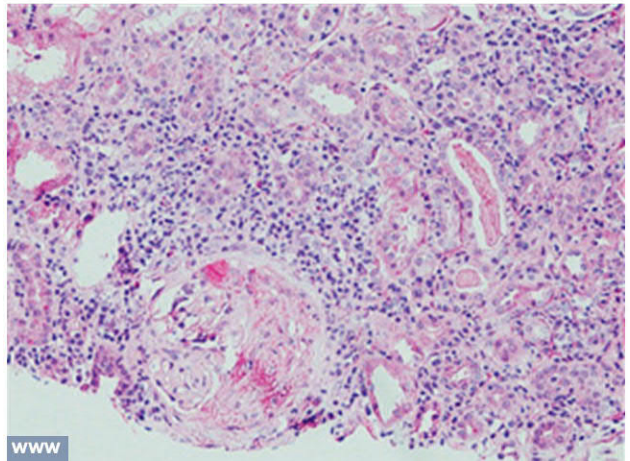


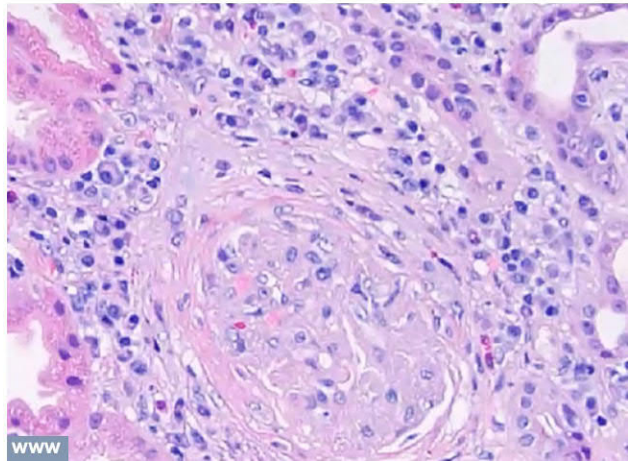


Wegener's - GPA - Granulomatous Polyangiitis

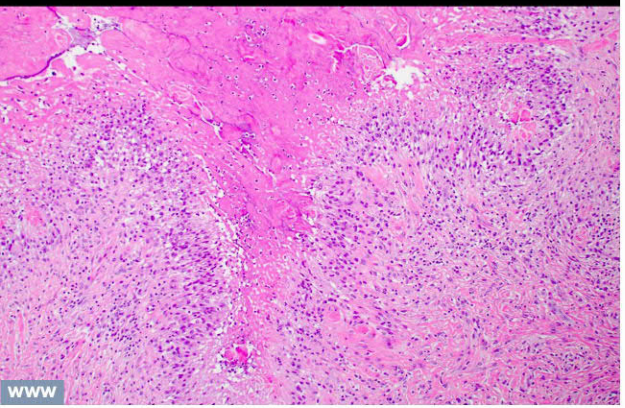
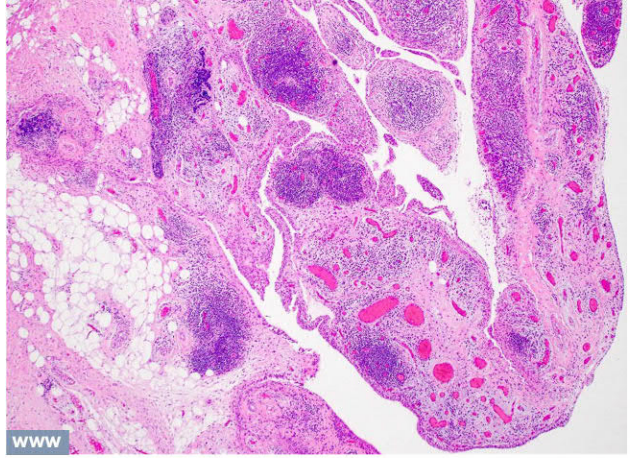
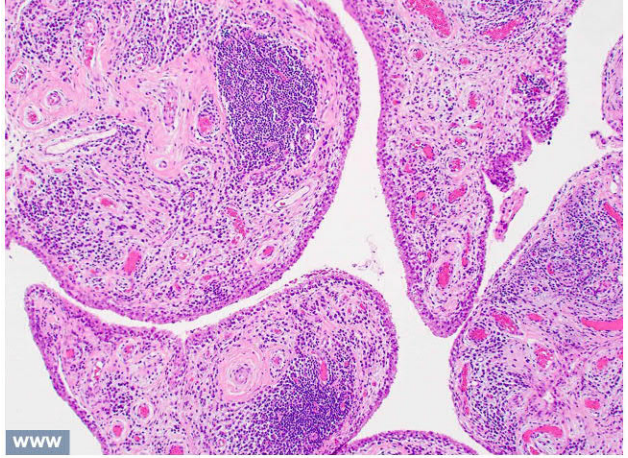
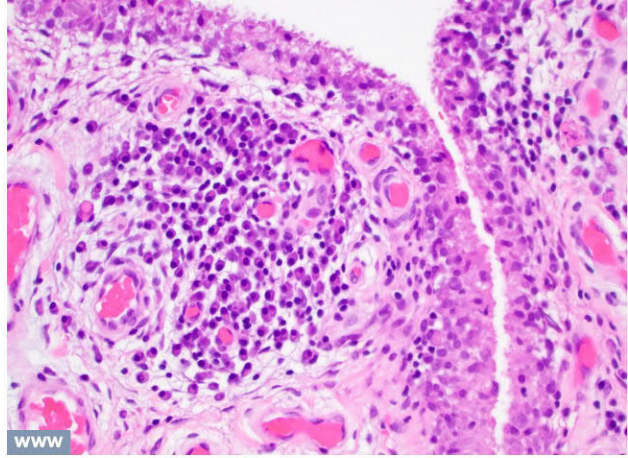




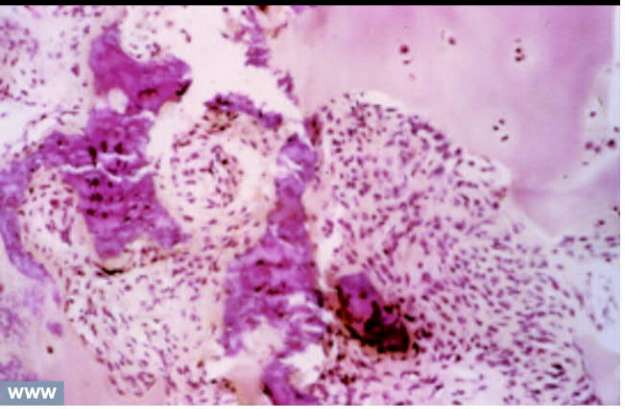
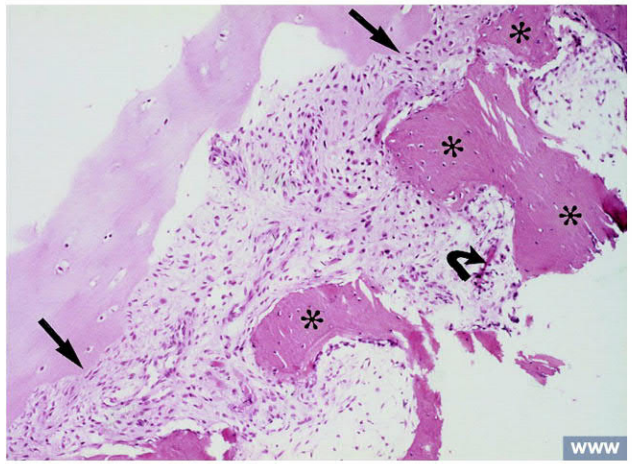
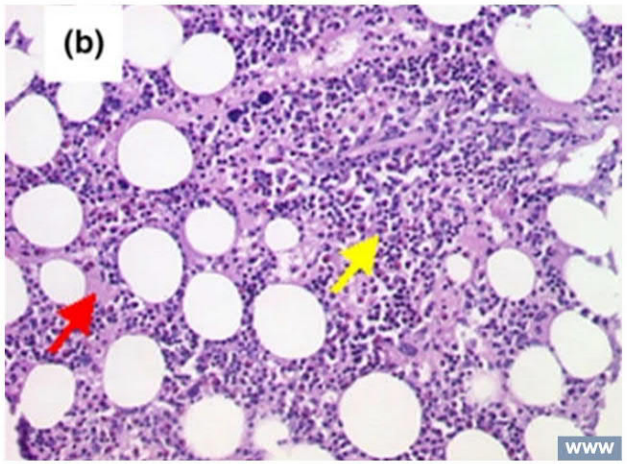


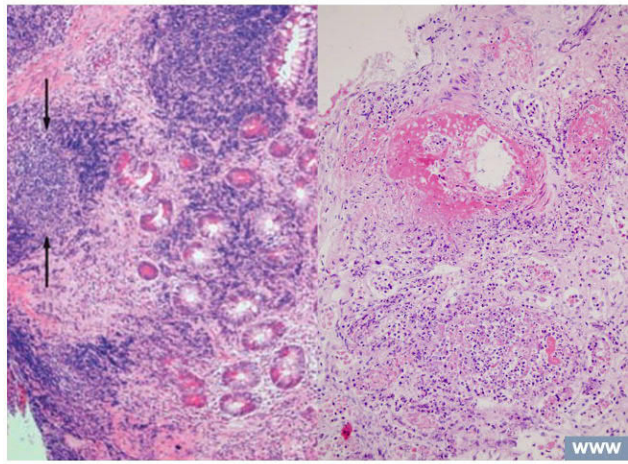


Rheumatoid Arthritis

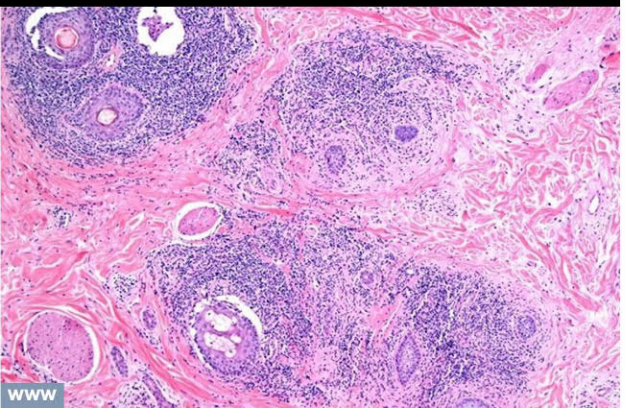
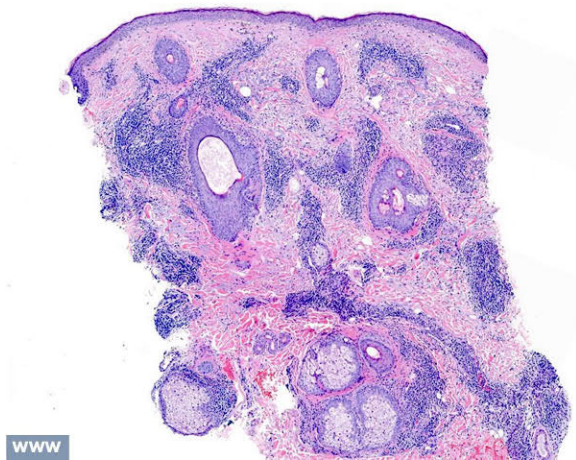
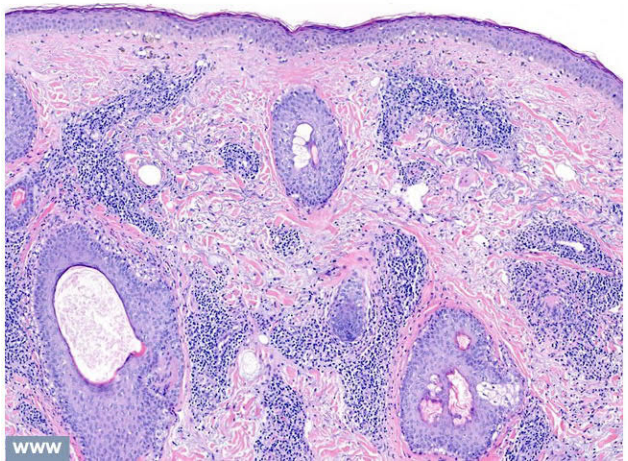
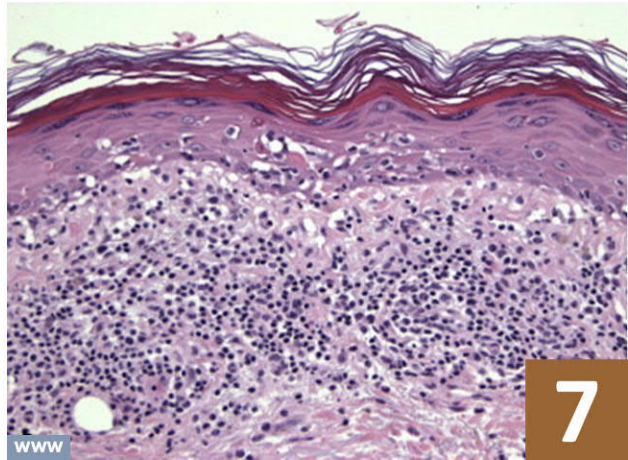





Ankylosing Spondylitis

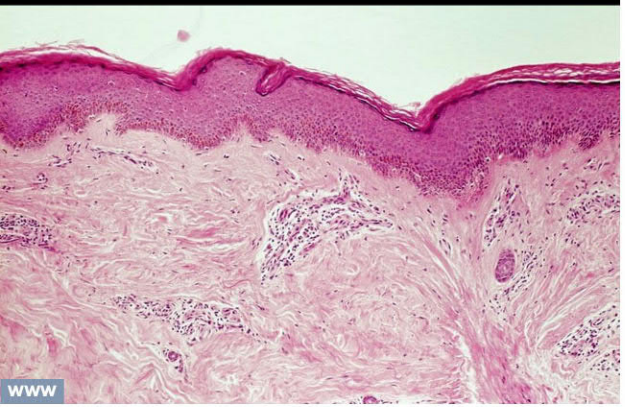




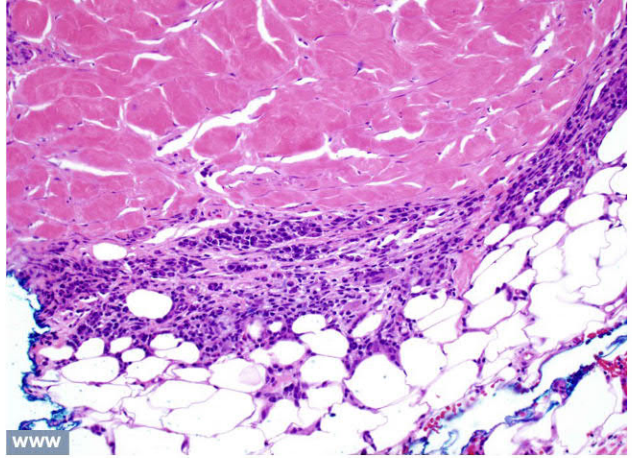


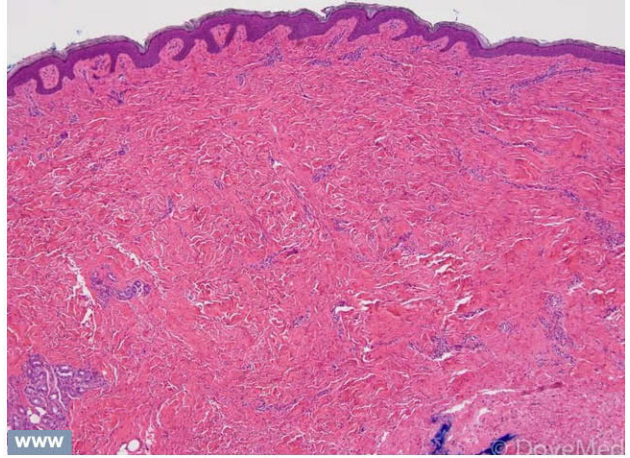
Lupus - SLE

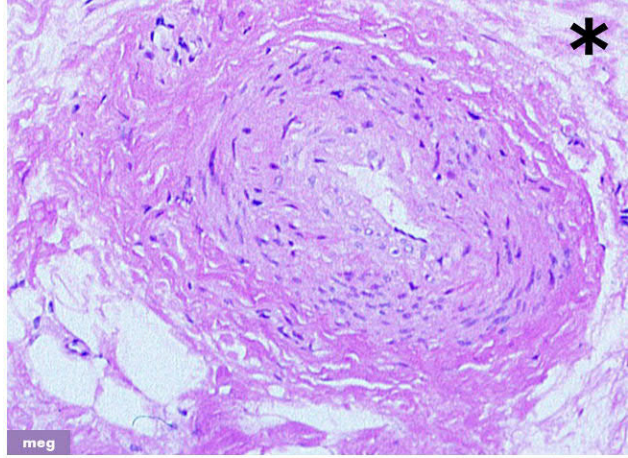





Scleroderma

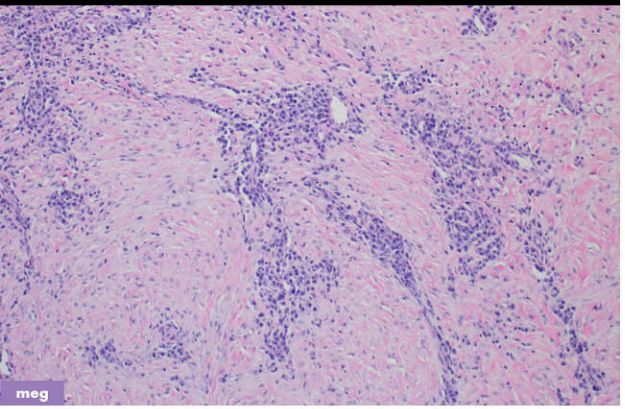


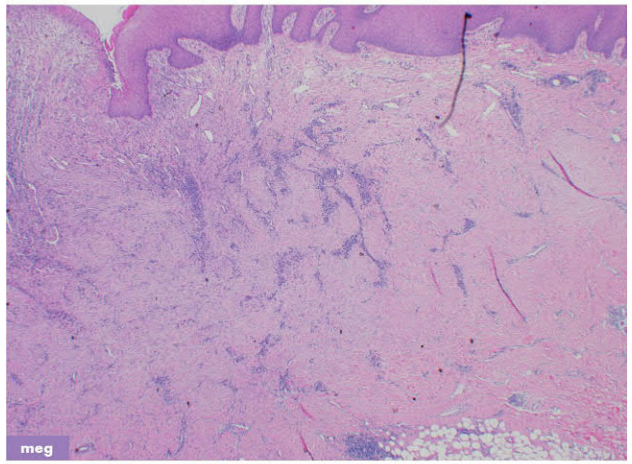


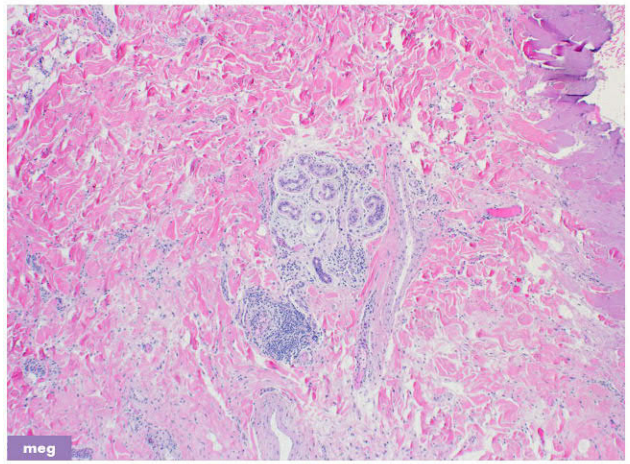


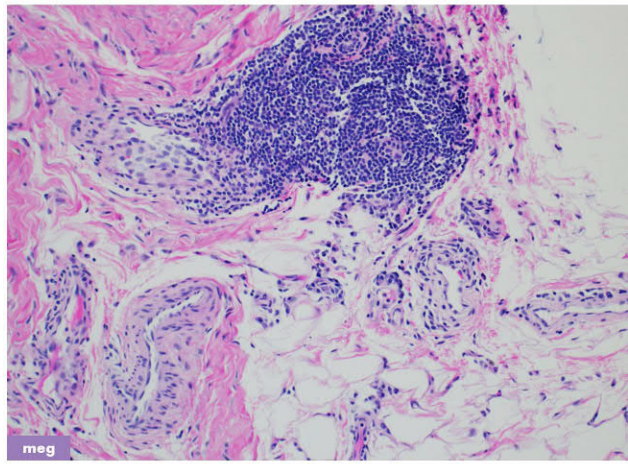


Morphea

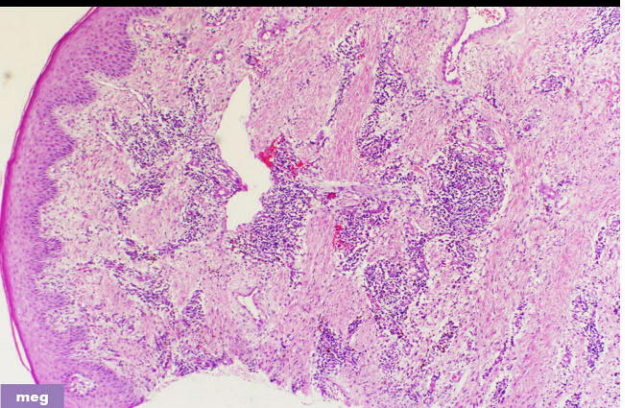


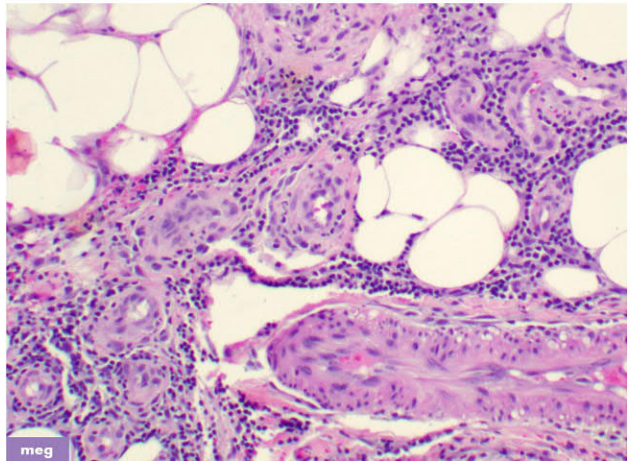


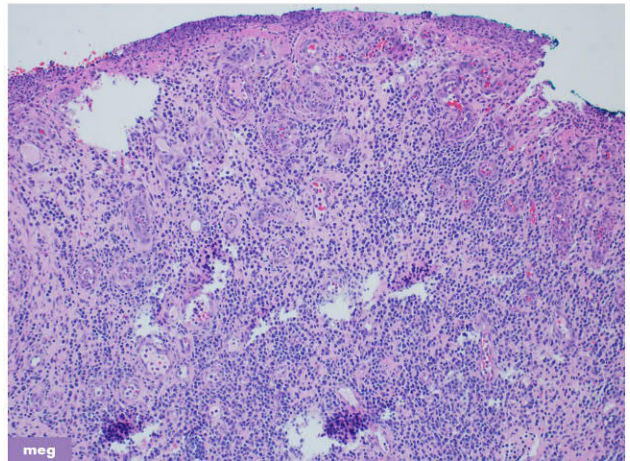


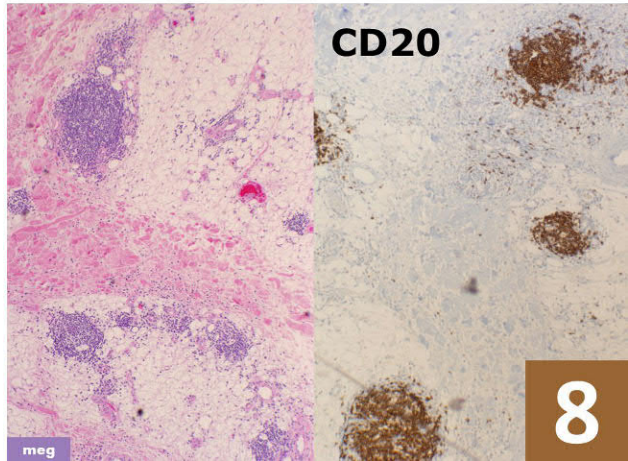


Chronic Wound - Intrinsified

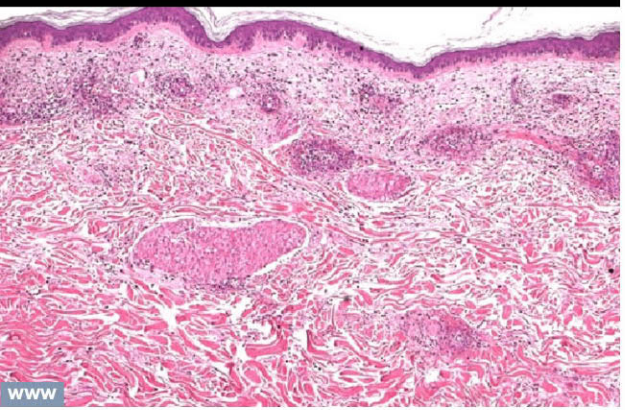


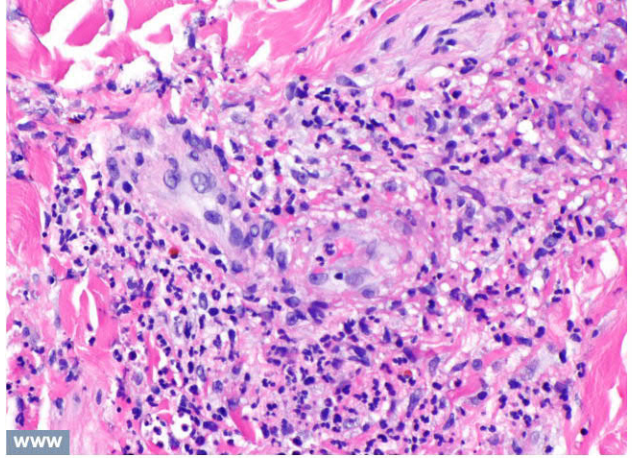


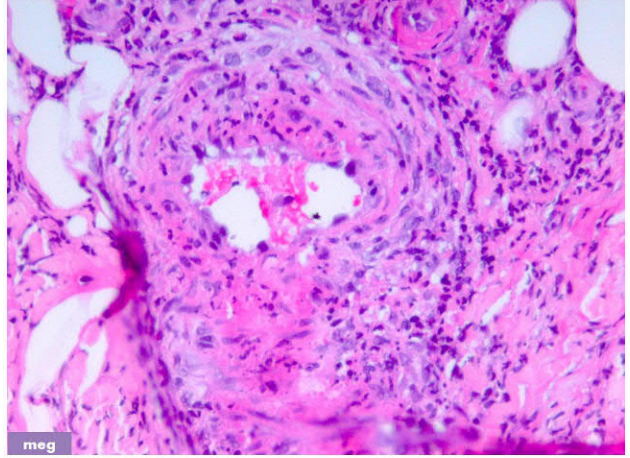


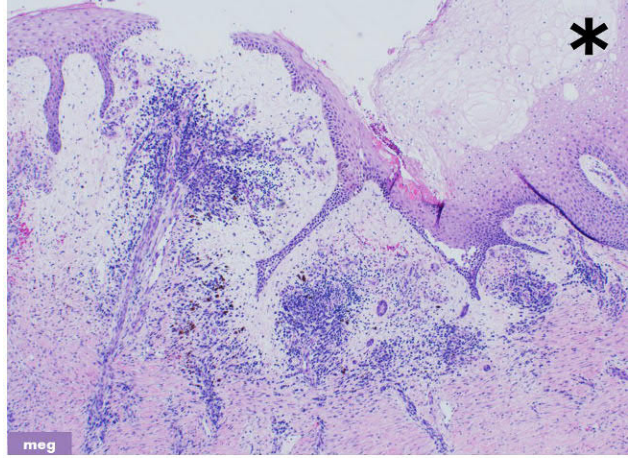


Vasculitis - LCV, Mixed

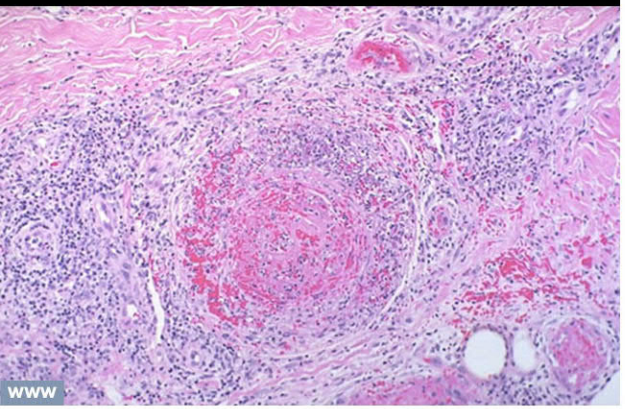


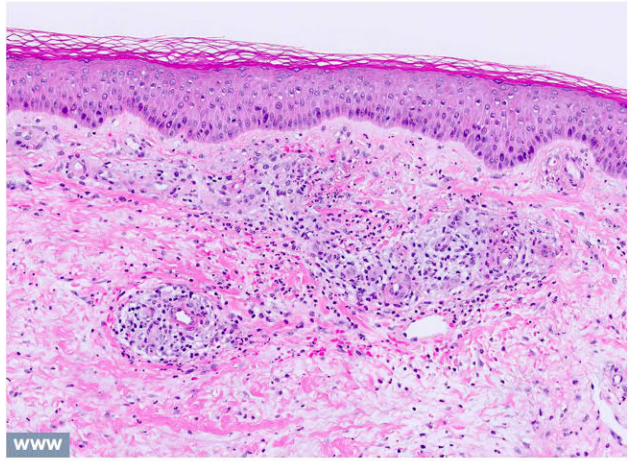


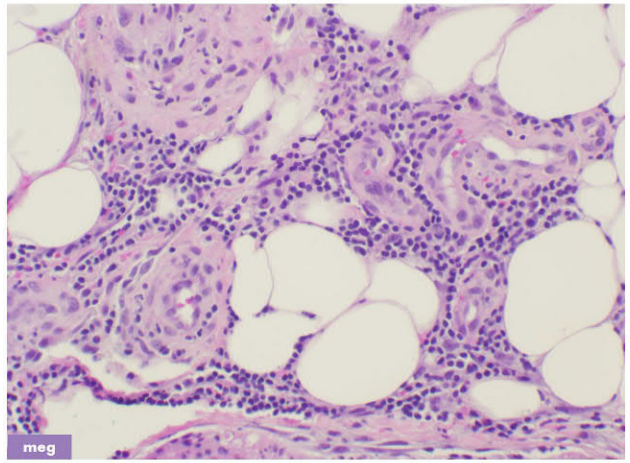


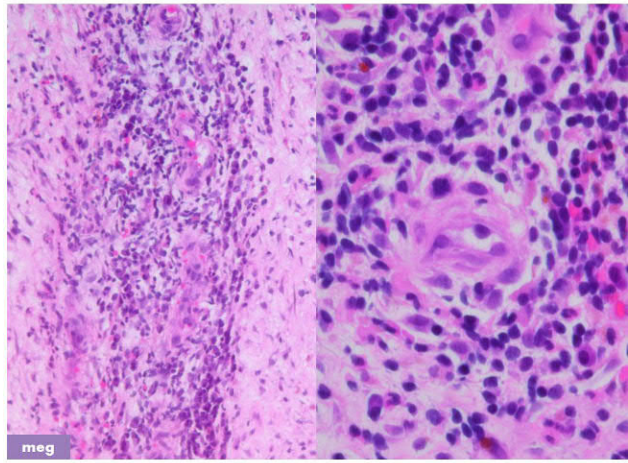


Vasculitis - Perivasculitis

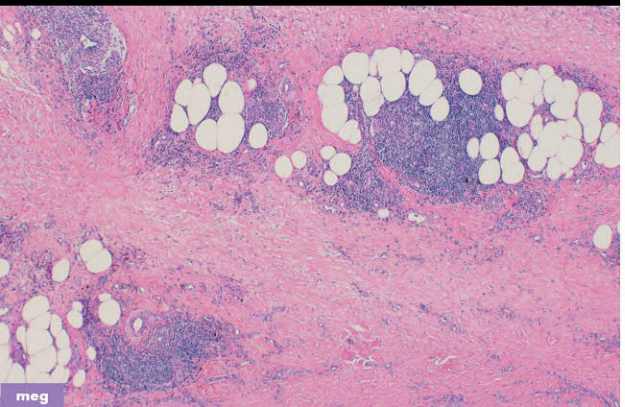


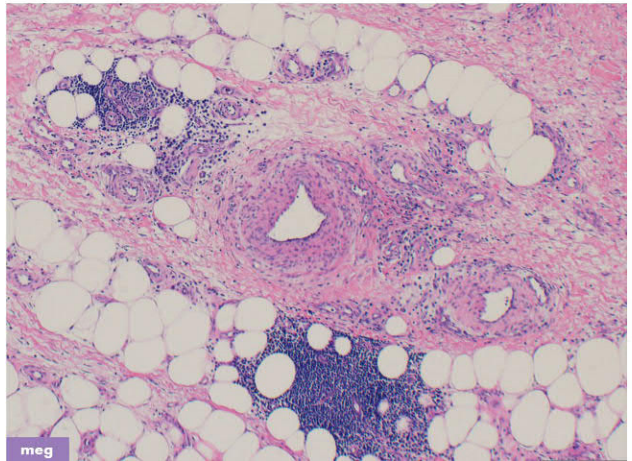


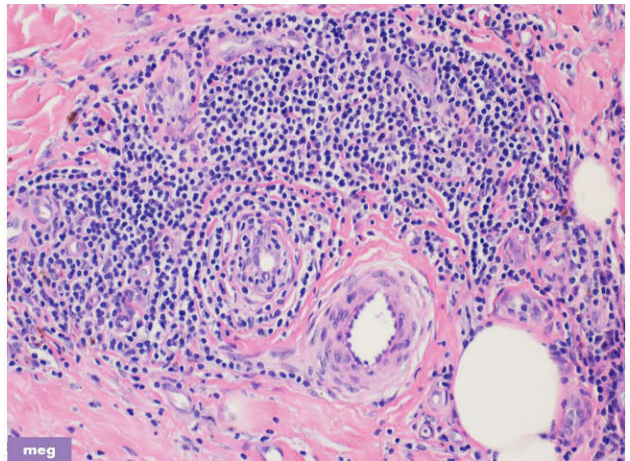


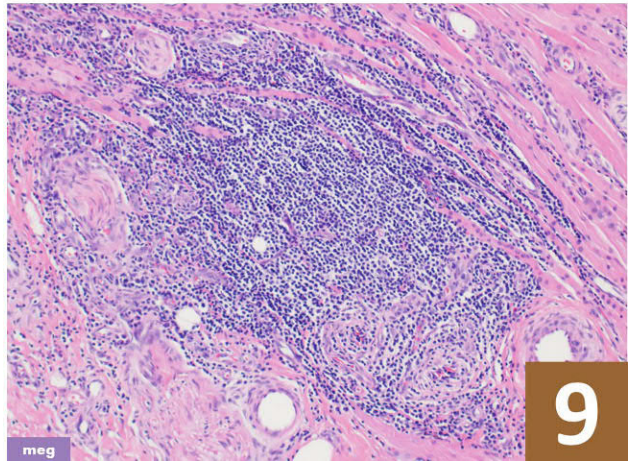


Vasculitis - Buerger - Thromboangiitis obliterans

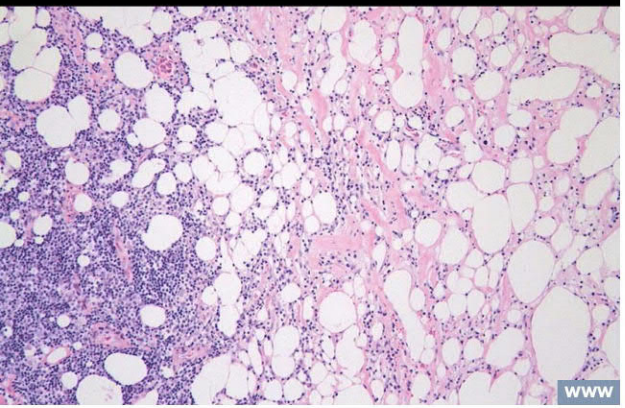


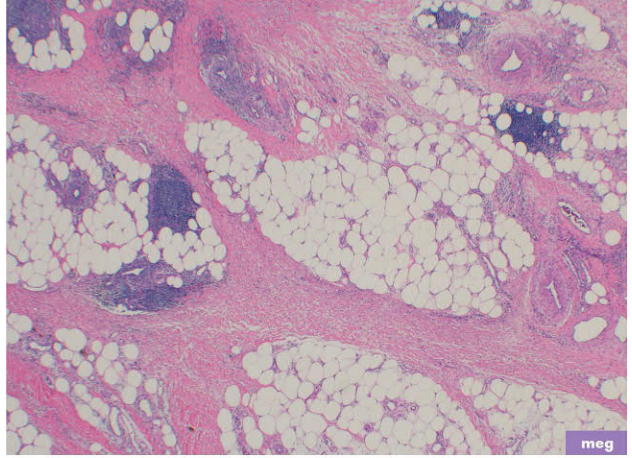


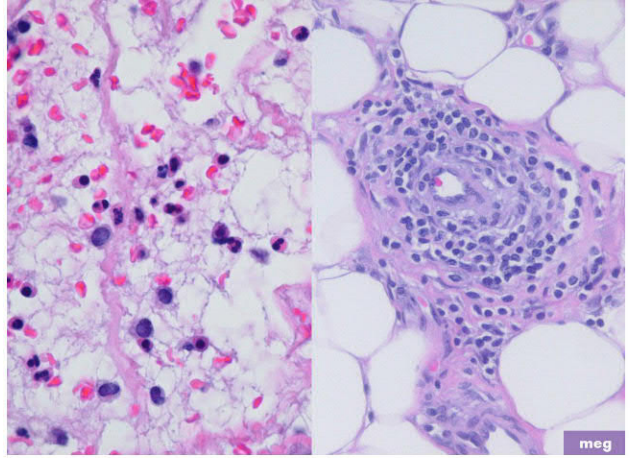


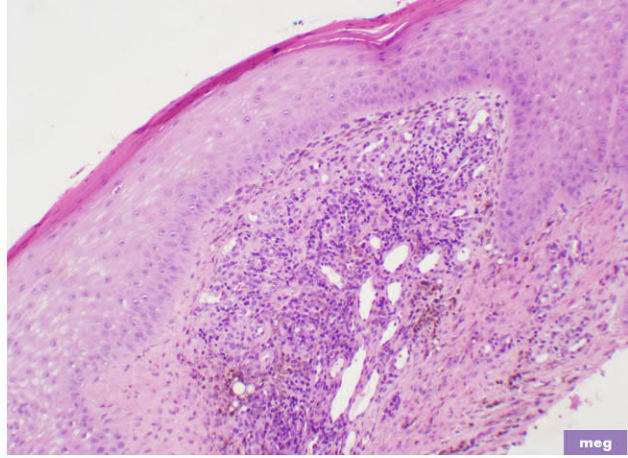


Inflammatory - Autoimmune Panniculopathy

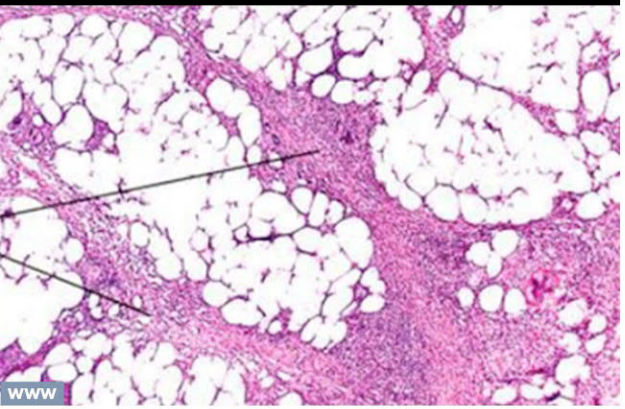


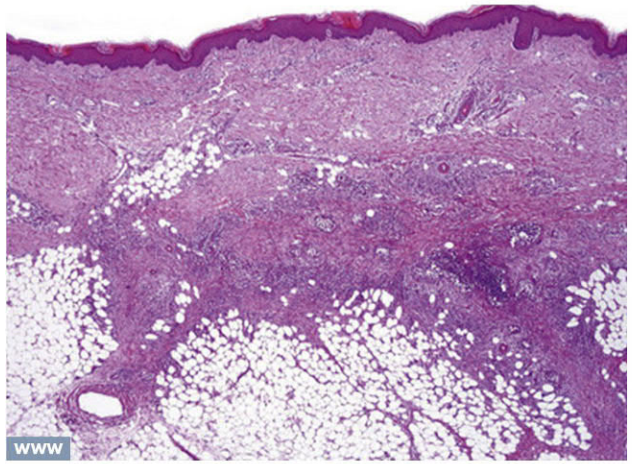


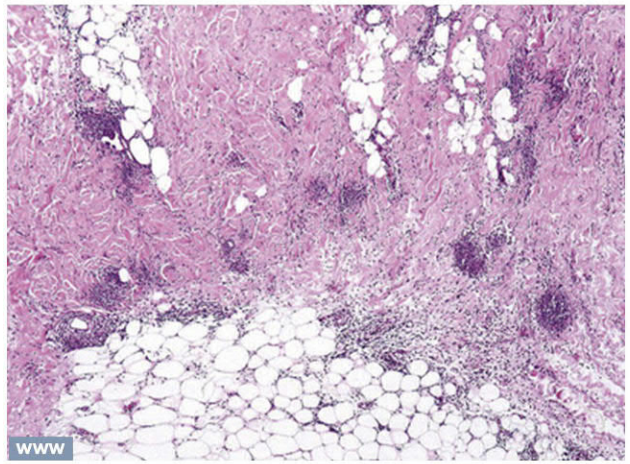


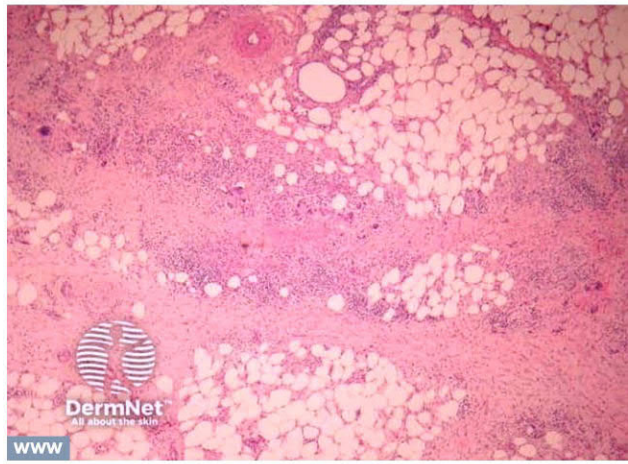


Erythema Nodosum / Septal Panniculitis

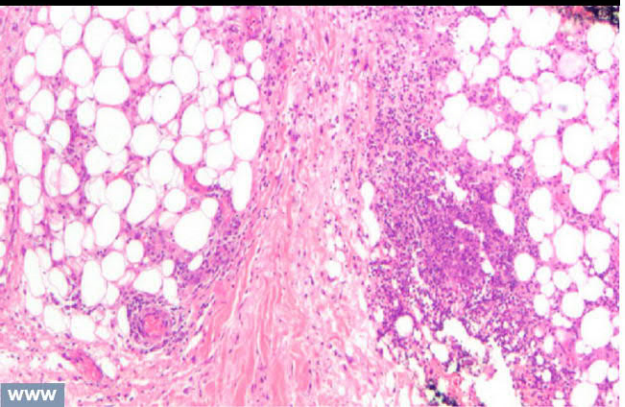


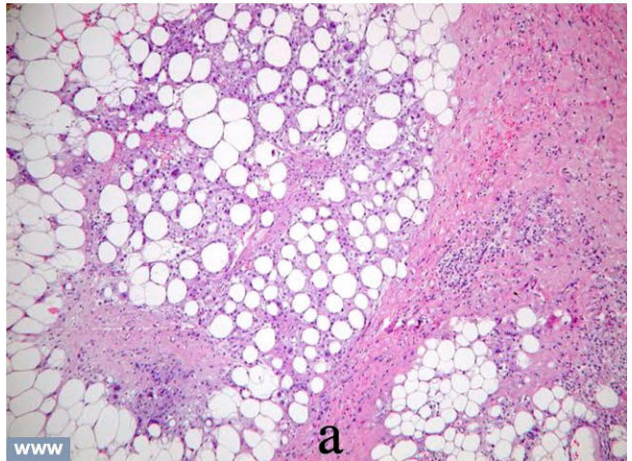


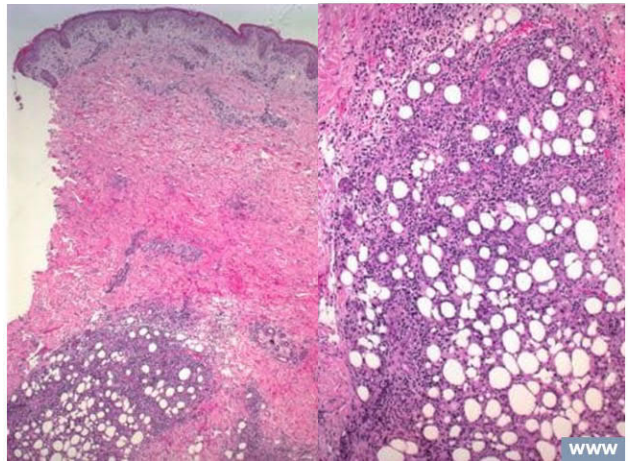


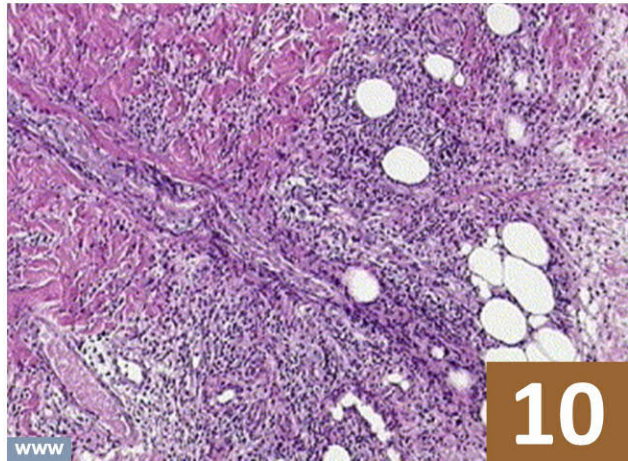


Weber- Christian / Lobular Panniculitis

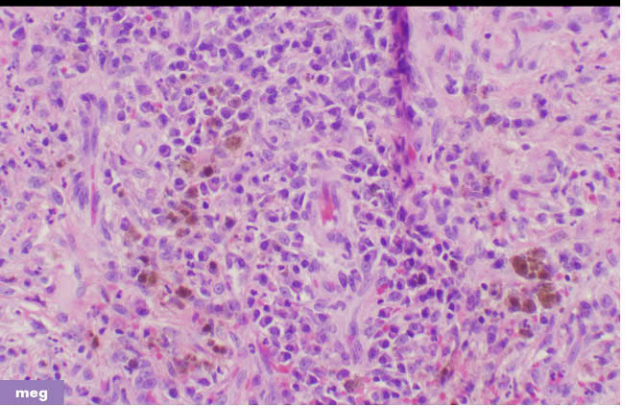


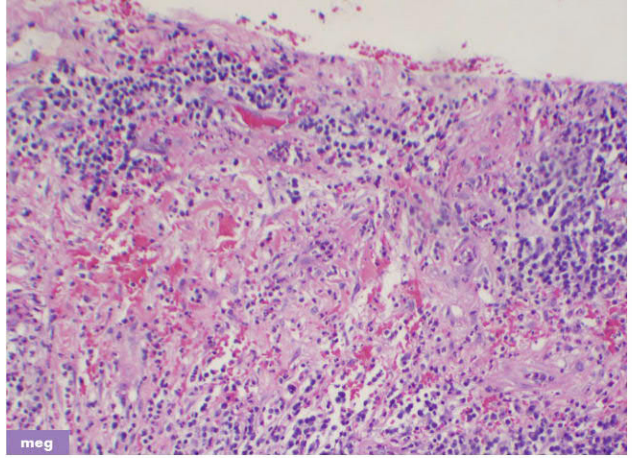


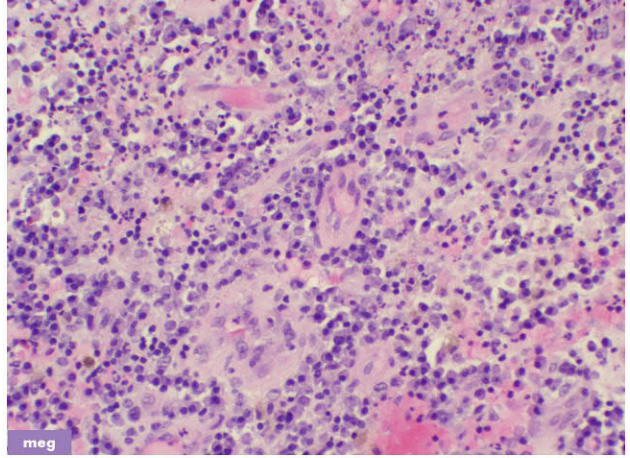


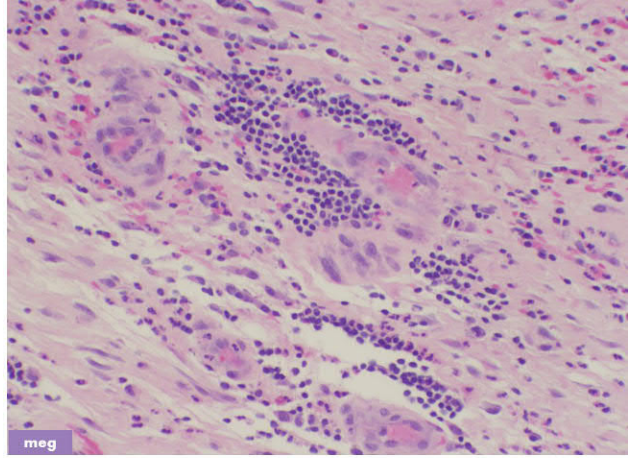


Chronic Wound - Intrinsified

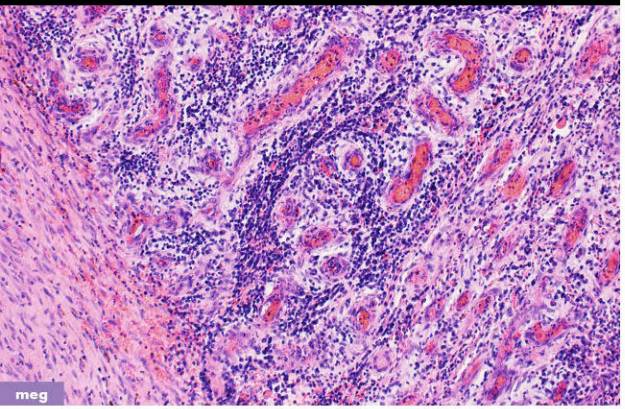


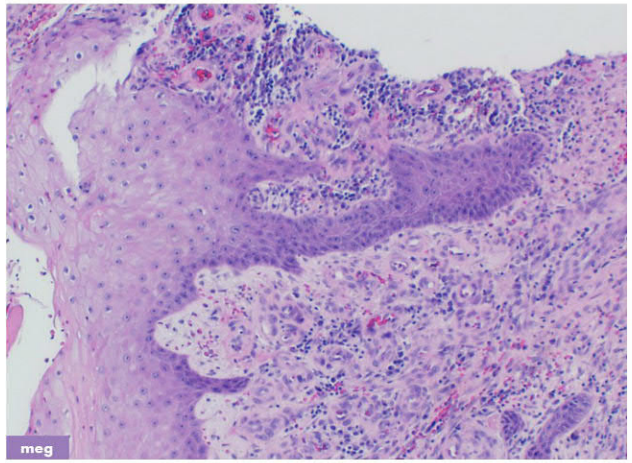


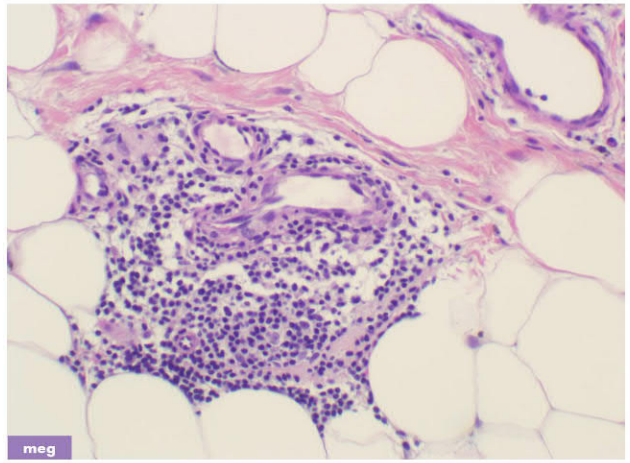


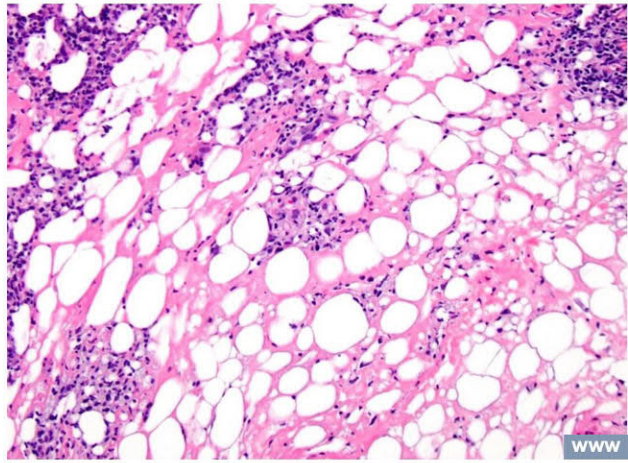


Lupus - SLE

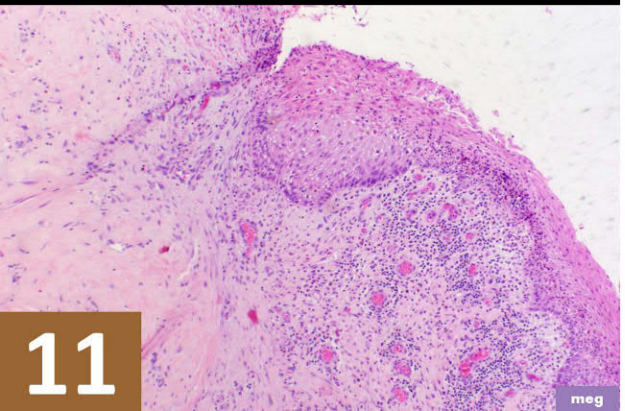


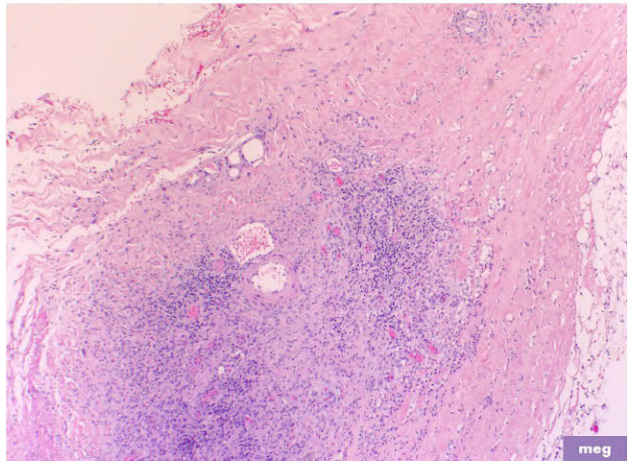


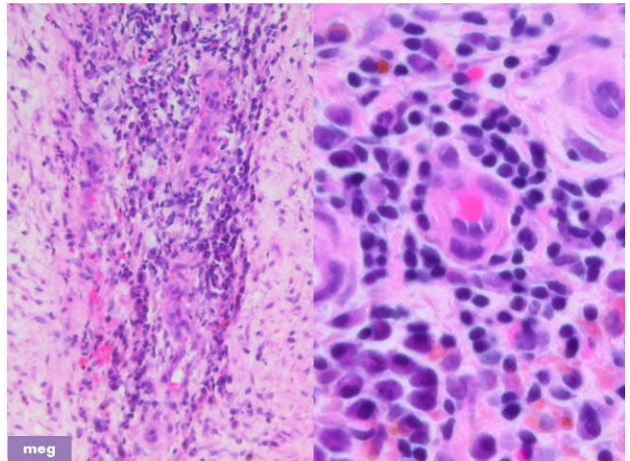


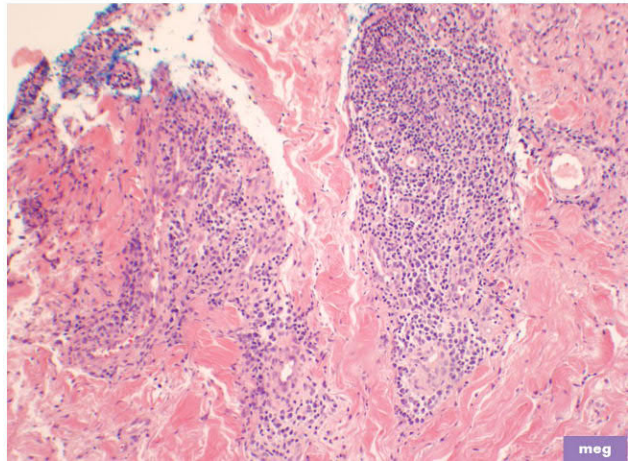


Chronic Wound - Intrinsified

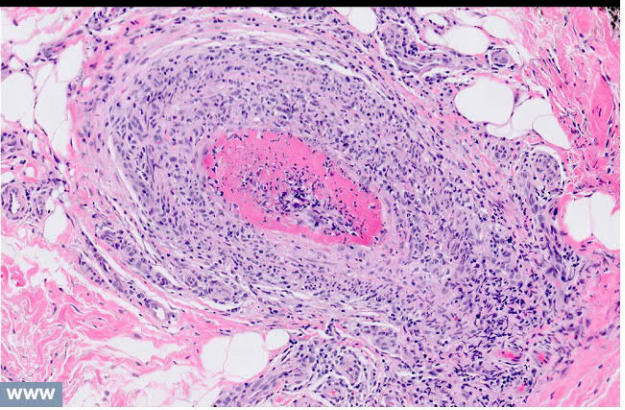


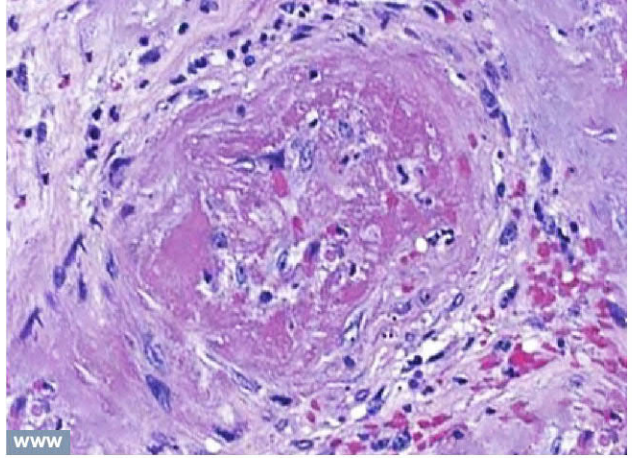


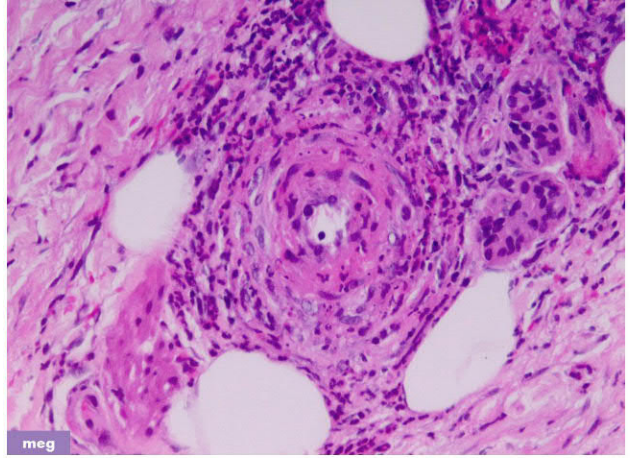


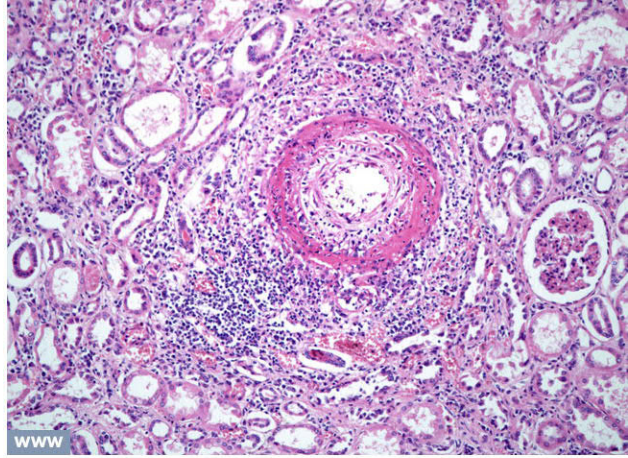


Neutrophilic & Mixed AI - MPA & PAN

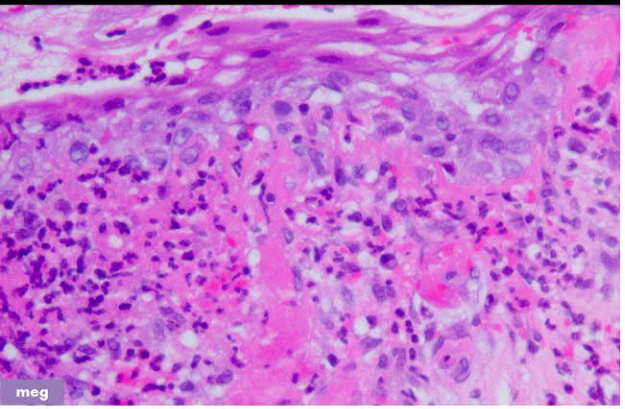


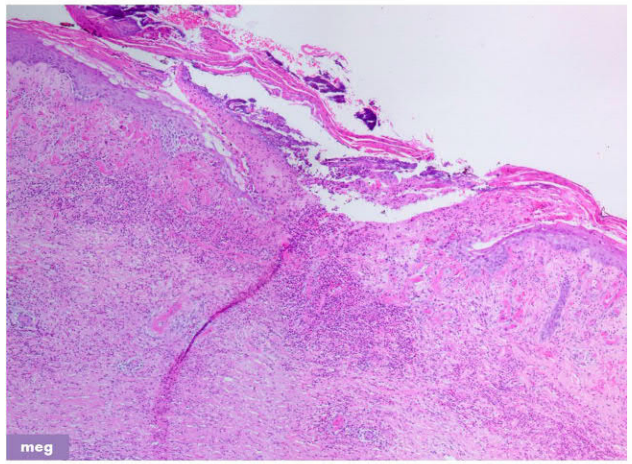


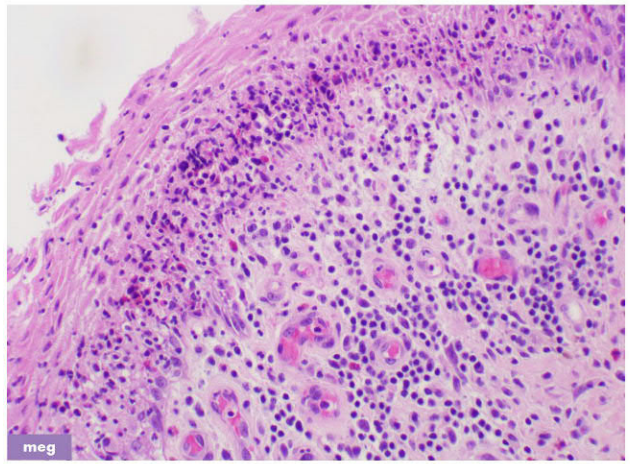


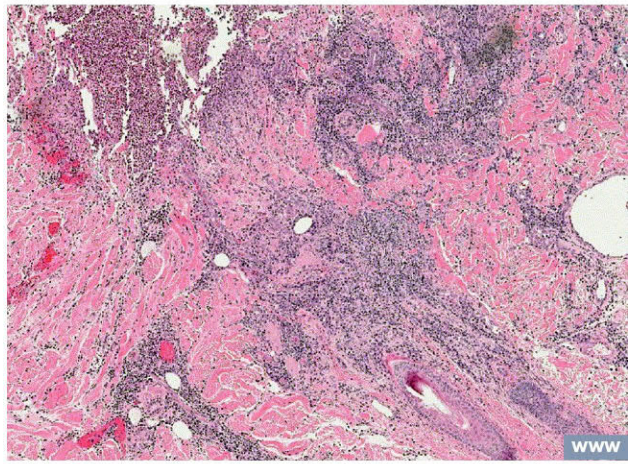


Neutrophilic AI - Pyoderma, PG &al

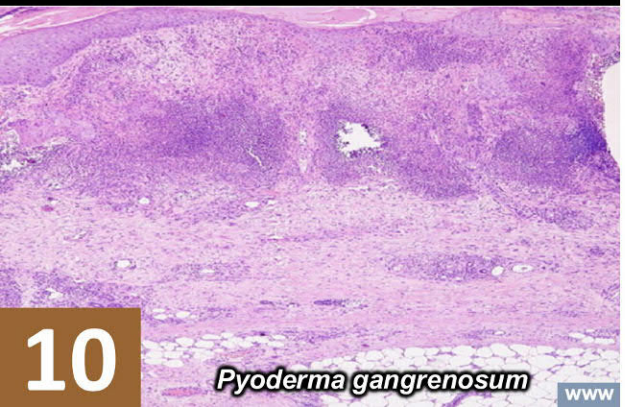


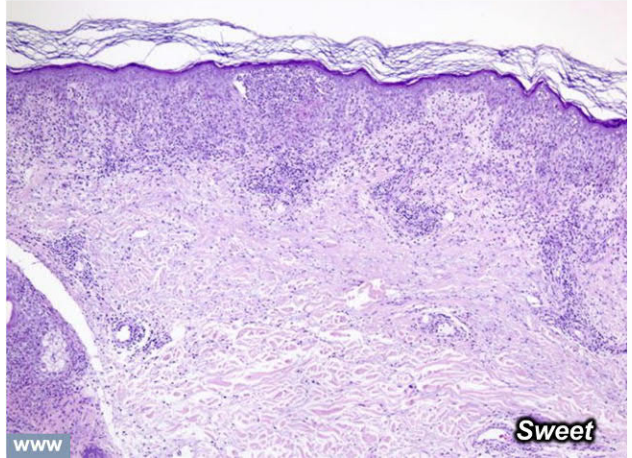


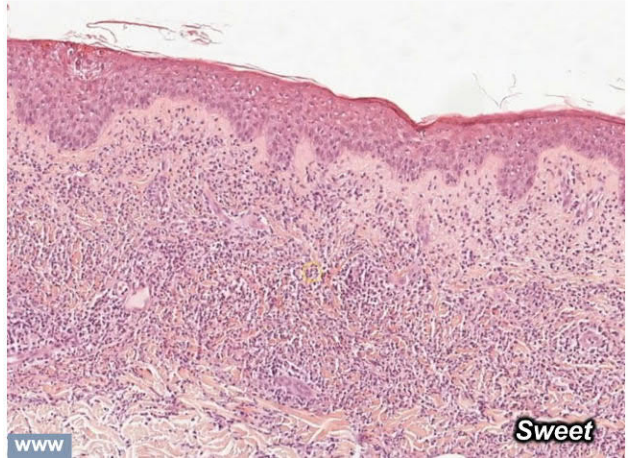


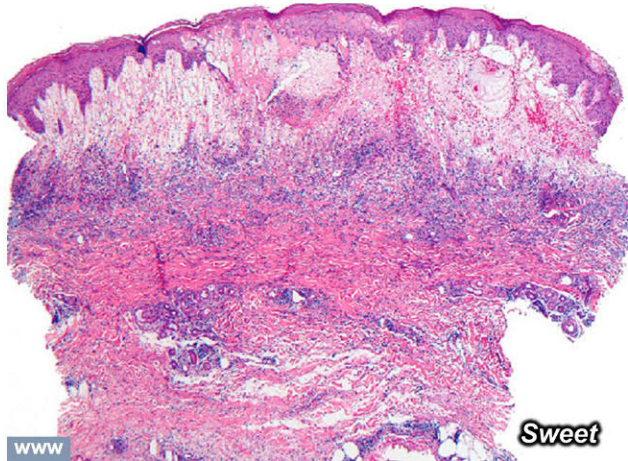


Neutrophilic AI - Sweet's Syndrome, PG

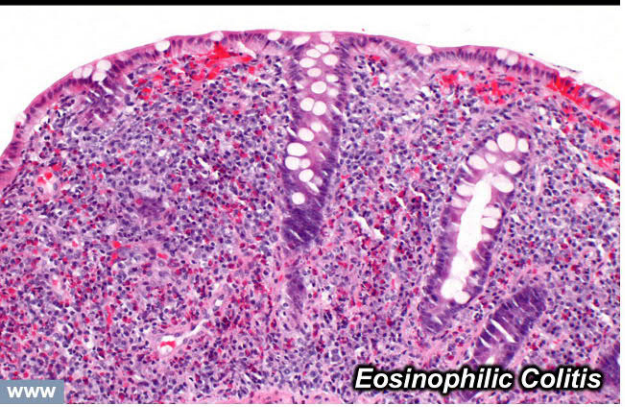


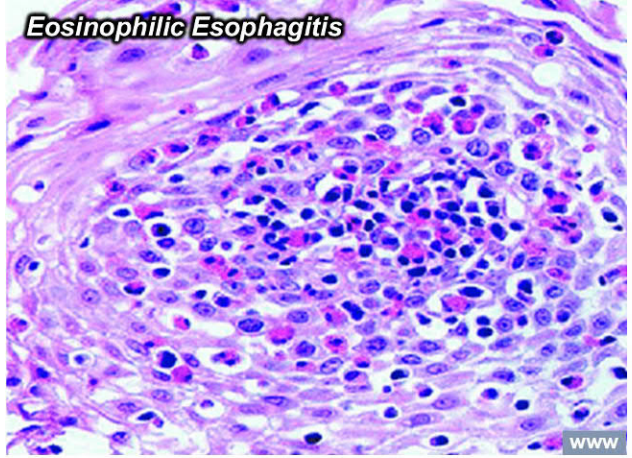


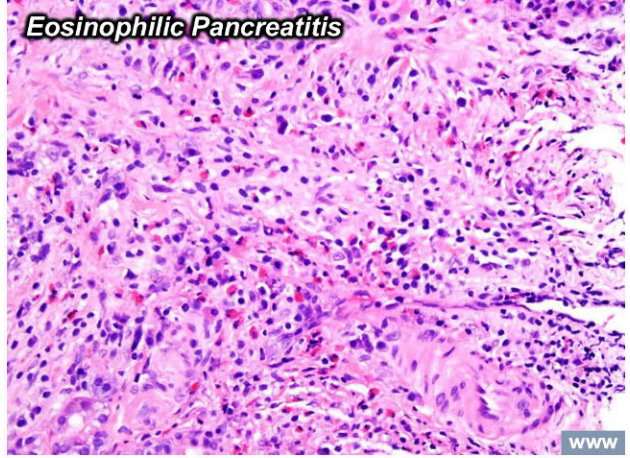


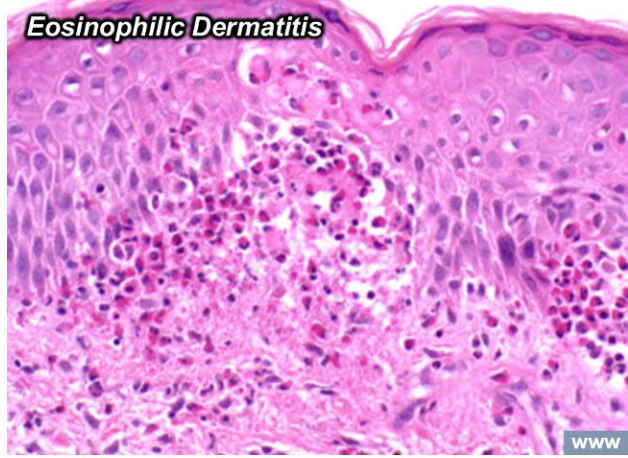


Eosinophilic AI

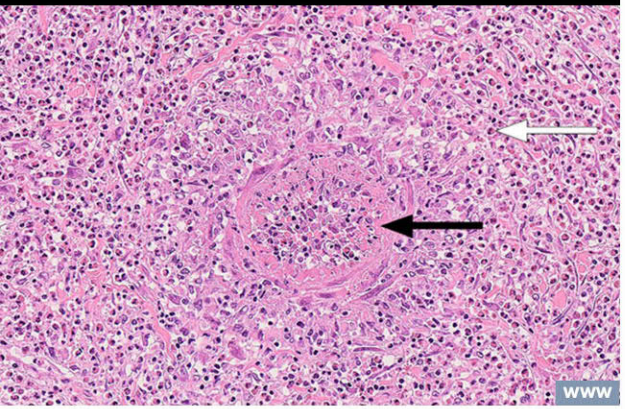


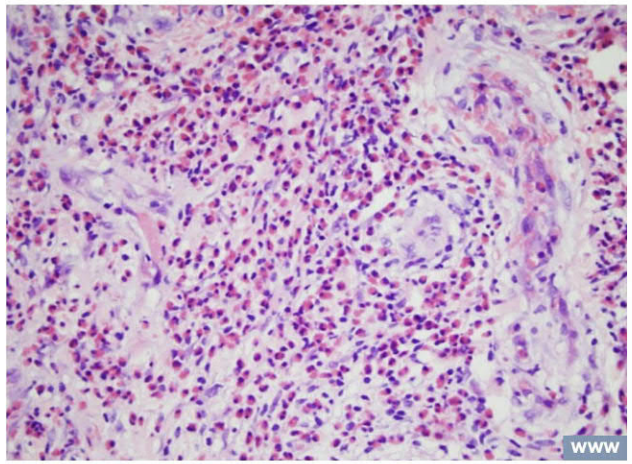


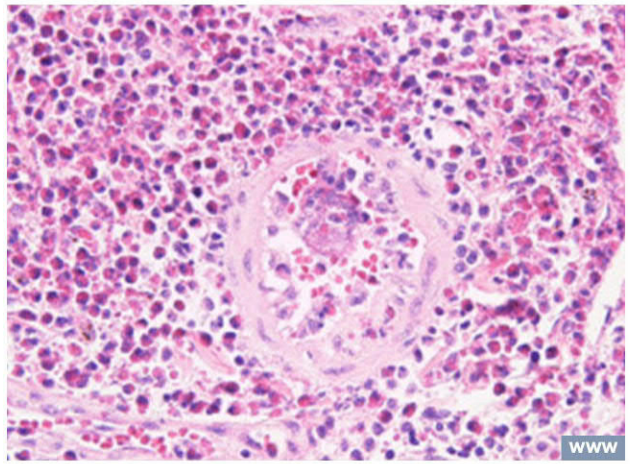


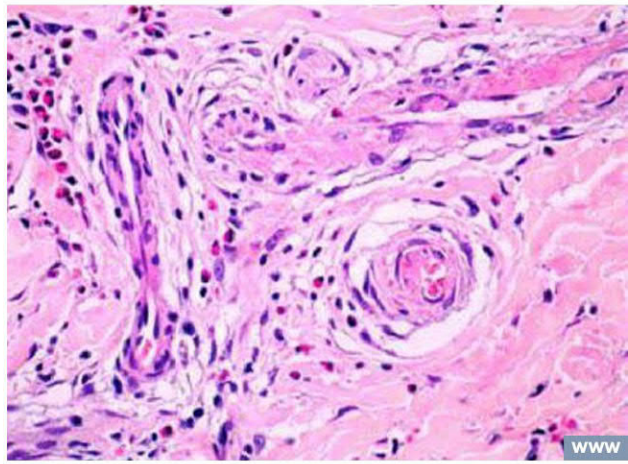


Eosinophilic AI - Eosinophilic Vasculitis

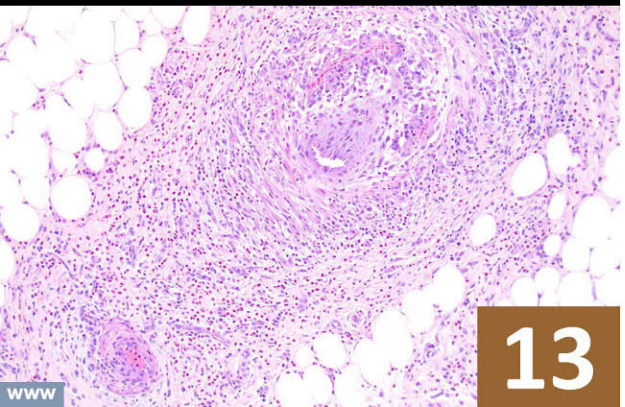


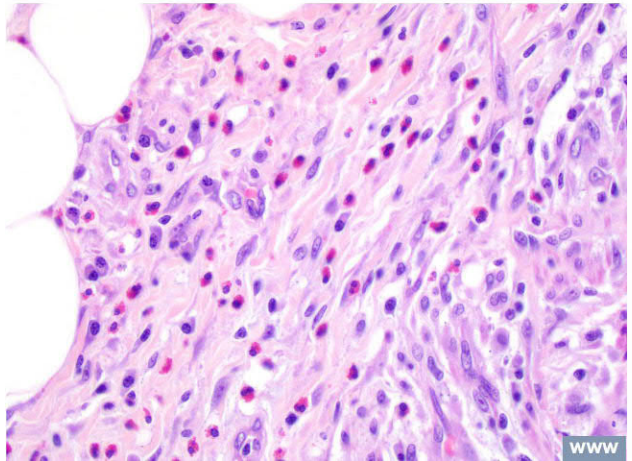


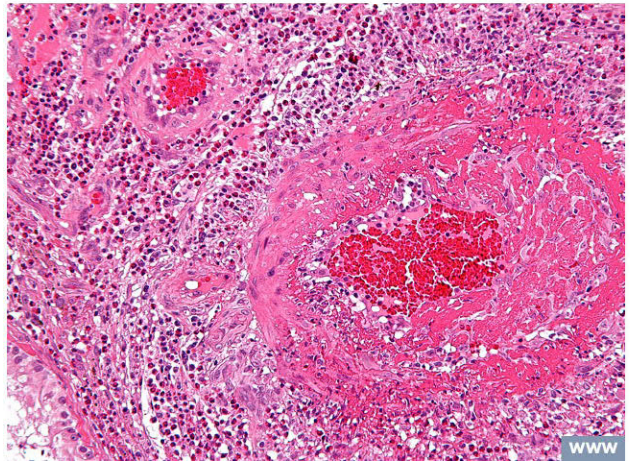


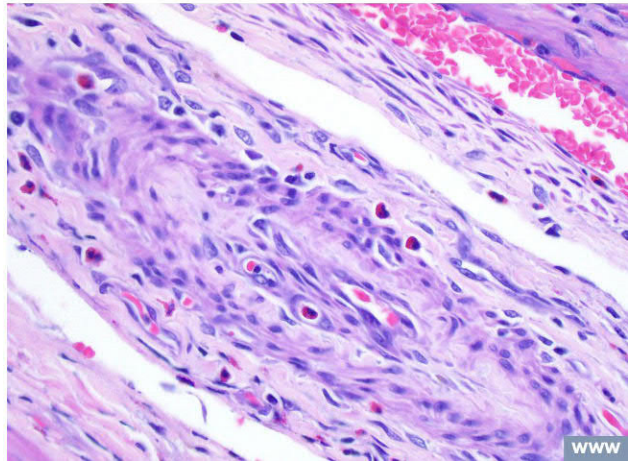


Eosinophilic AI - EGPA (Churg-Strauss)

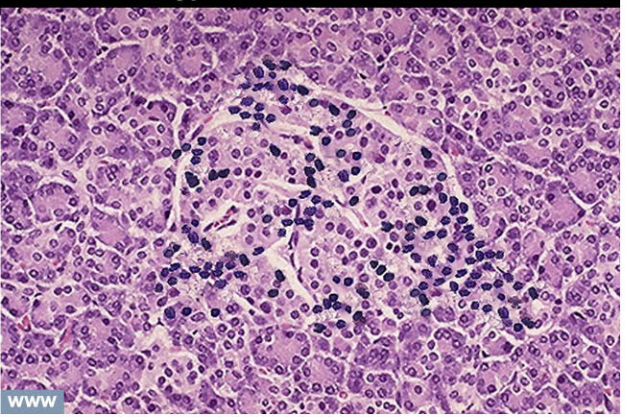


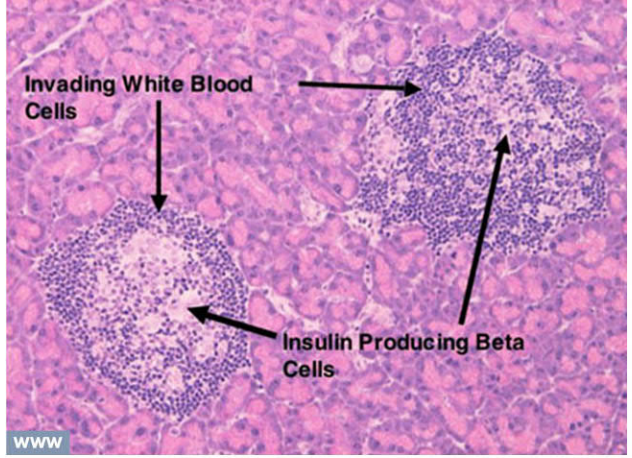


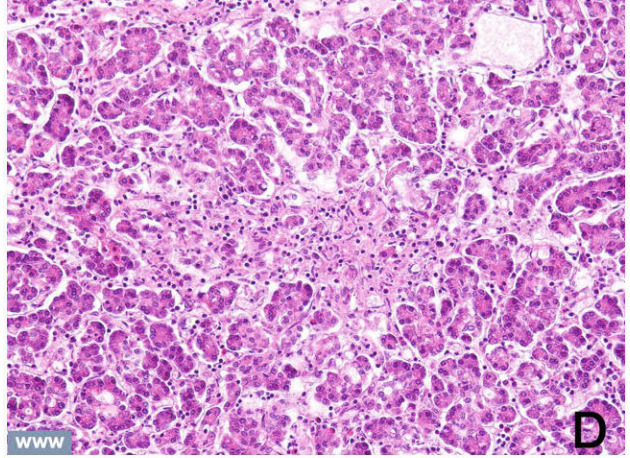


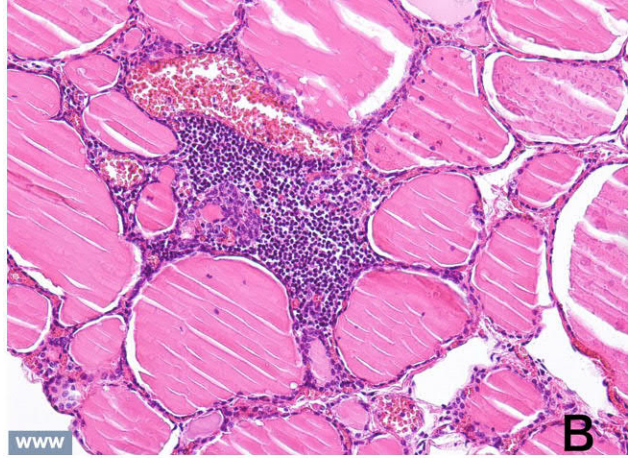


Diabetes – Type 1

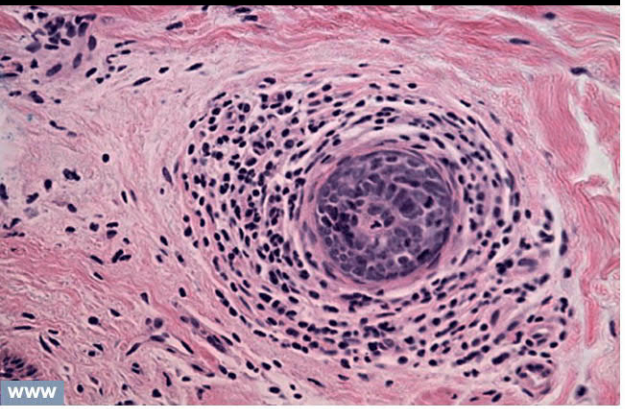


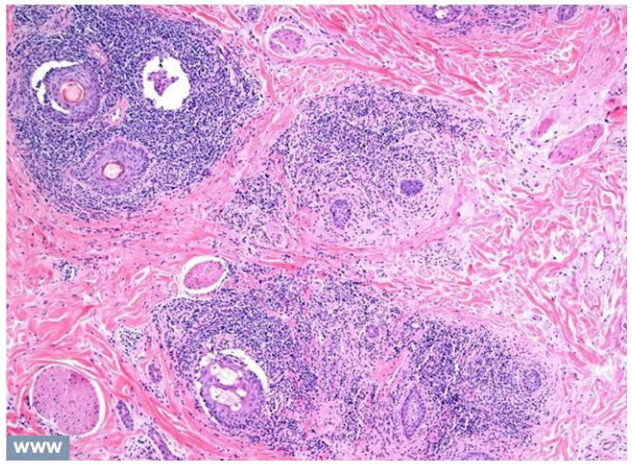


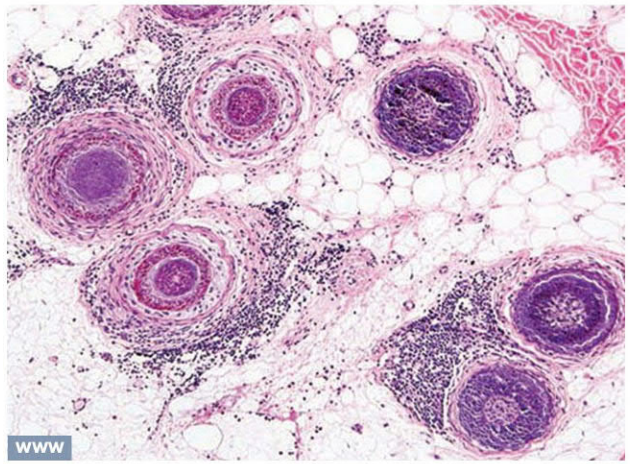


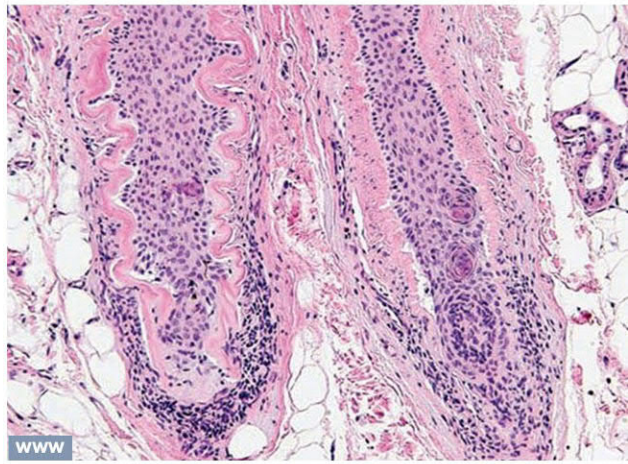


Alopecia Areata

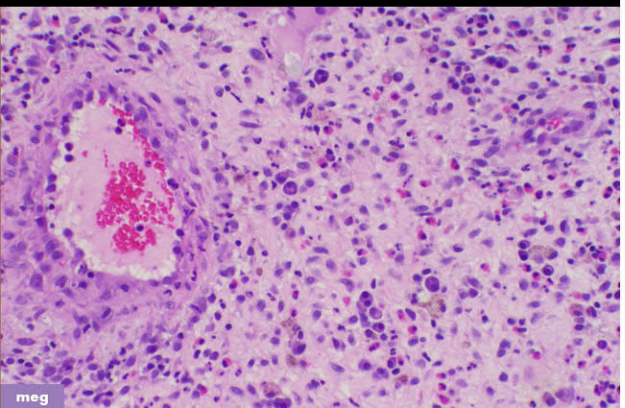


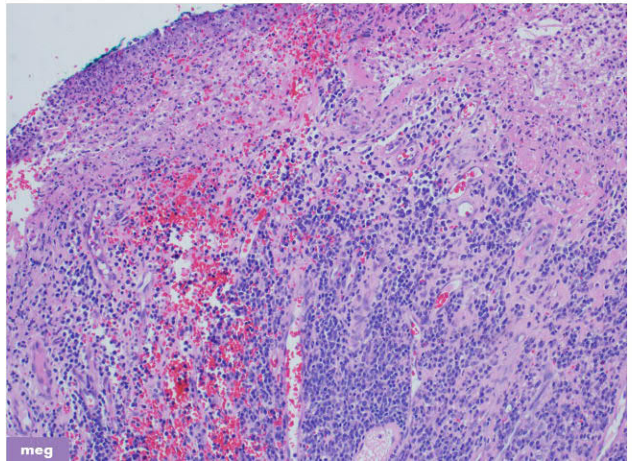


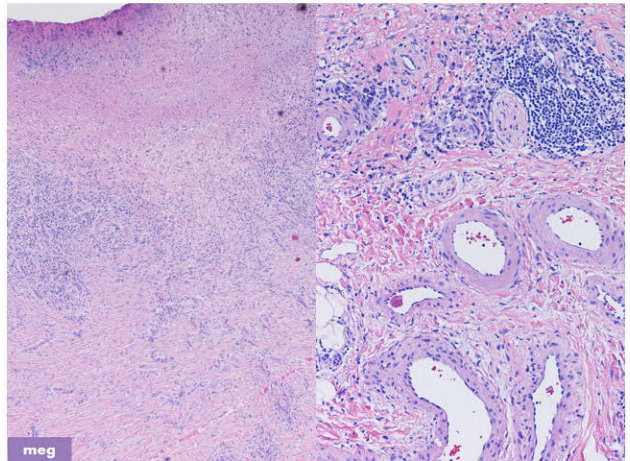


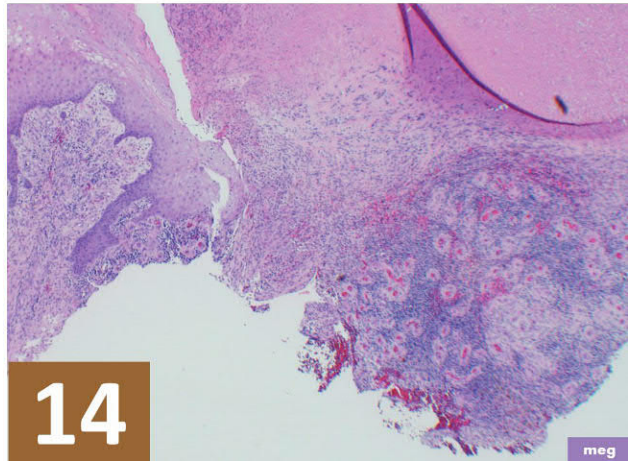


Chronic Wound - Intrinsified









Autoimmune Disorders

Autoimmune Pathology

Complex disorder, multifactorial etiology and evolution

Sine qua non is the appearance of lymphocytes, plasma cells, and antibodies targeted against endocellular, endonuclear, and epithelial or parenchymal auto-antigens.

Personal idiosyncracies, genetics, epigenetics.
Environmental exposure, food & environmental allergy.
Drug - device - materials - toxin sensitivities.
Occult or overt infection.
Repetitive trauma.
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Hematological and miscellaneous other disorders.

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Eosinophils + / - .

***** Lymphoid tertiary organs.**

*** Chronic interference, disorganization, atrophy of host / target tissues.
*** Ability to awaken and trigger acute inflammation.
Standby vs active.
Subject to endocrine effects of remote inflammation.

78F Sjögren's

fibrinogen	565	++
protein C	60	–

67F Rheumatoid Arthritis

F.V Leiden	heterozyg	+
fibrinogen	640	++
plasminogen	135	+
protein C	136	+

57M Cirrhosis

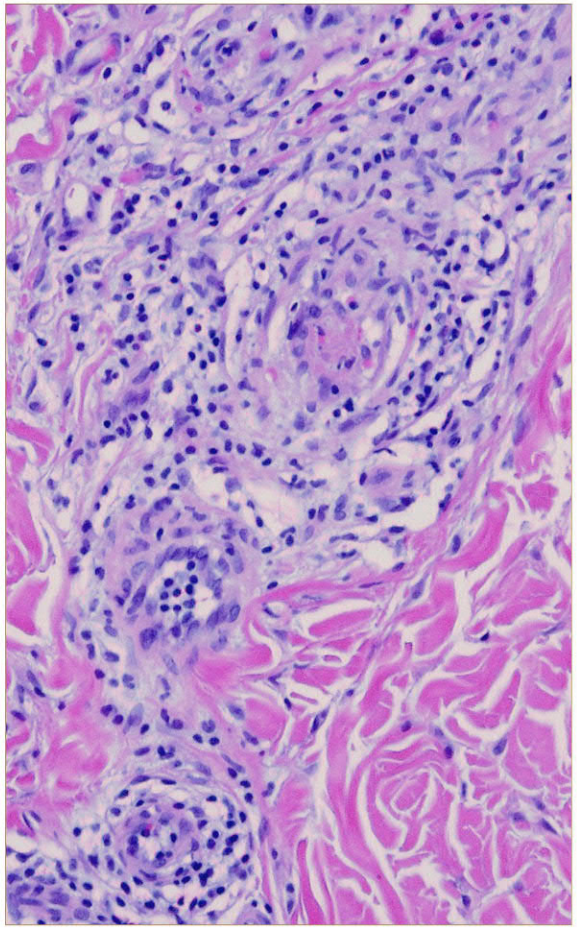
bili	2.1	+
alk phos	160	+
RF	44	+
ANA	1:80	+
AT-III	47	–
protein C	35	–
protein S	55	–

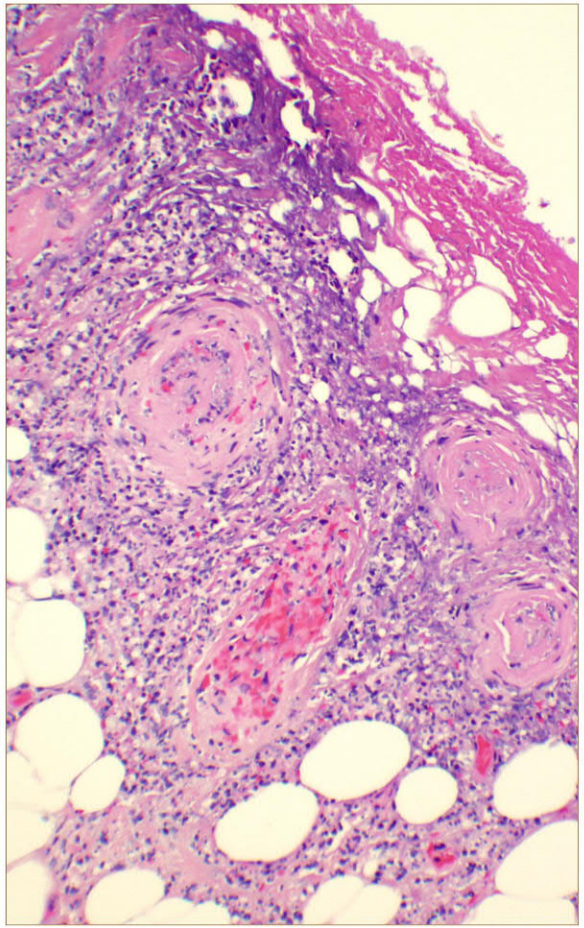
72F Polycythemia Vera

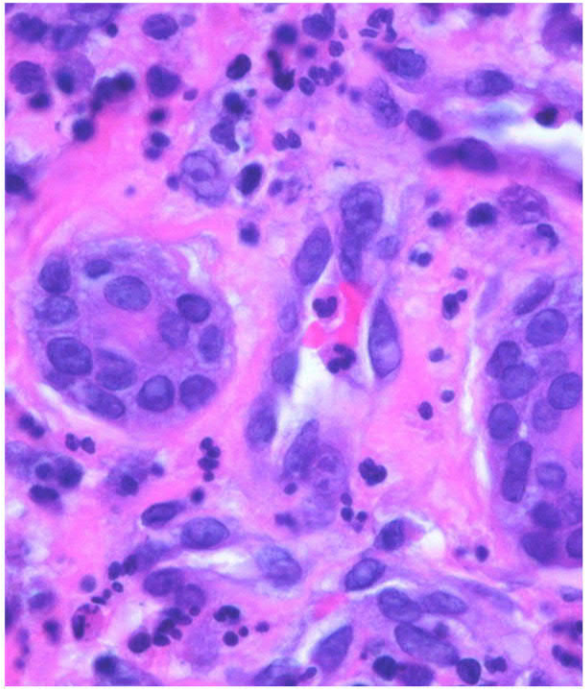
ANA	1:160	+
cardiolipin IgM	80	++
protein S	53	-

54M No prior diagnosis

FactorV Leiden	heterozyg	+
ANA	1:80-sp	+
lupus anticoag	pos	+
cardiolipin IgA	15	+
cardiolipin IgG	>150	+++
cardiolipin IgM	20	+
protein C	60	-
protein S	56	-
homocysteine	14.6	+







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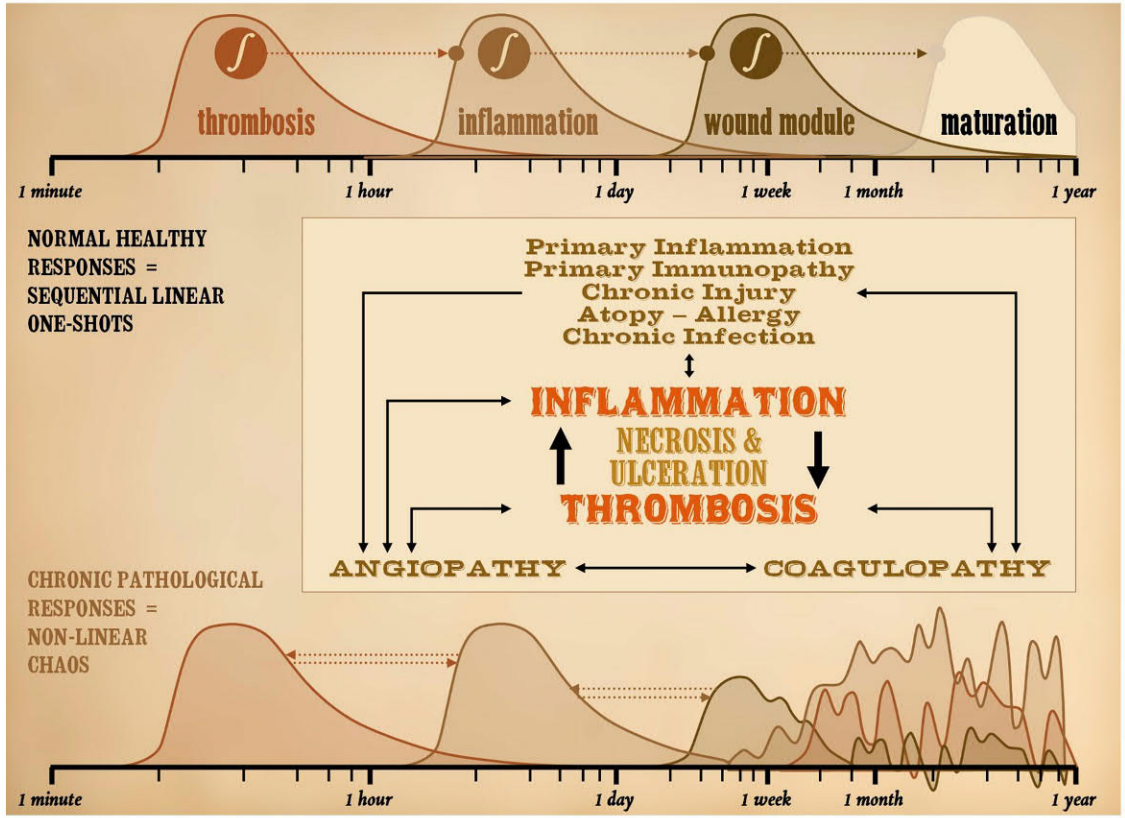

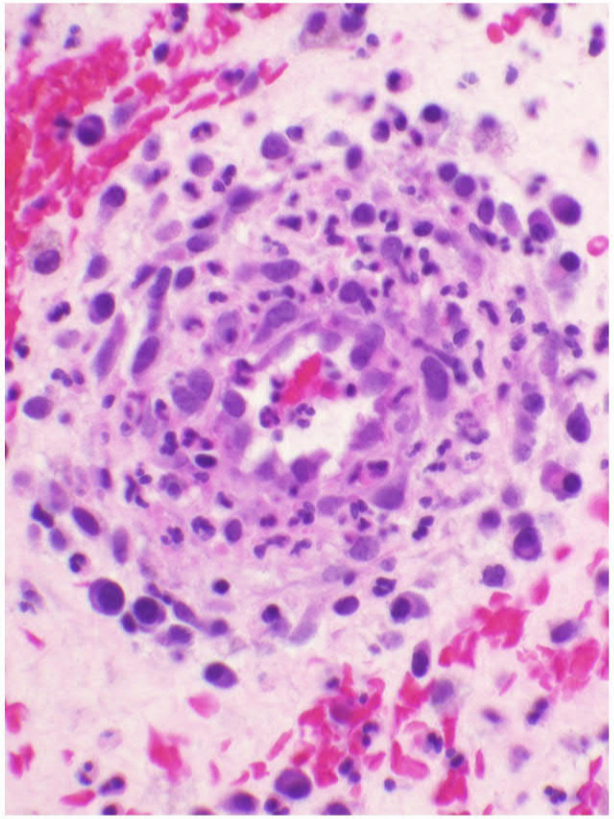

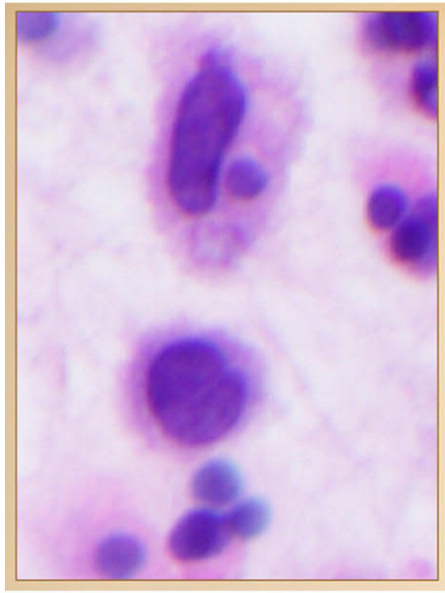

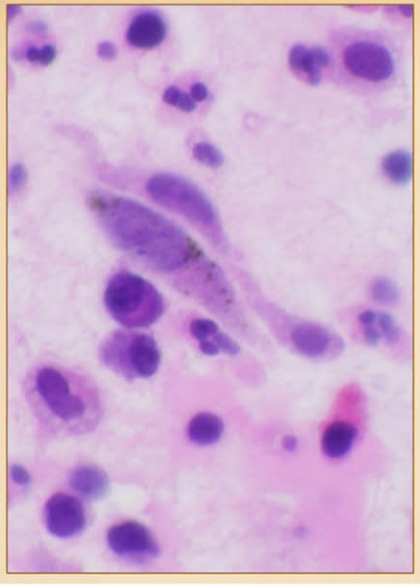

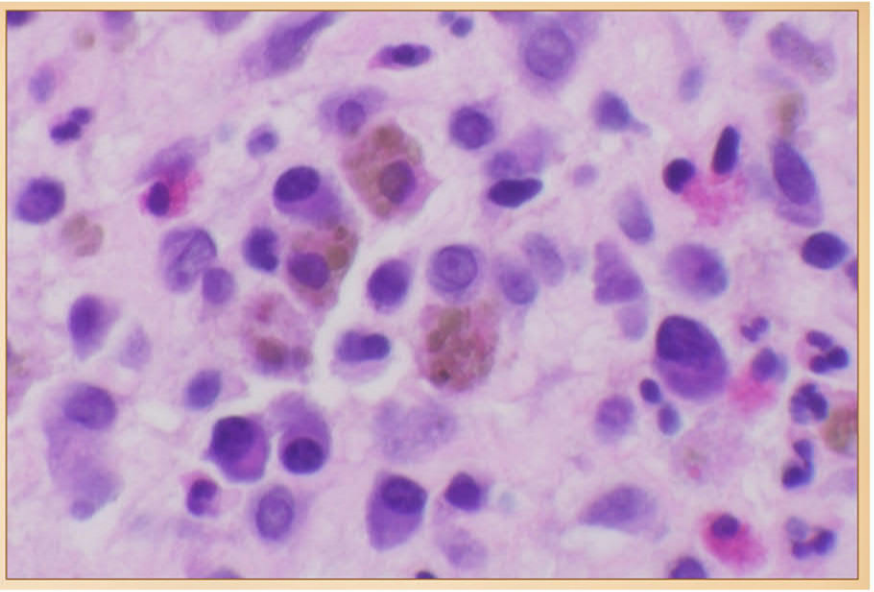

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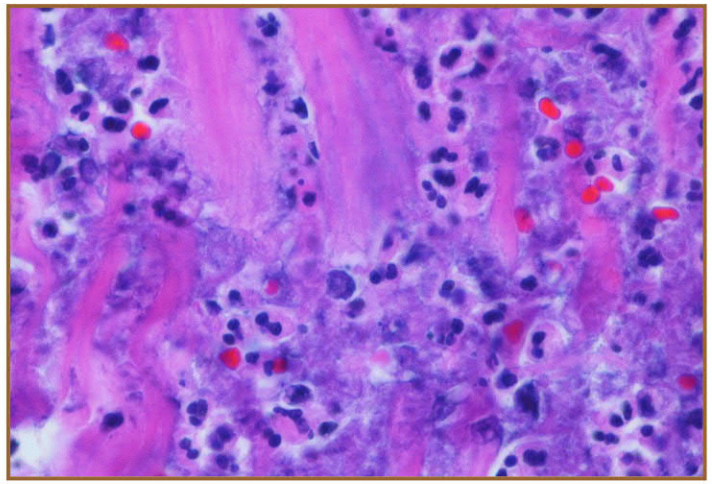
Lymphoid tertiary organs.

Chronic interference, disorganization, atrophy of host / target tissues.
Standby vs active.
Ability to awaken and trigger acute inflammation.
Subject to endocrine effects of remote inflammation.

Occult Antigen Exposure

Anti-nuclear & Anti-cytoplasmic Antibodies

actin (smooth muscle)
antinuclear antibodies
cardiolipin
centromere
chromatin
cyclic citrullinated peptide (CCP)
dsDNA
endomysial
histone
interleukin-2 receptor
Jo-1(histidine-tRNA ligase)
liver kidney microsome (LKM-1)
mitochondrial
neutrophil cytoplasmic (ANCA)
perinuclear ANCA
ribosomal P
ribonucleo-protein RNP
scleroderma (Scl-70)
sjögren's SS-A Ro
sjögren's SS-B La
Sm, Sm-RNP
tissue transglutaminase (ATA)



Rheumatic and Related Disease Screening

Table 1. Systemic Lupus Erythematosus (SLE) & Mixed Connective Tissue Disease

Test	Systemic Lupus Erythematosus	Mixed Connective Tissue Disease
dsDNA antibody[a]	+	-
Chromatin antibody[a]	+	-
Sm antibody[b]	+	-
Sm/RNP antibody	+	+ (high titer)
RNP antibody	+	+ (high titer)

[a] Highly sensitive for SLE.
[b] Highly specific for SLE.

Table 2. Sjögren's Syndrome, Scleroderma, and Polymyositis

Test	Sjögren's Syndrome	Scleroderma	Polymyositis
SS-A antibody	+	-	-
SS-B antibody	+	-	-
Scl-70 antibody	-	+	-
Jo-1 antibody	-	-	+

Table 3. CREST Syndrome and Neurologic SLE

Test	CREST Syndrome	Neurologic SLE
Centromere antibody	+	-
Ribosomal P antibody	-	+

SLE, systemic lupus erythematosus.

Autoimmune Disorders

Autoimmune Pathology

Dynamical Features

- Localized disease in area of primary injury or inflammation.
- Systemic disease or protean or cross-tissue inflammation.
- Local disease flaring up systemic activity.
- Systemic disease complicating local events.

- Inhibitory or trophic effects on local tissues.
- Triggers acute inflammation to actuate hot neutrophils and tissue lysis.

- Continuously active disease.
- Quiet or "hibernation" phase.
- Endocrine "wake up" effects of remote inflammation.

Nosological Features

Common disease with multiple avatars and aliases.
Commonality of basic pathology and effects, tissue-independent.
Specific sequelae from effects on specific tissues or organs.
Spectrum of auto-antibodies.

Target organs and tissues governed by site of origin and specific antibodies.
Even with localized or organ specific disease, if prolonged, certain "lowest common denominator" systemic signs and symptoms occur.

Evaluation and Diagnosis

Clinical profiles :

Each such unlucky patient gets a grab-bag of signs, symptoms, features.
If features fit defined syndromic profiles, then specific diagnoses are made.
(e.g. lupus, RA, Sjögren's, AS, dermatomyositis, scleroderma-crst, etc.)
Else, Mixed MCTD, Unspecified UCTD, Non-specific NCTD - or -
Organ specific and localized diseases.

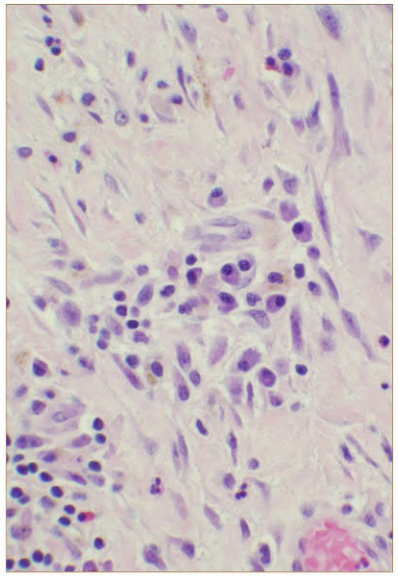
Diagnosis :

Well defined syndromic presentations are diagnosed largely by H & P, with confirmation by select diagnostic specific tests.
Lists of diagnostic criteria. *(e.g. RA-7, lupus-13)*
Selective x-ray.
(e.g. RA: joints; AS: spine-SI joints; lupus-crst angiopathy: angios)
Blood - can be diagnostic, confirmatory, non-diagnostic, misleading.
Seronegativity.

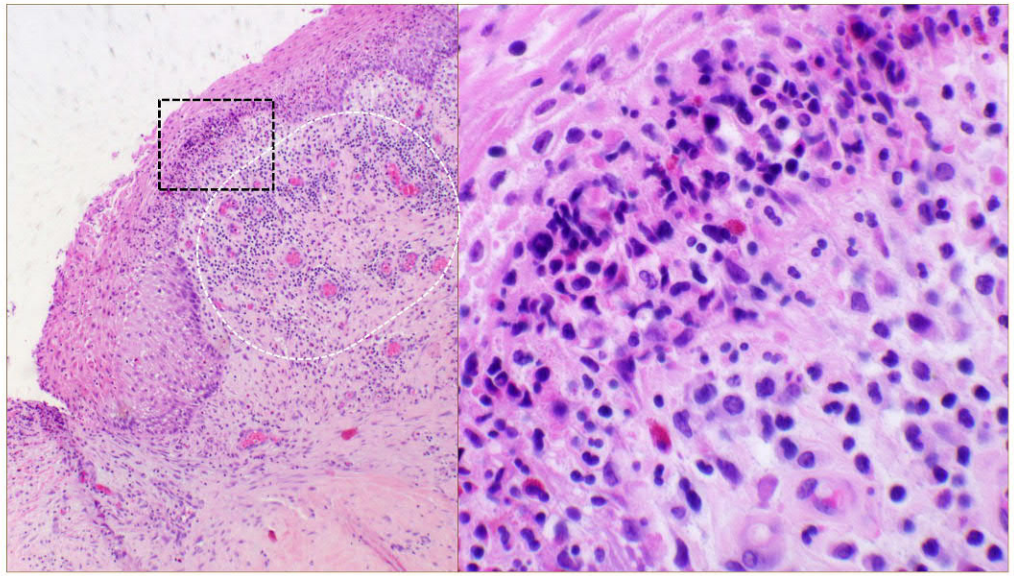
ANA (w/ reflex), specific anti-nuclear or anti-cytosolic ab's.
Spep, complement, paraproteins, ab-fragments & condensates.
(don't fail to identify gammopathies)
Ab's -vs- markers of active disease. *(e.g. 14-3-3-eta, cf troponin-bnp)*

Workup breeder diseases.
(e.g. hypercoagulability, drug induced lupus, allergy, hematological)

Biopsy-histology not needed if there is clear clinical dx of common cvd-ctd, but essential for visceral auto-immunopathies and many wounds.

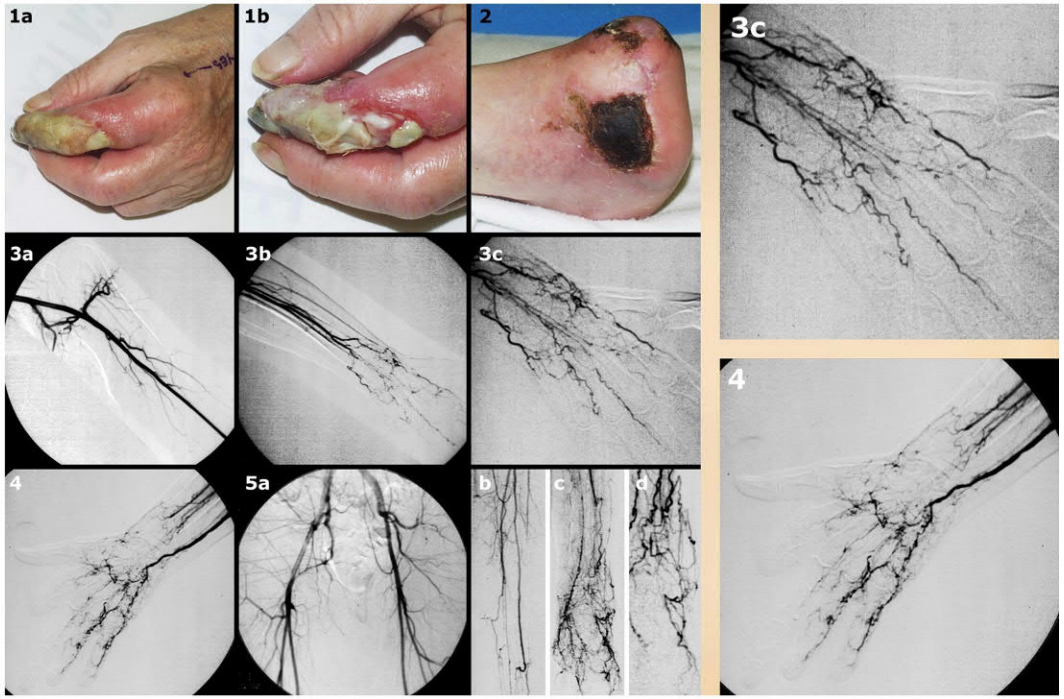


inhibition of host functions without acute inflammation



activated acute inflammation, in old skin graft, with re-ulceration

lupus - scleroderma angiopathy



LCD = "lowest common denominator" symptoms :

LCD

symmetrical large joint polyarthralgias
morning stiffness
malaise
sicca

SLE

4 of 11

malar rash
discoid rash
photosensitivity
oral ulcers
arthritis
serositis
renal disorder
neurologic disorder
hematologic disorder
positive ana
anti-dna or le prep

Rheumatoid Arthritis

synovium is primary target

4 of 7

morning stiffness
3 or more joint areas
hand joints
symmetric arthritis
rheumatoid nodules
radiographic changes
serum rheumatoid factor

(In short : symmetrical large joint poly-arthralgias with morning stiffness.)

Sjögren's

6/6 for 1° dx, 3/6 for 2° dx

ocular symptoms
oral or parotid symptoms
ocular signs
ocular symptoms
lip bx lymphocytic sialoadenitis
ab's Anti-SSA (Ro), Anti-SSB (La)

Behçet's

oral ulcers
genital ulcers
eye lesions
skin lesions
positive pathergy test
& al

Autoimmune Disorders

Risks to Wounds and Surgery

How these diseases intersect with Plastic Surgery

Treating complications of these diseases.
(e.g. rheumatoid hand, chronic wounds, nose recon after gpa)

Consultant / co-surgeon for closing wounds & complications.
(e.g. ortho close joints & implants, general surgery fistulas)

Your patients who coincidentally have autoimmune or cvd-ctd dx.
(avoid disease flareup, avoid wound-surgery complications)

Your patients with established ai-cvd-ctd dx who have flareups.
(get control to protect patient and your surgery and wounds)

Your patients without prior ai-cvd-ctd dx,
who have unexpected complications of trauma or surgery.
(need evaluation, diagnosis, initial rx, planning & referrals)

Complex disorder, multifactorial etiology and evolution.

Complex multifactorial risks, treatment, management.

Risks for Surgery

Risks for flaring up the primary disease or syndrome :
Lupus, Behçet's, pyoderma, multiple sclerosis especially notorious. All are at risk, especially if undiagnosed or breaking through rx.

Risks for flaring up generalized autoimmunity or systemic inflammation :
Can range from malaise, excess pain, fevers, arthralgias, sicca, and other minor symptoms - transient or easily controlled with steroids - through profound cardiovascular collapse and death.

Risks for wound pathergy — lysis, dehiscence, infarcts :
Can be unexpected but minor superficial skin-adipose dehiscence, to dehiscence of muscular fascias or structural repairs, to major ruptures such as bowel-pelvic-chest organ dehiscence.

Risks for thrombotic complications :
Because of high correlation of autoimmune disorders with hypercoagulability, incidental or pre-existing, these risks are high for the wounds, incisions, repairs, and other organs.

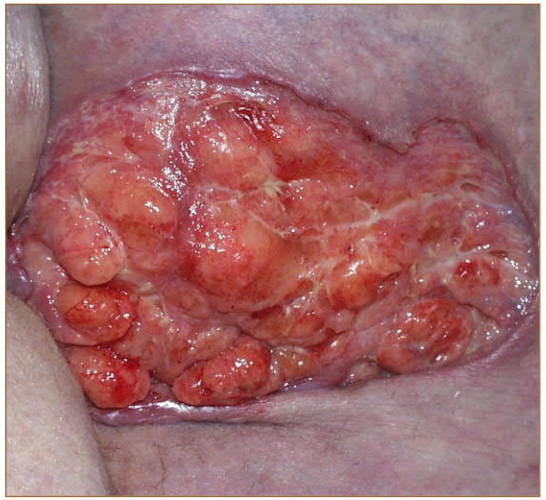
Drug allergy risks :
More so if there is a history of multiple drug allergies, reaginic illness, drug induced lupus.
Seasonal wound-surgery risks, based on environmental allergies.

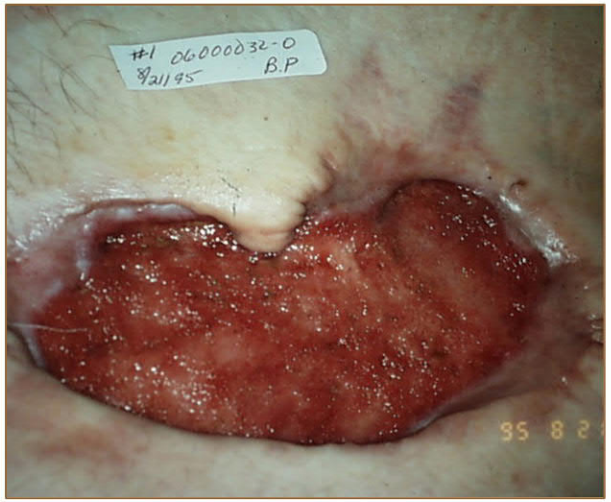
Severity :
Can range from minor symptoms as above, nuisance wound complications, or need to adjust disease rx — to transient and manageable renal injury, pulmonary complications, neurological alterations, joint-physical impairments (all manageable and recoverable) — through atypical infections, catastrophic infarcts, surgery failure, single or multiple organ failure, death.

Implications :
Treat acute complications, diagnose undiagnosed disease, or assess state of known disease, and start or adjust rx.
Prednisone, methylprednisolone, and heparin are your friends.









Management

Complex disorder, multifactorial etiology and evolution.

Complex multifactorial risks, treatment, management.

General Treatment Principles

Acute control versus long term suppression and management.
As for all complex disease, it is easier to maintain control than achieve it in the first place. Once under control, do not lose it.
Management of the disease and autoimmunity.
Rx for general disease, inflammation, auto-immunity, breeder dx.
Rx then rehabilitation for complications & sequelae.

For Disease Per Se

General Concepts

Aggressively control inflammation and disease . . .
until signs-symptoms are controlled enough that jeopardy is gone.
High doses may be needed, drugs with non-trivial dose-dep. side effects.
Taper doses to maintain parity with disease severity as it improves.
Once acute illness is controlled, long term outpt management is needed.
This includes ongoing disease monitoring and rx adjustments.

The disease is NEVER gone, even if quiet. Respect this principle when
acute inflammation risk is high (trauma, surgery, incidental illness).
Always be alert for flareups, and quash as quickly, thoroughly as possible,
returning patients to their pre-(acute)-morbid drug or rx levels.
*(*** Disease-damage can get out of control within hours to days; returning to pre-morbid status and rx can take weeks or months.)*

Even if disease is well managed and controlled, long term sequelae and functional complications develop slowly, sometimes insidiously.
Keep alert for them, especially specialty complications. Manage to prevent-preempt-delay problems, or treat by surgery or other means when such modalities work well - do not wait too long.

Scenarios likely to be encountered by surgeons and specialists

Treating complications of these diseases.
(e.g. rheumatoid hand, chronic wounds, nose recon after gpa)

Consultant / co-surgeon for closing wounds & complications.
(e.g. ortho close joints & implants, general surgery fistulas)

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who have unexpected complications of trauma or surgery.
(need evaluation, diagnosis, initial rx, planning & referrals)

Autoimmune Disorders

For Disease Per Se, Pharmaceuticals et al

*** The following are all important Rx. Pick and choose based on severity of illness, severity of symptoms, specific nosological diagnosis, impending or post facto complications, risk profiles, side effects and prior intolerance, efficacy, etc.

Steroids

Oral, intravenous, intra-lesional, intra-articular, etc., based on circumstances.
until signs-symptoms are controlled enough that jeopardy is gone.

***** The sine qua non of treating active inflammation and auto-immunity.**

There is no tachyphylaxis - they work dependably well, every time.

For short term use, side effects are easily recognized, usually benign and transient, manageable, and thus should not dissuade use.

Today, unusual cases needing excessive high doses have effective alternates.

Because of intermediate term risks at higher doses,
and long term risks even at low doses, doses need regular adjustment.

Goal is to lower steroid dose to lowest level that keeps disease in check.

*** There are three situations for lowering — "tapering" — steroids :

1 - Acutely, to maintain parity with disease as it is brought under control.
(Minimizes the short term risks of high doses.)

2 - Ongoing, for controlled disease, seeking lowest effective dose.
(Minimizes long term risks of lower doses.)

3 - Discontinuation after chronic use, to test HPA axis and coax it to recover.
(To avoid Addisonian states and complications.)

Introductory & low level Rx for lesser or non-severe problems.

Aspirin, nsaid's, sulfasalazine-mesalamine, tetracyclines.

Topicals and injectables.

OTC, naturopathy, etc., for symptom relief.
(Do not permit patient to confuse symptom relief with definitive rx.)

Physical modalities.

Review and treat contributory problems.

Risk reduction by allergy - diet - environmental review and adjustments.

Look for and treat breeder disorders —
coagulopathies, allergies, chronic infections, etc.

Review medications and rule out drug induced lupus —
if present, work with patient's other doctors to revise rx.

If workup indicates hypercoagulability, even if equivocal, start anticoagulants.

Surgery, etc.

If needed for sequelae or for independent problems, delay until
AI - inflammatory disease is under control.

If urgent, treat AI - inflammation preemptively before, during, after surgery.

Autoimmune Disorders

For Disease Per Se, Pharmaceuticals et al

For acute disease not responsive to reasonable doses of steroids . . .
For chronic disease where steroid side effects are problematic . . .
For chronic disease where control is incomplete on current rx . . .
For chronic disease that has escaped or become refractory to prior rx . . .
Based on published art and science of managing specific diseases . . .

**** Many other options are available.*

Depending on agent, allow changes in Rx 1-2 months, or 3-4 months observation.
For promising choices, titrate doses to best effect.
For lack of promise, switch to another agent.

DMARD's

Generation 1 — Anti-metabolites

Azathioprine, 6-MP, leflunomide, cyclophosphamide, methotrexate, etc.
**** in the past 25 years, methotrexate has become a preferred rx.*
Use RA-AI-cvd-ctd dosing rather than cancer dosing.

Generation 2 — Mycotics, CNI's, and similar

Cyclosporine, tacrolimus, mycophenolate, rapamycin, etc.
**** these have become preferred rx for transplant rejection.*

Generation 3 — Mab's and similar recombinant rx.

Etanercept, infliximab, adalimumab, rituximab, etc.
**** revolutionary and effective rx for neoplasia and inflammatory dx.*

Incidental other Rx

Plasmapheresis. Very effective to clear circulating ab's and paraproteins.
Use for severe or refractory disease, or where steroid use is problematic.

Immunoglobulin infusion, IVIG, pooled IgG.
Indications-effects similar to plasmapheresis, more suited for chronic dx.

Treatment Principles as Surgeon or Specialist

*** Recognize at-risk patients, and manage care and surgery to preempt disease flareup and complications.

*** Know how to manage acute flareups and get disease back under control, and to avoid wound pathergy and failed surgery.

*** Use steroids and anticoagulation for acute or short term control.

*** Make sure acute disease is controlled as best as possible before undertaking non-urgent rx *(especially for high pathergy prone dx)*.

*** If wounds fail or exhibit features of immunity or acute inflammation, hold off on further procedures or elective surgery until controlled.

*** If wounds fail / pathergy for urgent unavoidable surgery-trauma, minimize injury & tissue stress, treat disease aggressively.

*** "Fool me once ..." No more non-urgent surgery until under control.

***** Know how to do proper wound care.**

Autoimmune Disorders

Consultants, Referrers, Primaries, and other Cast

Be prepared to recognize and treat these diseases,
even within the parochial limits of specialty consultation and care.

Consultants and colleagues

Find a rheumatologist and dermatologist to have in your "inner circle" of preferred consultants, plus other specialties.

Rheumatologists are the "top dogs" of this knowledge and care, but . . .
not enough, not available for inpatient, office appt's hard to get.

Dermatologists can be equally good, especially with mab's, new drugs,
but few are interested in these disorders.

GI for *IBD, &al*; Pulmonary for *ILD, PHtn*; Nephrology for *lupus, &al.*; Neurology for *MS & demyelinating dx*; etc.

Your role

Be prepared to recognize these diseases, do basic evaluation, initiate introductory rx, and carry through on rx,
to protect your surgery and wounds, and until others can take over.

Support your consultants by getting studies before consultation,
blood tests, x-rays, biopsies, etc.

Scenarios

Chronic quiet disease, established diagnosis, now on no or minimum rx :
Preemptive rx with lower doses of steroids (and anticoagulants), versus close observation.

Chronic active disease, controlled on rx :
Continue rx; boost as needed in peri-op, peri-trauma period.
Dual role steroids – replacement rx, disease suppression rx.

Acute active disease, patient with established diagnosis and prior rx :
Postpone elective surgery, and start rx for flareup.
Unavoidable surgery – rx to suppress dx and avoid complications.

Known disease, quiet, unexpected flareup or complications after surgery :
Active rx to curtail flare, and avoid wound-surgery complications.

Unexpected flareup or surgery complications, leading to new diagnosis :
If suspected, steroids and anticoagulants, plus workup and rx.

Known or active disease, pt needs urgent-emergency surgery :
Boost steroids, anticoagulants, plasmapheresis in severe cases.

Known or active disease, pt needs time sensitive surgery :
e.g., flap delays, staged recon, etc. - usually enough time to stabilize disease state and prepare for pending procedures.

Known or active disease, or new dx, pt needs elective necessary surgery :
Consultations, disease stabilization before surgery, 1-2, 3-4 months.

Known or active disease, pt wants cosmetic or non-essential surgery :
Carefully consider severity and state of disease, etc.
e.g., low grade RA, IBD well treated, okay for surgery with added rx;
e.g. Behçet's, Buerger's, function-impaired ILD, learn to say "no".

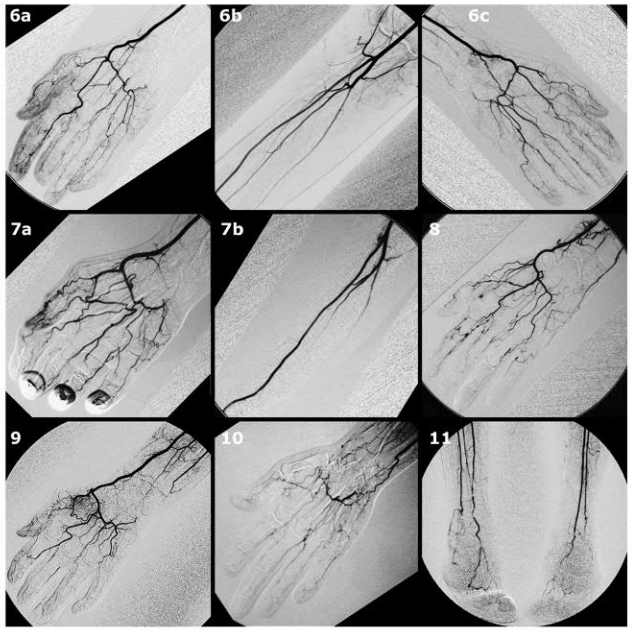
* * * ***Prednisone, methylprednisolone, and heparin are your friends.***

Special Topics

In no special order :

Rheumatoid hand :
Prototype of plastic surgery related connective tissue disorder.

Lupus-scleroderma angiopathy :
Acral fibro-stenotic arteriopathy,
distinctive for scleroderma-crst and lupus.



Drug induced lupus :
Unusually pernicious or refractory effects until drug withdrawn.
Easily overlooked, but once suspected, can be confirmed.

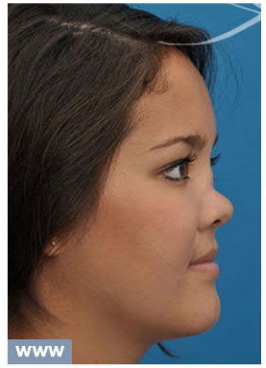
Skin and pannicular auto-immune and cvd-ctd's :
e.g., scleroderma, pyoderma gangrenosum, behçet's, pemphigus, pemphigoid, morphea, hidradenitis & acne's, Weber-Christian.

Calcific panniculopathy of dermatomyositis :
Distinctive pathology, once ulcerated and abscessed, requires total dermatofasciectomy and skin reconstruction.

Saddle nose deformity of Wegener's / GPA :
Technically similar to gummas, post-trauma, post-rhinoplasty recon, but ai vasculopathy and inflammation must be controlled.

Connection to hypercoagulable states and disorders :
They often go together, either genetic hypercoag disorder breeds auto-immunity, or active AI disease unbalances coag system.

* * * ***Prednisone, methylprednisolone, and heparin are your friends.***



AI Wounds Heal with Steroids and Anti-Lymph Rx

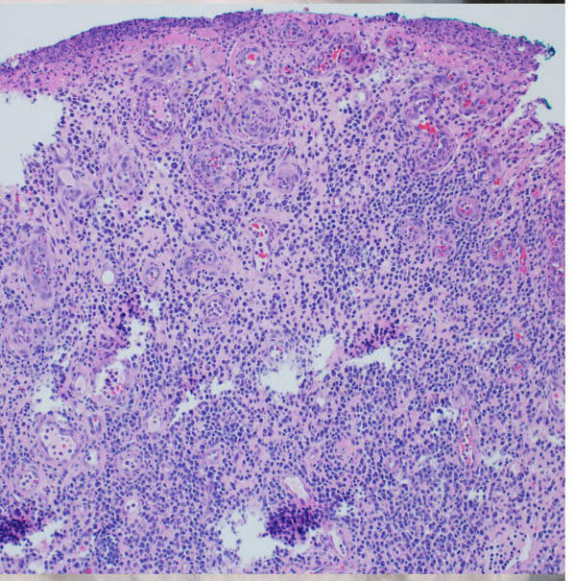
Lymphoid 3-population wounds

Normal healthy healing wounds have two cell populations :
1 - Proper reactive (acute) inflammation.
Neutrophils, monocyte-macrophages.
2 - Reparative stroma.
Angiocytes, fibroblasts.

Auto-immunized wounds have three cell populations :
3 - Secondary lymphoid (chronic) inflammation.
Lymphocytes, plasma cells, eosinophils.

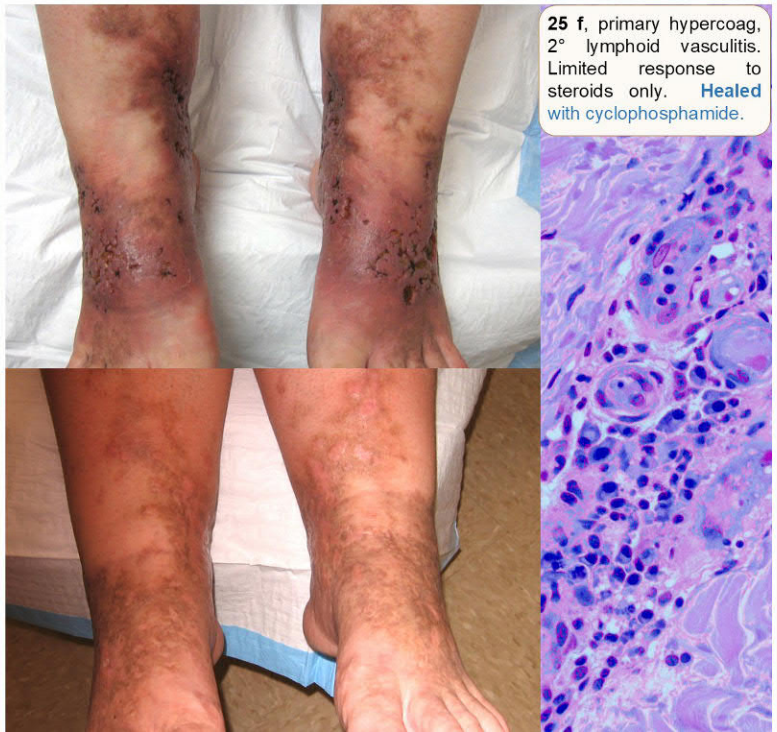
They require steroids and anti-immune therapies to heal.

71m RA 20 yrs, uncontrolled. Ankle ulcers 2 years. Rx : intra-lesional triamcinolone & oral prednisone.

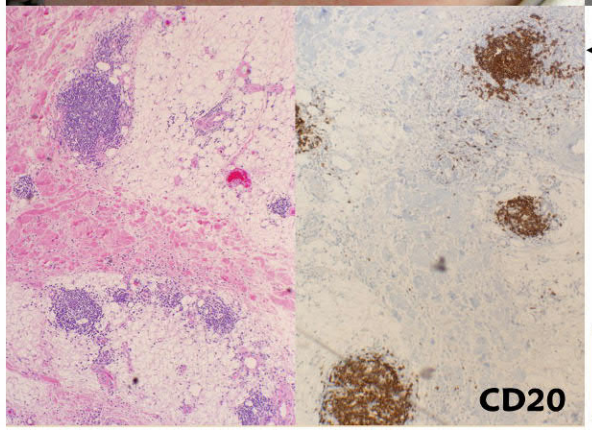


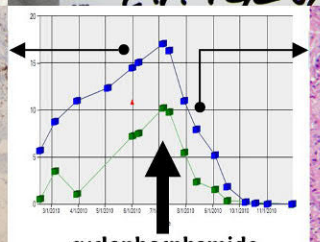
45 f, **lupus**, chronic leg-ankle ulcers, secondary chronic thigh ulcers after errant skin grafts. **Healed** with cyclophosphamide.

35 mf, **lupus**, post-trauma bullous pemphigoid, 2° lymphoid panniculitis. (Chest, abd, leg.) Partial response to steroids (center). **Healed** with azathioprine (right).

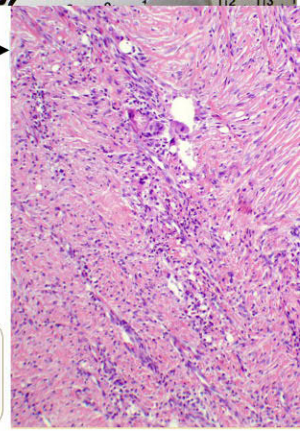


25 f, primary hypercoag, 2° lymphoid vasculitis. Limited response to steroids only. **Healed** with cyclophosphamide.





44 f, **calcifying panniculitis**, probable forme fruste dermato-myositis, lymphoid vasculitis. **Healed** with cyclophosphamide.

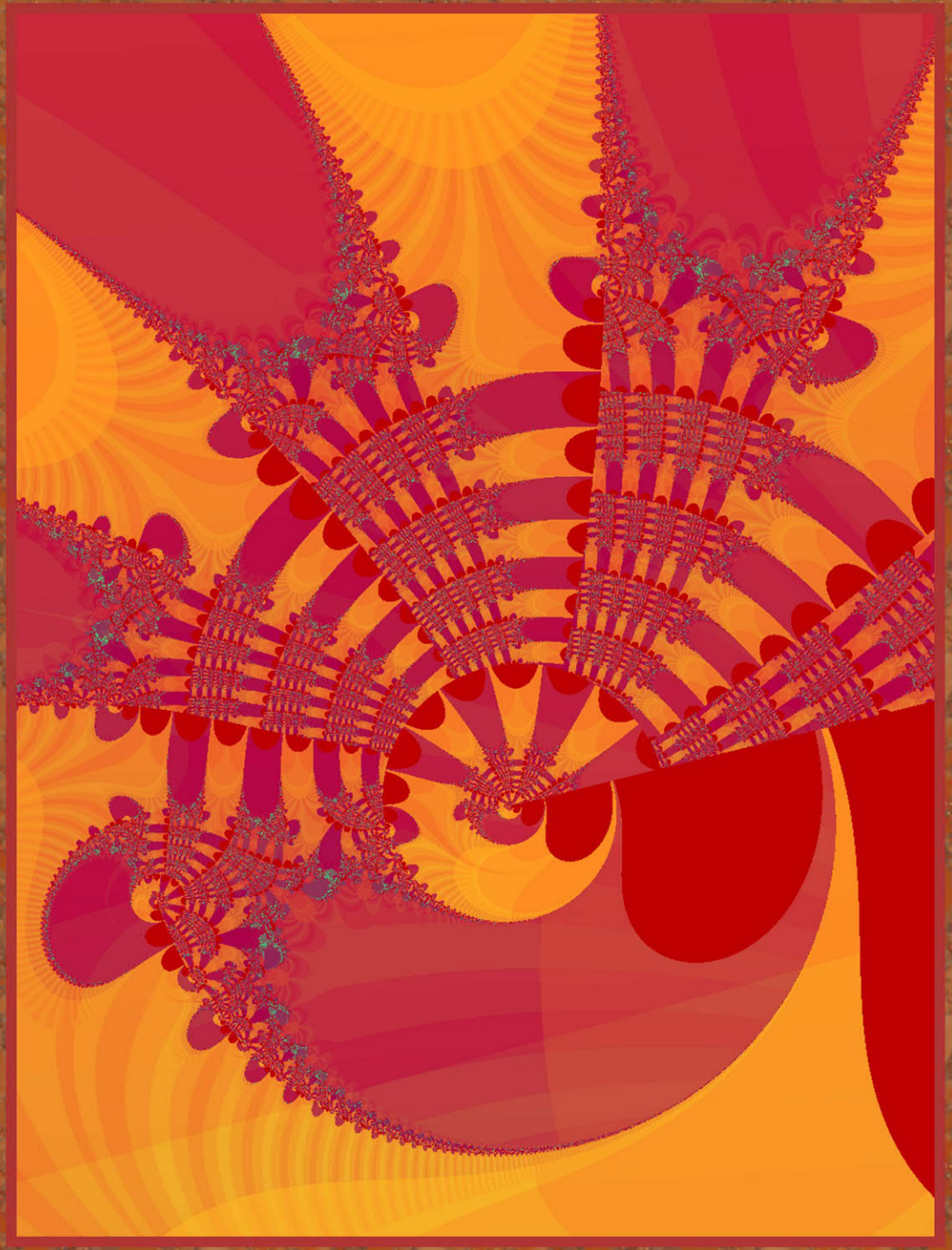


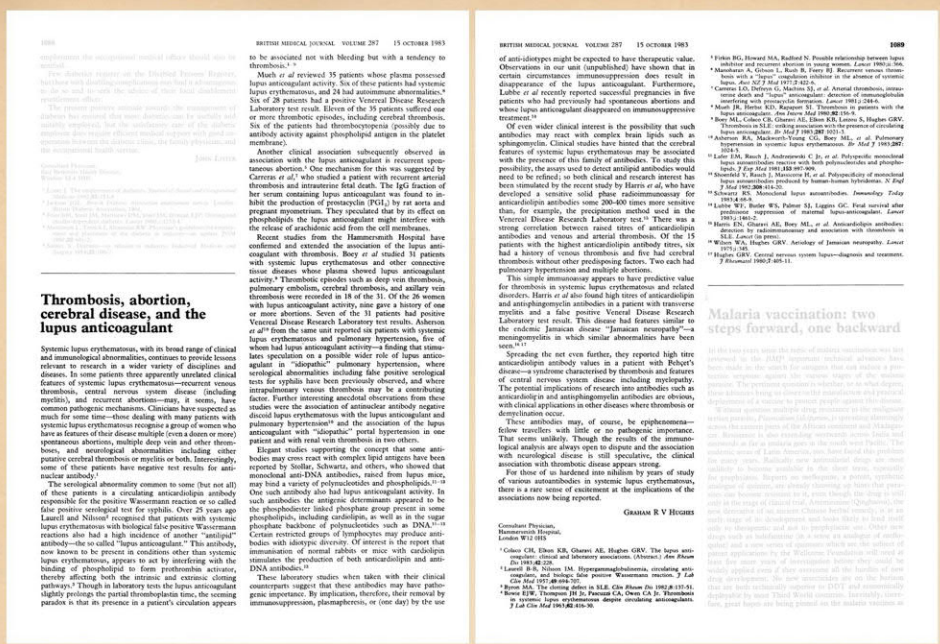
51 f, **lupus**, lupus and hypercoag disorder. Malleolar ulcer. **Healed** with intralesional and oral steroids.

Autoimmune & Hypercoagulable Disorders

Autoimmune,
Chronic
Inflammatory,
CVD - CTD

**Hypercoagulable,
Micro-occlusive
Disorders**





BRITISH MEDICAL JOURNAL VOLUME 287 15 OCTOBER 1983

Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

Systemic lupus erythematosus, with its broad range of clinical and immunological abnormalities, continues to provide lessons relevant to research in a wider variety of disciplines and diseases. In some patients three apparently unrelated clinical features of systemic lupus erythematosus—recurrent venous thrombosis, central nervous system disease (including myelitis), and recurrent abortions—may, it seems, have common pathogenic mechanisms. Clinicians have suspected as much for some time—those dealing with many patients with systemic lupus erythematosus recognise a group of women who have as features of their disease multiple (even a dozen or more) spontaneous abortions, multiple deep vein and other thromboses, and neurological abnormalities including either putative cerebral thrombosis or myelitis or both. Interestingly, some of these patients have negative test results for antinuclear antibody.[1]

The serological abnormality common to some (but not all) of these patients is a circulating anticardiolipin antibody responsible for the positive Wassermann reaction or so called false positive serological test for syphilis. Over 25 years ago Laurell and Nilsson[2] recognised that patients with systemic lupus erythematosus with biological false positive Wassermann reactions also had a high incidence of another "antilipid" antibody—the so called "lupus anticoagulant." This antibody, now known to be present in conditions other than systemic lupus erythematosus, appears to act by interfering with the binding of phospholipid to form prothrombin activator, thereby affecting both the intrinsic and extrinsic clotting pathways.[3] Though in laboratory tests the lupus anticoagulant slightly prolongs the partial thromboplastin time, the seeming paradox is that its presence in a patient's circulation appears to be associated not with bleeding but with a tendency to thrombosis.[4-9]

Much *et al* reviewed 35 patients whose plasma possessed lupus anticoagulant activity. Six of these patients had systemic lupus erythematosus, and 24 had autoimmune abnormalities.[4] Six of 28 patients had a positive Venereal Disease Research Laboratory test result. Eleven of the 35 patients suffered one or more thrombotic episodes, including cerebral thrombosis. Six of the patients had thrombocytopenia (possibly due to antibody activity against phospholipid antigen in the platelet membrane).

Another clinical association subsequently observed in association with the lupus anticoagulant is recurrent spontaneous abortion.[5] One mechanism for this was suggested by Carreras *et al*,[6] who studied a patient with recurrent arterial thrombosis and intrauterine fetal death. The IgG fraction of her serum containing lupus anticoagulant was found to inhibit the production of prostacyclin (PGI_2) by rat aorta and pregnant myometrium. They speculated that by its effect on phospholipids the lupus anticoagulant might interfere with the release of arachidonic acid from the cell membranes.

Recent studies from the Hammersmith Hospital have confirmed and extended the association of the lupus anticoagulant with thrombosis. Boey *et al* studied 31 patients with systemic lupus erythematosus and other connective tissue diseases whose plasma showed lupus anticoagulant activity.[7] Thrombotic episodes such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, and axillary vein thrombosis were recorded in 18 of the 31. Of the 26 women with lupus anticoagulant activity, nine gave a history of one or more abortions. Seven of the 31 patients had positive Venereal Disease Research Laboratory test results. Asherson *et al*[8] from the same unit reported six patients with systemic lupus erythematosus and pulmonary hypertension, five of whom had lupus anticoagulant activity—a finding that stimulates speculation on a possible wider role of lupus anticoagulant in "idiopathic" pulmonary hypertension, where serological abnormalities including false positive serological tests for syphilis have been previously observed, and where intrapulmonary venous thrombosis may be a contributing factor. Further interesting anecdotal observations from these studies were the association of antinuclear antibody negative discoid lupus erythematosus with the lupus anticoagulant and pulmonary hypertension[8] and the association of the lupus anticoagulant with "idiopathic" portal hypertension in one patient and with renal vein thrombosis in two others.

Elegant studies supporting the concept that some antibodies may cross react with complex lipid antigens have been reported by Stollar, Schwartz, and others, who showed that monoclonal anti-DNA antibodies, raised from lupus mice, may bind a variety of polynucleotides and phospholipids.[10-13] One such antibody also had lupus anticoagulant activity. In such antibodies the antigenic determinants appeared to be the phosphodiester linked phosphate group present in some phospholipids, including cardiolipin, as well as in the sugar phosphate backbone of polynucleotides such as DNA.[10-13] Certain restricted groups of lymphocytes may produce antibodies with idiotypic diversity. Of interest is the report that immunisation of normal rabbits or mice with cardiolipin stimulates the production of both anticardiolipin and anti-DNA antibodies.[13]

These laboratory studies when taken with their clinical counterparts suggest that these antibodies may have pathogenic importance. By implication, therefore, their removal by immunosuppression, plasmapheresis, or (one day) by the use of anti-idiotypes might be expected to have therapeutic value. Observations in our unit (unpublished) have shown that in certain circumstances immunosuppression does result in disappearance of the lupus anticoagulant. Furthermore, Lubbe *et al* recently reported successful pregnancies in five patients who had previously had spontaneous abortions and whose lupus anticoagulant disappeared on immunosuppressive treatment.[14]

Of even wider clinical interest is the possibility that such antibodies may react with complex brain lipids such as sphingomyelin. Clinical studies have hinted that the cerebral features of systemic lupus erythematosus may be associated with the presence of this family of antibodies. To study this possibility, the assays used to detect antilipid antibodies would need to be refined, so both clinical and research interest has been stimulated by the recent study by Harris *et al*, who have developed a sensitive solid phase radioimmunoassay for anticardiolipin antibodies some 200-400 times more sensitive than, for example, the precipitation method used in the Venereal Disease Research Laboratory test.[15] There was a strong correlation between raised titres of anticardiolipin antibodies and venous and arterial thrombosis. Of the 15 patients with the highest anticardiolipin antibody titres, six had a history of venous thrombosis and five had cerebral thrombosis without other predisposing factors. Two each had pulmonary hypertension and multiple abortions.

This simple immunoassay appears to have predictive value for thrombosis in systemic lupus erythematosus and related disorders. Harris *et al* also found high titres of anticardiolipin and antiphingomyelin antibodies in a patient with transverse myelitis and a false positive Venereal Disease Research Laboratory test result. This disease had features similar to the endemic Jamaican disease "Jamaican neuropathy"—a meningomyelitis in which similar abnormalities have been seen.[16,17]

Spreading the net even further, they reported high titre anticardiolipin antibody values in a patient with Behçet's disease—a syndrome characterised by thrombosis and features of central nervous system disease including myelopathy. The potential implications of research into antibodies such as anticardiolipin and antiphingomyelin antibodies are obvious, with clinical applications in other diseases where thrombosis or demyelination occur.

These antibodies may, of course, be epiphenomena—fellow travellers with little or no pathogenic importance. That seems unlikely. Though the results of the immunological analysis are always open to dispute and the association with neurological disease is still speculative, the clinical association with thrombotic disease appears strong.

For those of us hardened into nihilism by years of study of various autoantibodies in systemic lupus erythematosus, there is a rare sense of excitement at the implications of the associations now being reported.

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Malaria vaccination: two steps forward, one backward

Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

Graham RV Hughes, British Medical Journal 1983

Describes an association of SLE, multiple miscarriage, multiple dvt, and neurological abnormalities with lupus anticoagulant, anticardiolipins, anti-phospholipid antibodies.

"These antibodies . . . the clinical association with thrombotic disease appears strong."

Antiphospholipid Antibody Syndrome: A New Cause of Nonhealing Skin Ulcers

Daniel P. Goldberg, M.D., Victor L. Lewis, Jr., M.D., and William J. Koenig, M.D.

Chicago, Ill.

Antiphospholipid antibody syndrome causes many problems that are usually treated by rheumatologists. Included within the manifestations of the syndrome, however, are painful, refractory leg ulcers, which, with the causative vascular damage, may lead to limb loss. The report of such a case, the patient's course and treatment, and the causes and diagnosis of the syndrome are presented. (*Plast. Reconstr. Surg.* 95: 837, 1995.)

The etiology of most leg ulcers plastic surgeons are asked to evaluate is clinically evident. The common patient histories, locations, and appearance of venous, neurotrophic, and arterial ulcers are well known. Occasionally, the plastic surgeon sees a very different wound, one not easily categorized, which causes the patient serious trouble and the debridement, culture, and biopsy of which yield no patient benefit or diagnosis. This report describes such a patient, his course and treatment, and the method of diagnosing a recently recognized, uncommon cause of leg ulceration.

Case Report

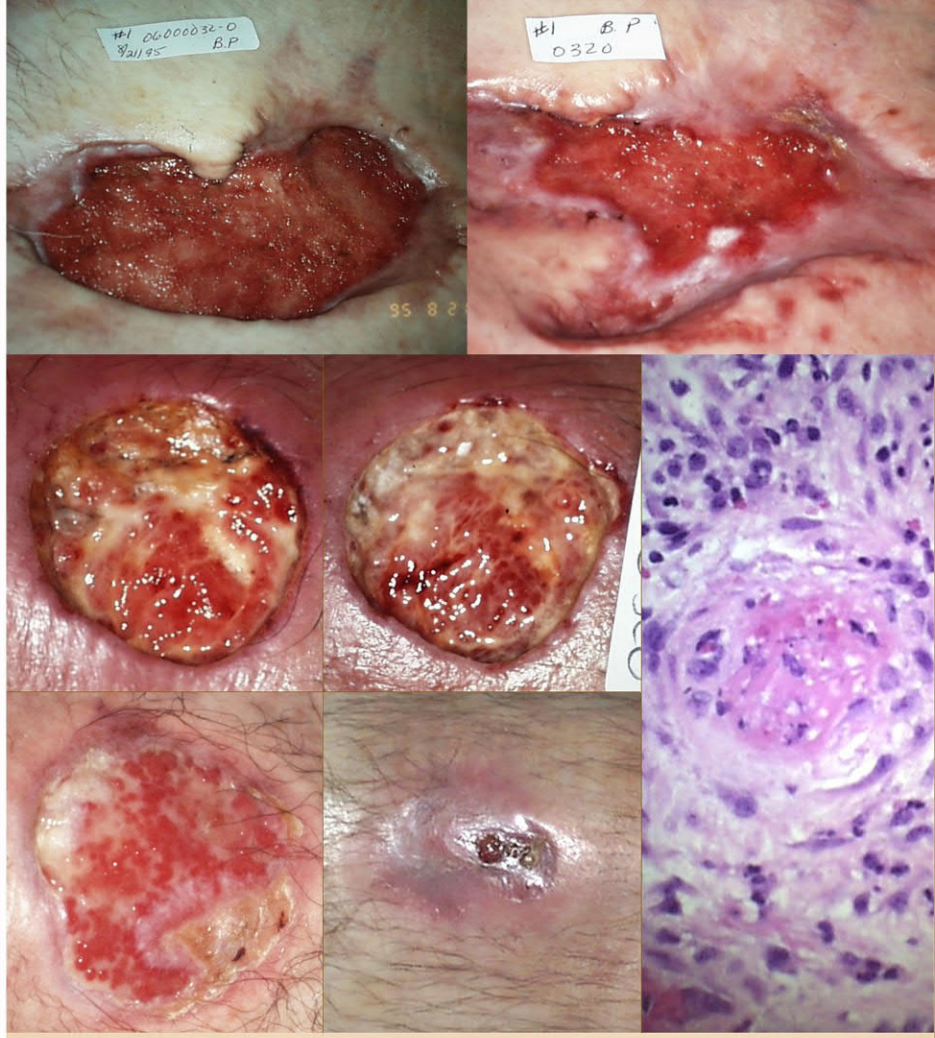
A 50-year-old man with a 10-year history of nonhealing ulcers of the right leg presented to the Plastic Surgery Service at our hospital. Approximately 12 years earlier, he had undergone a below-knee amputation of the left leg, subsequently revised to an above-knee level for what was apparently the same problem. A formal diagnosis was never made. Further history revealed that the right leg lesions had chronically and intermittently recurred and slowly healed over the past decade. Notable medical history included hypertension, mild glucose intolerance, and an 80 pack-year smoking history.

On admission, the lesions were noted to be erythematous, purple, macular lesions with central, shallow ulcerations, and tended to coalesce (Fig. 1). The ulcers, as well as some smaller satellite lesions, were located predominantly in the lower medial pretibial region. There were multiple, small depressed scars about the leg and small regions of hyperpigmentation over the entire thigh and leg. The ulcerated areas were profoundly tender to touch. The skin of the foot was warm and well perfused, and pulses were palpable. Significant laboratory results included mildly elevated white blood cell count and erythrocyte sedimentation rate, a positive lupus-like anticoagulant, and elevated cardiolipin antibodies. Arterial Doppler studies were normal. Arteriography revealed

Fig. 1. Photograph of patient's right leg at presentation. Note the erythematous, macular lesions with shallow, central ulcerations.

From the Division of Plastic, Reconstructive, and Maxillofacial Surgery at the Northwestern University Medical School. Received for publication November 13, 1992; revised April 5, 1994.
Presented at the Annual Meeting of the Midwestern Association of Plastic Surgeons, in Bismarck, North Dakota, on June 19, 1992.

Plastic and Reconstructive Surgery, April, 1995



34 M **Dx: Lupus, Antiphospholipid antibody syndrome**

Wound pathergy, then multiple failed surgery after trivial hand trauma.
Multiple subsequent wounds from failed grafts and flaps.
Second set of wounds after elective hip replacement (for lupus arthritis).

Suspicious history.

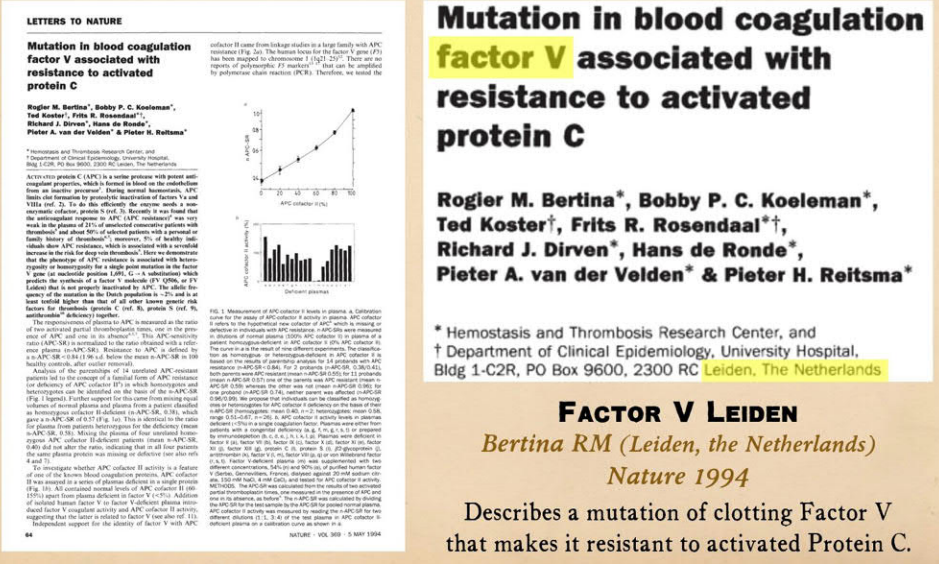
Lab: **anticardiolipins high**.

Confirmatory tests.

Healed by warfarin only (& basic topicals).

Proper wound behavior only after warfarin.

Later: mva, abdominal wall infarct with wounds & colon fistula.
Later: home fall, minor non-skeletal back injury, tardive 2° cord infarct, paraplegia.



LETTERS TO NATURE

Mutation in blood coagulation factor V associated with resistance to activated protein C

Rogier M. Bertina*, Bobby P. C. Koeleman*, Ted Koster†, Frits R. Rosendaal*†, Richard J. Dirven*, Hans de Ronde*, Pieter A. van der Velden* & Pieter H. Reitsma*

* Hemostasis and Thrombosis Research Center, and
† Department of Clinical Epidemiology, University Hospital, Bldg 1-C2R, PO Box 9600, 2300 RC Leiden, The Netherlands

DANGER

Mutation in blood coagulation factor V associated with resistance to activated protein C

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Factor V Leiden

Bertina RM (Leiden, the Netherlands) Nature 1994

Describes a mutation of clotting Factor V that makes it resistant to activated Protein C.

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Hypercoagulable Disorders – Implications For Wounds & Surgery

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Wound Pathergy – When Not to Operate

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HYPERCOAGULABLE DISORDERS – IMPLICATIONS FOR WOUNDS & SURGERY

PATHOPHYSIOLOGY, CLINICAL FEATURES, DIAGNOSIS & TREATMENT

AND

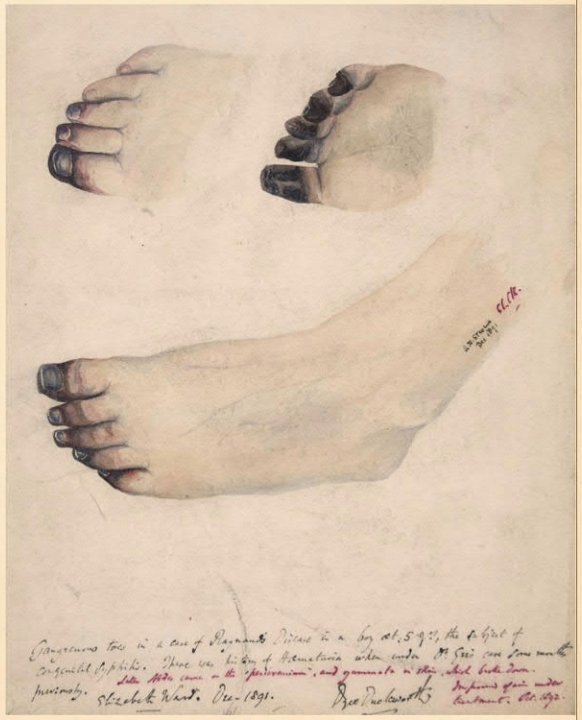
Insights About the Historical Understanding of this Subject and Why These Problems Remain Perpetually Under Appreciated, Under Recognized, and Under Treated.

Marc E. Gottlieb, MD, FACS September, 2018 Phoenix, Arizona Arimedica.com

Mortification, gangrene of the toes. Robert Carswell, London, 1837.

Dry gangrene after ligature of popliteal aneurism. Thomas Godart, London, 1880.

Gangrene of the hand from idiopathic arteritis. Thomas Godart, London, 1880.



Gangrenous toes from Raynaud's Disease, 5 year old boy with congenital syphilis. A.F. Stevens, 1891.

Hypercoagulable Disorders

Key Points

Hypercoagulable disorders cause serious, profound, many times lethal complications of illness, trauma, surgery.

Problems can be chronic wounds or other sequelae, affording an opportunity to make the diagnosis and treat before catastrophe.

If an occult disorder surfaces unexpectedly after surgery (wound pathergy) without prior suspicion, it is imperative to diagnose and treat quickly before any attempts at further surgery.

If a patient is known to have a problem, patients will heal and future problems averted simply by using anti-coagulants.

Photos at beginning not available.

Four months into effective care.

Most of the original wound is closed and healed. Open areas shown are part of the deliberate staging of this reconstruction.

— BUT ALSO —

Four weeks absent from hospital.

RA and inflammation have flared. Vascular stasis and signs of incipient tissue infarction give a sense of the original presentation.

Prompt correction after starting steroids and argatroban.

---

50 day interval from above image.

Small incidental wounds all healing.

Wound at confluence of flaps (low center) is expected.

Wound at base of spine (L2) is open by design to protect rest of the repair (to be repaired in a few weeks).

Stasis, cyanosis, ischemia, necrosis, infarction, & abnormal inflammation have all ceased with anticoagulants.

UNDERLYING PROBLEM

34 m :: Paraplegia and pressure ulcers.

Wound pathergy and progressive surgical wound infarcts resulting in translumbar amputation.

Recent onset severe Rheumatoid arthritis.

STATUS AT ACCEPTANCE

TLA infarcted, complex abdomino-pelvic wounds.

SUCCESS AFTER:

Proper wound care.

Coagulation w/u then Rx.

Heparin (–> HIT), then argatroban, then rivaroxaban.

Continuous argatroban during & after surgery.

Steroids & multimodal Rheumatoid Rx.

Proper staged surgery.

Positive Lab Studies

Species	*Value*		*Normal*
Fibrinogen	632	H	< 465
D-dimer	892	H	< 500
TAT cmplx	4.5	H	< 4.0
F.VIII	231%	H	50-150
Protein C	69	L	70-140
RheumF	108	H	< 13
CCP IgG	119	H	< 16

Left top, wound & fistula.

Left bottom, start of the exposure.

Right top, completed surgery with stoma through hypogastric flap.

Right bottom, 8 days, no ischemia or necrosis except next to stoma, from perforating the flap, not coagulopathy.

UNDERLYING PROBLEM

52 m :: Diverticulitis & complications.

Wound pathergy and surgical infarcts resulting in abdominal wall loss and entero-cutaneous fistula.

Multiple infarcts & leaks: bowel, anastomoses, wall.

STATUS AT ACCEPTANCE

Complex abdominal wound, open bowel & fistula.

SUCCESS AFTER:

Proper wound care.

Coagulation w/u then Rx.

Heparin, then apixaban.

Continuous heparin during & after surgery.

Inflammatory bowel disease ruled out.

Proper staged surgery.

Positive Lab Studies

Species	*Value*		*Normal*
Fibrinogen	1101	H	< 465
MTHFR	heterozyg		neg
F.VIII	271%	H	50-150
AT-3	73	L	83-128
Protein S	53	L	55-146
ANA	pos	H	neg
Chrom.Ab	pos	H	neg
dsDNA	7.0	H	< 4.0
Saccharo.A	113	H	neg
Saccharo.G	76	H	neg

Hypercoagulable Disorders

Key Points

Clinical implications are comparable for all classes of micro-occlusive disorders.

. . . but . . .

Hypercoagulopathies are apt to be “silent” until an acute unexpected seminal event.

They can be inborn-genetic, acquired, associated with other diseases.

Distinguish **hypercoagulable states** from **hypercoagulable disorders** : :

Someone can have a hypercoagulable disorder but, at a given time, not be in a hypercoagulable state.

Someone can not have a hypercoagulable disease but still be in a hypercoagulable state due to transient illness.

A NOMENCLATURE OF THROMBO- & MICRO-OCCLUSIVE DISORDERS

Hemodynamic Disorders	vessels, blood, & coagulation normal **Fluid Dynamics Abnormal**	Hemodynamics & macro-vasculopathies *Examples :* a-v malformations, atrial fibrillation vascular compression, low flow states
Endo-Vasculopathies	blood & coagulation normal **Vessels Abnormal**	Intrinsic disorders of blood vessels *Examples :* atherosclerosis thromboangiitis, alloplastic implants
Exo-Vasculopathies	blood & coagulation normal **Vessels Abnormal**	Extrinsic disorders of blood vessels *Examples :* vasculitis, hyperparathyroidism, immune cv-ct disorders
Non-Hypercoag Hemopathologies	vessels & coagulation normal **Blood Abnormal**	Altered blood elements, non-plasma *Examples :* formed element abnormalities, hemoglobinopathies, dys- & cryoproteinemias
Hypercoagulability	vessels & blood normal **Coagulation Abnormal**	Disorders of the plasma coagulation system Intrinsic: thrombophilic - prethrombotic disorders Extrinsic: immune-apl, estrogens, cancer

Micro-occlusive disorders are a major cause of chronic ulceration, impaired wound healing, and complications of trauma and surgery. Little appreciated by most physicians, this subject requires broader awareness. Here is a conspectus of the subject, and a nomenclature of disease, focused on hypercoagulopathies.

These categories can each be subcategorized.

This presentation will focus solely on the further nomenclature of the hypercoagulable disorders.

Hypercoagulable Disorders

Key Points

Hypercoagulable states arise from imbalance or loss-of-tune of a complex non-linear multi-control system.

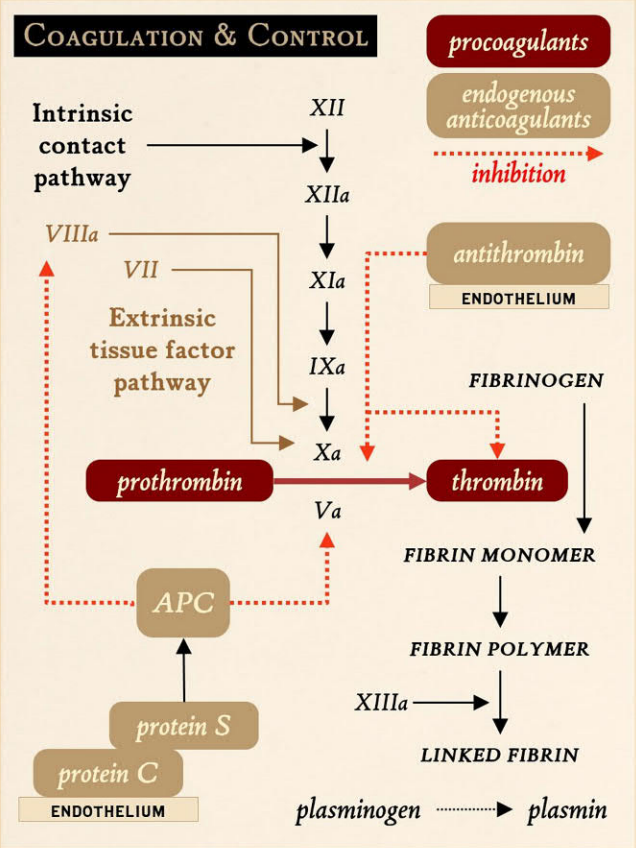
Normal blood does not clot in vessels, but clots immediately on exposure to anything other than vessel endothelium.

Hypercoagulable blood will clot in blood vessels. It has an "itchy trigger finger" and will shoot with minimum or no provocation.

In addition to acute thrombo-infarctive events, it causes long term problems, most notably induction of auto-immunity and connective tissue disorders, including chronic non-healing wounds.

This arises from the intimate interplay of thrombosis and inflammation.

COAGULATION PHYSIOLOGY & PATHOLOGY



1 - Normal coagulation

Thrombosis stops bleeding.
It is a complex control system tuned to not trigger if plasma stays within normal blood vessels.
Altered vessels or flow trigger the healthy process, rightly (trauma) or wrongly (e.g. vasculitis).

2 - Hypercoagulopathy

Normal blood does not clot in normal blood vessels, but System can become untuned:
- less prone to clot when it should (hemorrhagic hypo-coagulopathy), or
- overly prone to clot when it shouldn't (thrombotic hyper-coagulopathy).

Hypercoagulable blood clots spontaneously in vessels, or is more sensitive to ordinary triggers.

3 - Pathophysiology of errant clotting

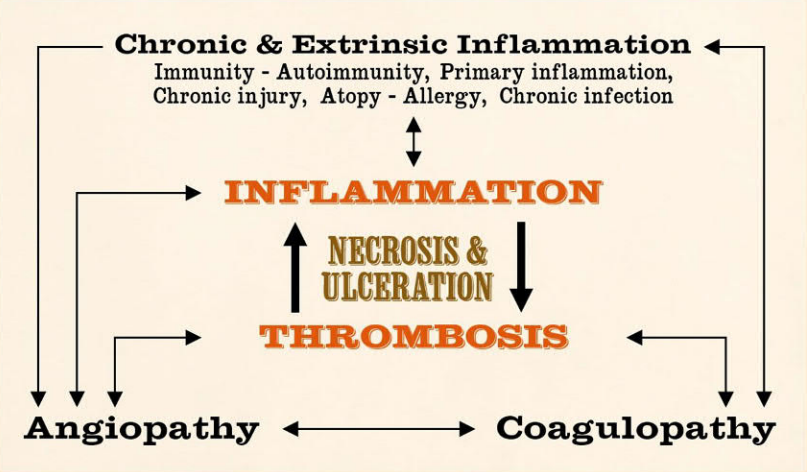
Thrombosis occurs in intact vessels, interrupting blood flow.
Large vessels and structures are at risk for major infarct or death.
Small vessel non-lethal events cause vascular stasis and micro-infarction (becoming ulcers).
Inflammation is triggered. Stasis & inflammation are in turn normal triggers for thrombosis.
Hypercoagulopathic events are thus auto-amplifying, and self-perpetuating.

4 - Biochemistry

The main sequence cascades and proteins are basic medical education.
Every step in the process has multiple promoters and inhibitors.
All can become unbalanced or dysfunctional to promote abnormal clotting.

5 - Dynamical disorder

This is a complex non-linear multi-control system. Dynamics are chaotic.
When healthy, it is self-stable.
When unstable or in a stable but unwanted state, unpredictable events can occur.
This means is that patients can be variably normal then abnormal.
Hypercoag. patients are not always hypercoagulable, even with hypercoag. genes.



Hypercoagulable Disorders

Key Points

The causes of hypercoagulability can be grouped and understood based on several categories of underlying pathology.

A NOMENCLATURE OF THE HYPERCOAGULABLE DISORDERS

Primary Alteration	Effects	Example Species
Intrinsic disorders "Pre-thrombotic" or "Thrombophilic"	Defects, deficiencies, altered levels of primary clotting factors and para-thrombotic proteases. Includes gene mutations and acquired or episodic variances and imbalances of any of these factors.	proteins C & S, AT-3, f.VIII, fibrinogen, f.V Leiden (gene R506Q), prothrombin mut. (gene 20210G)
Extrinsic	Coagulation imbalances triggered by disease, injury, metabolism, drugs, hemodynamics, etc. Conditions causing inflammation, vascular stress or injury, stasis, platelet activation, plasma imbalance.	inflammation, platelets, hemodynamics, formed element hematopathologies, dys- & cryoproteinemias
Immune - inflammatory	Autoimmune procoagulants. Association with connective tissue disorders. Intimate association of clotting and inflammation - mutual triggers and breeders, dynamic amplification.	apl-abx (lupus anti-coagulant, anticardiolipin), anti: beta-2-glycopr, anca, mpo, pr-3, autoimmune disease, general inflammation
Metabolic	Extrinsic triggers from disorders of specific organs or pathologies, or dietary and acquired factors. (In distinction to the generalized extrinsic stresses of inflammation, injury response, and altered circulation.)	warfarin, homocysteine, gene MTHFR, estrogen, pregnancy, pnh, para-neoplastic

Trigger conditions	Coagulation balance	Implications & examples
Trauma	Normal trigger for thrombosis.	Local and remote, trauma and surgery.
Inflammation	Normal & errant trigger for thrombosis.	Acute & reactive, immune, circular amplification.
Hemodynamic	Errant trigger for thrombosis.	Macrovascular stasis & eddies, small vessel rheology.
Hematological	Elements that engage the plasma system.	Platelets, granulocytes, immune & lytic red cell events.
Metabolic & Pharma	Trigger offsets or hypersensitivity.	Whatever affects blood or coag, including Rx meds.
Disease Associations	Other serious dx.	Immune, cancer, infections, etc.
Dysdynamia	Chaotic behavior of integrated coag system.	Large effect of small perturbations, basins of stability.
Combinations	Effects & risks additive.	System more sensitive, closer to triggering.

Hypercoagulable Disorders

Key Points

The hypercoagulable disorders have a broad spectrum of clinical complications, sequelae, clinical presentations, and disease associations.

Hypo-coagulability and bleeding are often overt and dramatic.

Large vessel thrombosis is usually acute and dramatic, but mostly due to non-hypercoagulable states.

In contrast, **hypercoagulable and micro-occlusive states** are often chronic, insidious, slowly destructive.

Know the Hypercoagulable Syndrome

Tetrad - Pentad

Thrombotic or embolic event
Autoimmune cvd-ctd
Wound pathergy
Miscarriage
Family history of same

CLINICAL PATHOLOGY OF THE HYPERCOAGULABLE DISORDERS

Macrothrombosis

Large vessel
Acute
Overt
Life and limb risk

"Old hat"
Often easily recognized
Defined clinical syndromes

large vessel arterial thrombosis
large vessel venous thrombosis
other peripheral thrombosis
various thrombophlebitis
pulmonary embolism

coronary artery thrombosis
intracardiac thrombosis
graft and valve thrombosis
cerebrovascular thrombosis

subclavian v. (paget-schroeder)
hepatic veins (budd-chiari)
pituitary apoplexy (sheehan)
retinal artery & vein occlusion
intracranial sinus thrombosis
spinal apoplexy
visceral apoplexy *(renal, adrenal, bowel)*

The underlying hypercoagulopathy might nonetheless be overlooked.

Microthrombosis

Small vessel
Subacute, chronic, recurring
Occult, missed diagnosis
Tissue and wound risk

Under appreciated
Often non-obvious
Perplexing refractory problems

vascular occlusion not overt
often not life threatening
recognized by secondary events
young age
family history
associated diseases *(e.g. cvd-ctd)*
special tip-offs *(e.g. warfarin resistance)*
long history of failed care
long hx care for wrong diagnosis

complications of trauma & surgery
wound pathergy and infarction
non-anatomical flap necrosis
non-healing ulcers

miscarriage
complications of contraceptives

non-immune glomerulonephritis
primary pulmonary thrombosis
warfarin necrosis

Related Disorders

Other micro-occlusive classes
Hematological, vascular
Autoimmune cvd-ctd
Trigger diseases & conditions

Disease Associations

immune & chronic inflammatory
acute & chronic venous
estrogens, pregnancy
cancer (Trousseau)
parox. nocturnal hemoglobinuria

Others of Interest

primary pulmonary thrombosis
pulmonary hypertension
non-immune lupus nephritis, RPGN
digital ischemia of CTD / CVD
visceral infarcts & apoplexies
(e.g. pituitary, adrenal, bowel, spine)
an open field for inquiring minds

Hypercoag Syndrome

Tetrad – Pentad

Thrombotic or embolic event
Autoimmune cvd-ctd
Wound pathergy
Miscarriage
Family history of same

Core Pathophysiology

Normal blood is tuned to clot immediately on seeing non-endothelial matter, but never to clot when within normal blood vessels.

Hypercoagulable blood clots spontaneously within normal vessels.

Cf. Hypocoagulability

Consequences of hypocoagulability are often acute, overt, dramatic, immediately threatening, affect body and life as a whole, or else fit well defined dx (e.g. hemophilia).

The same is true for large vessel macro-vascular occlusive events.

In contrast, hypercoagulable states causing micro-thrombosis are often slow, subtle, insidious, chronic, occult, affect local or isolated tissues, and apt to be repeatedly missed, unrecognized, or misdiagnosed.

Hypercoagulable Disorders

Key Points

Infarcts and ulceration occur for two general pathological reasons : :

Tissue lysis by inflammation.

Tissue infarction by ischemia.

Physical exam will reveal :
- a thrombo-infarctive pattern of injury,
- an inflammatory-lytic pattern of injury,
- or both.

Features of each are easily recognized, making direct physical exam a crucial first step in diagnosis,

along with history, especially the points of the Hypercoagulable Syndrome.

NECROSIS & ULCERATION – TWO GENERAL PATHOLOGIES & PATTERNS

THROMBO-INFARCTIVE

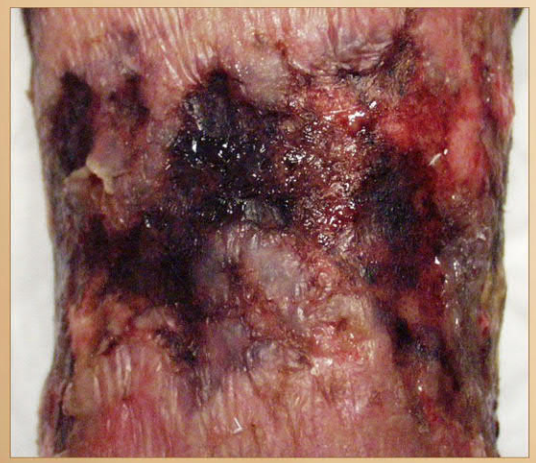
The pattern of ischemia and stromal deprivation.

Macro-occlusive
Micro-occlusive
Micro-angiopathies
Hemopathologies
Hypercoagulable / Coagulopathic

INFLAMMATORY-LYTIC

The pattern of inflammation and stromal predation.

Inflammatory
Autoimmune
Atopic, Suppurative
Connective Tissue Disorders
Lymphoreticular / Reticuloendothelial




Hypercoagulable Disorders

Key Points

Here are typical clinical features that are found on history and physical exam.

Laboratory studies can be confirmatory, can resolve uncertain differential diagnoses, and can guide therapy.

- BUT -

Accurate diagnosis, at least identification of a bona fide hypercoagulable state, can usually be made by history and physical.

CLINICAL PATHOLOGY OF HYPERCOAGULABLE WOUNDS & ULCERS

Onset of Illness

Acute micro-thrombosis & vascular stasis.
Severe local ischemia of skin and fascias.
Skin infarcts, progressing to ulceration.
Gross inflammation +/-, often absent.
Pseudo-inflammation from severe stasis.

Spontaneous -vs- triggered by an event.
Chronic or chronically recurring.

Common on lower extremities.
Can occur anywhere.

Link to Inflammation

Coagulation & inflammation are linked:
1° thrombosis triggers 2° inflammation.
1° inflammation triggers 2° thrombosis.

Some injuries purely one or the other domain.
Some wounds are inextricably mixed.

Strong association with CVD–CTD:
Ongoing trigger from chronic 1° inflamm.
Sustained 2° inflamm. induces autoimmunity.
Many patients have mixed lab profiles.

Findings

Ischemic infarction: skin, fascias, wounds.
Active ulceration, thrombo-infarctive.
Edema & gross inflammation often absent.

Periwound stasis, low TcpO2, pain.
Mixed wound module, non-healing.
No signs of other dx.
Good pulses.

Confirmatory blood tests & histology.

Acute necrosis.

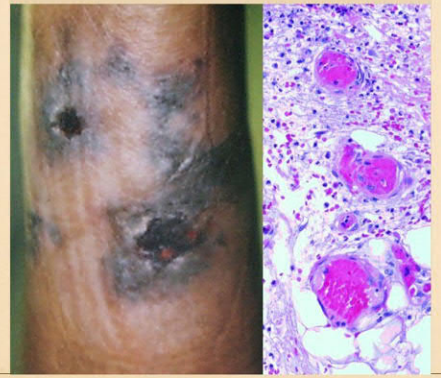
Skin infarcts are usually small, scattered, isolated, but sometimes large and life threatening.

35 yo woman, acute lupus.
Extensive skin infarcts (hips & thighs shown). Antiphospholipid antibodies. Low skin TcpO2s.

Stasis and infarcts.

Around the infarcts are zones of severe stasis which may die and ulcerate (or recover).

43 yo man, spontaneous leg ulcers.
Very low proteins C and S (leg & ankle shown). Small vessel thrombosis and organization, with adjacent stasis, congestion, and hemorrhage.



Chronic active ulceration.

Post-infarct eschar separates, leaving ulcers. The problem can be chronically active.

61 yo woman, protein S deficiency.
Long history DVT, PE, and leg ulcers. Perpetual stasis, inflammation, active infarction and ulceration. Old recanalizing thrombus shown.

Trauma pathergy, morbidity.

Trauma and injury can trigger microthrombosis, with unexpected wound infarcts, dehiscence, failed repair.

53 yo woman, rheumatoid arthritis.
Dogbite, forearm. Many complications of repeated surgery. Proteins C&S deficient. Confirmatory histology.

Hypercoagulable Disorders

Key Points

More clinical features of hypercoagulable disorders.

Some of these depend on sequential observations to reveal the behavior of the process and response to interventions.

CLINICAL PATHOLOGY OF HYPERCOAGULABLE WOUNDS & ULCERS

Dynamical Behavior

refractory impaired wound behavior
characteristic of severe ischemia

recalcitrant and continuously pathological
persistent active necrosis and ulceration
can be self-perpetuating and amplifying

chaotic dynamics
net misbehavior over time
rapid evolution, but (very) slow resolution
variable state with each observation

Complications

necrosis, dehisce, ulcerate after biopsy
necrosis, dehisce, ulcerate after debride
necrosis, dehisce after trauma and surgery
necrosis, dehisce, failed repair or closure
graft loss, flap necrosis
potentially lethal severity and extent
intercurrent thrombotic events

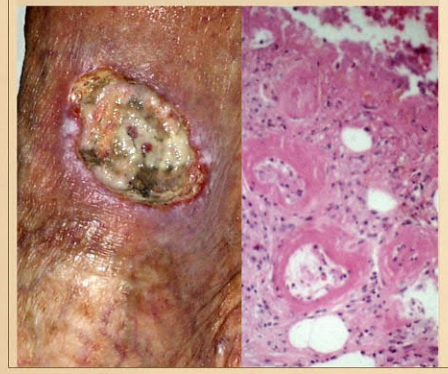
Treatments & Outcomes

chronic, persistent, recurring
consistent failures of general wound care
multiple failed procedures
patient and provider frustration
chaotic dynamics of therapy
warfarin hard to regulate

Surgical complications.

For surgery & controlled injury, risks are the same. Patients need perioperative anticoagulation.

69 yo woman. Wound dehiscence. Complication of active ulceration after biopsy for minor skin lesion. Protein S deficient, and cryoglobulins. Histology shows thrombi, vessel and tissue necrosis.



Failed therapy.

Ischemia and necrosis impair healing and impede success, often repeatedly, for even mundane benign events.

72 yo woman, high anticardiolipins, ANA. Ulceration and impaired healing of primary leg wound; then same for skin graft donor site, stasis & infarcts shown.

Unexpected profiles.

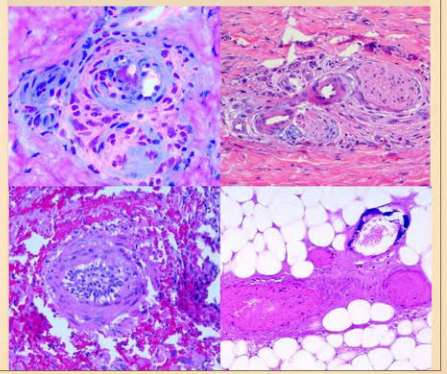
Think of hypercoagulopathies for young patients with peculiar ulcer histories and features.

39 yo man. Refractory leg ulcers. Chronic since femur fracture & DVT at age 14. F.V Leiden (young men with venous ulcers have this mutant gene). Healed with 2 months of warfarin.

Histology.

Beyond general wound histology, the microscope reveals: thrombi in various stages, stasis, vessel and tissue necrosis, overlying ulceration, micro-angiopathy, 1° and chronic 2° vasculitis, vessel fibrosis and stenosis.

4 patients with various diagnoses.



Hypercoagulable Disorders

Key Points

Hypercoagulable states and disorders are positive diagnoses made on affirmative criteria.

Here are particulars to be asked about or observed on : :

personal history

family history

wound history

general physical exam

wound exam

(continued on next page)

DIAGNOSIS & APPROACH TO THE HYPERCOAGULABLE DISORDERS

Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

1-A · Personal History

Any recurrent, unexpected, or inexplicable thromboembolism

arterial
deep venous
pulmonary
common types *(mi, cva)*
peculiar or rare events
(e.g. Budd-Chiari, Padgett-Schroeder)
events triggered by illness, injury
events in healthy young people
events in spite of treatment

peculiar profiles
(e.g. tardive paraplegia after non-cord spine injury, retinal artery occlusion in young person)
absence of common risks

Related diseases and events

miscarriages
venous disease
autoimmune, cvd-ctd
visceral autoimmune disease
angiopathies, blood disorders
cancer *(Trousseau)*, PNH
estrogens, warfarin resistance
absence of these or other risks

1-B · Family History

Equally important as personal hx, diagnostic when personal history is weak or lab tests are negative.

miscarriages
thrombosis & embolism
autoimmune disease

1-C · Wound & Tissue History

Wounds and ulcers

continuous pathological behavior
absence of identifiable injury
long history failed rx
pain

Other events

trauma-induced pathergy
(tissue infarction, dehiscence, etc.)
complicated or failed operations
identified event *(e.g. warfarin, oral contr.)*
multiple such events
things that just don't add up
or defy the logic of common ailments

2-A · Physical Exam - Wound

Distinctive or consistent findings

sick / active wound
impaired / non-healing wound
thrombo-infarctive pattern
necrosis & infarcts *(as opposed to lysis)*
absence of inflammation *(or presence)*
progressive ulceration
persistent pathological behavior
pathergy/necrosis after debridement
signs of severe ischemia
vascular stasis, periwound cyanosis

Discrimination from other diagnoses

infarction vs. lysis
inflammation, or not
venous changes, or not
pulses / macrovessels normal
peculiar or non-specific locations
not in pressure / mechanical areas
not confined to tendons, synovium

Hypercoagulable Disorders

Key Points

Details of clinical examination, continued.

Included here are labaroratory studies.
Main laboratory diagnostics are :

Blood tests, hypercoagulability.
Blood tests, hematological disorders.
Blood tests, autoimmunity.

Measures of tissue perfusion, transcutaneous oxygen most useful.

Histology.

Between history, physical, and judicious choices of lab tests, pertinent diagnoses can be made with 100% reliability, with predictably accurate choice of therapies and good response to treatment.

DIAGNOSIS & APPROACH TO THE HYPERCOAGULABLE DISORDERS

2-B • Physical Exam - General

age *(any age, including young)*
vascular & skin exam
signs of previous ulcers or infarcts
rheumatoid & immunopathic signs

2-C • Exam & F/u - Response to Rx

Failures of general care

behaviors of severe ischemia
resistance to ordinary treatment
failed response to customary care
progressive infarction in spite of rx
failed therapy for other diagnoses
failed rx: steroids, anti-immune

Complications of specific care

pathergy / necrosis after debride
necrosis, dehiscence after surgery
failure, complications of surgery

Aberrant Response to Care

warfarin necrosis
warfarin resistance
difficulty regulating PT-INR

"things that just don't add up"

Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

3-A • Lab - Clinical

General studies
CBC, platelet, CMP, U/A

Thrombotic species
gene: factor-V.Leiden (R506Q)
gene: prothrombin mut. (20210G)
antithrombin III, protein C, protein S
factor-VIII, thrombin generation
fsp, d-dimer, TAT, plasminogen
fibrinogen (common pathway)
gene: MTHFR, homocysteine

Immune procoagulants
apl: anticardiolipin
apl: lupus anticoagulant
anti: beta-2-glypr, anca, mpo, pr-3

Autoimmune
Screen CVD-CTD, vasculitis:
sed rate, crp, ldh
ANA w/reflex, & specific abx
complement

Other micro-occlusive
SPEP / SIFE
PF4, Hgb, cryoglobulins, cryofibrinogen
new and future tests

3-B • Lab - Special

Vascular

TcPO2, laser doppler
imaging
periwound hypoxemia
(not useful: abi, pvr, ppg, doppler)

Histology

microthrombi, aggregates
platelet thrombi, fibrin thrombi
reorganization, recanalization
tissue infarction, vessel infarction
minimum inflammation
microangiopathies
vascular fibrosis, stenosis
vasculitis, acute (neutrophilic)
vasculitis, chronic (lymphoid)

3-C • Differential Dx & R/O

pyoderma, immune dermatoses
immunopathies, CVD-CTD
vasculitis, angiopathies
hematological, other micro-occlusive

	ASSAY TYPE			INTERPRETATION		
Aggregate, *assay of integrated activity*				***Hypercoagulable implications of values above or below normal range.***		
Single species, *conc. or activity*	▼		*may vary with lab*			
Test	▼	▼	**Normal range**	**Low value**	**High value**	**Notes**
1 – Direct indicators of active thrombosis				These items are all direct measures of an active clotting process or of the actual clot or its degradation. *They indicate that active thrombosis has actually occurred or is still happening.*		
fibrinogen	•		150 – 400 mg/dl	Consumption & DIC, liver dx, misc. *Depletion can reflect thrombosis.*	Acute phase, inflammation, trauma. *General marker hypercoagulability.*	Thrombosis marker & vector, upregulated with coag. of other 1° causes.
fdp-fsp	•		< 10 mcg/ml		Fibrin degradation product. *Marker of thrombus being lysed.*	Fibrin split or degradation products imply prior or active thrombosis.
d-dimer	•		< 0.50 mcg/ml		Fibrin degradation product. *Marker of thrombus being lysed.*	Implies prior or active thrombosis (subtype of fdp-fsp).
fibrinopeptide A	•		< 1.3 pmol/ml		Split from fibrinogen to make fibrin. *Marker of fibrin being formed.*	Marker of active thrombosis. *Test not available from many labs.*
fibrin monomer	•		negative		Marker of fibrinogen catalysis. *Thrombin generation is occurring.*	Indicates active thrombosis, DIC, intravascular hypercoagulable state.
prothrombin fragm't 1.2	•		0.4 – 1.2 nmol/l		Split from prothr. to make thrombin. *Intravasc. thrombin being generated.*	Marker of ongoing coag. activation, correlated to thrombosis, DIC, etc.
TAT complex thrombin-antithrombin	•		< 4 mcg/l		Complex forms if thrombin present. *Intravasc. thrombin being generated.*	Marker of ongoing coag. activation, correlated to thrombosis, DIC, etc.
plasminogen	•		65 – 120%	Consumption & DIC, liver dx, misc. *Defic. increases thrombus; DVT, PE.*	Acute phase, inflamm., trauma, misc. *Upregulated in thrombotic states.*	Low = cause & mark of thrombosis. High = marker of thrombosis.
2 – Reflex or indirect markers of thrombosis				Items increased or compensatory upregulated in thrombic states; or marker of clotting potential or sensitivity. *They indicate active thrombosis has occurred or is still happening, probably long term if the values are high.*		
antithrombin III	•		activity: 80 – 120 % antigen: 19 – 30 mg/dl	The endogenous anticoagulants, all inhibit thrombin formation, AT-3 by itself, S+C as APC (activated prot C). Low = thrombin generation unopposed. *Deficiency increases clotting, highly correlated with thrombotic risks.*	Thrombotic states cause reflex upregulation of these endogenous anticoagulants, counterbalance effect to prevent excessive clotting. *Marker of a hypercoagulable state. Common with chronic hypercoag dx.*	Low = cause of thrombosis. High = marker of thrombosis, esp. chronic hypercoagulable state, *(often reported as >150%).* *(Also listed below as thrombophilics)*
protein C	•		activity: 70 – 140 % antigen: 70 – 140 %			
protein S	•		activity: 60 – 140 % antigen: 70 – 140 %			
tissue plasminogen activator (tPA)	•		< 13 ng/mL activity: mixed methods	Low antigen or activity, misc causes. *Fibrinolysis decr., causes thrombosis.*	Released from abn. vessels & flow. *High antigen indicates clotting risk.*	Low ant. or act. = thrombosis cause. High ant. marks thrombic conditions.
ANCA's *(see below)* anti-PR-3, anti-MPO	•		< 1:20 or, negative		Marker of thrombogenic vasculitis. Indicates non-plasma hypercoag risk.	ANCA's have complex biology, including direct thrombotic effects.
thrombin generation "normalized endogenous thrombin potential" nETP		•	85 – 140%	*Measure of thrombic capacity. Low potential risks or increases bleeding.*	Primary event that initiates clotting. *Indicates excessive thrombosis risk via common final path (but not why).*	Highly correlated with thrombotic states & risk. Evaluate cause of rise. *New tool, not available most labs.*
clotting time		•	variable based on specific test, sec	Lab or ex vivo clotting. *Rapid time can imply hypercoag but not specific.*	*Long times imply platelet disorder, hypocoag state, or anticoagulant rx. These tests usually more relevant to measure-monitor prolonged clotting.*	Best validated for long bleeding dx, but rapid clot often seen in hypercoag states. Time whole blood clotting in office, bedside, surg., debride.
bleeding time		•	2 – 9 min	Measures physiologic clotting. *Rapid implies hypercoag, but not specific.*		
3a – Pro-thrombotic species, thrombophilic				Direct agents of excess thrombosis: thrombotic system proteins & genes, prime sequence or 1° & 2° cofactors. *Coagulation being highly regulated, no species has autonomy to cause clots, but these are primary promoters.*		
factor VIII	•		50 – 150%	*Defic. causes bleeding, Hemophilia A.*	Genetic, acq'd, role of v.Willebrand. *Primary hypercoagulable when high.*	Potent hypercoag effects; amplifies fV.Leiden, APCR, estrogens, & plts.
von Willebrand factor (vWF)	•		activity: 60 – 150 % antigen: 50 – 150 %	*Deficiency. causes hemorrhagic von Willebrand's disease.* **(More below.)**	Potent promoter fVIII, increased clot. *Thrombosis in misc situations, often acute phase dx & prior thrombic risks.*	vWF: well known plt effects. Also: protects fVIII & role in NET neutrophil traps, causing plasma thrombosis.
factor IX	•		60 – 160%	*Defic. causes bleeding, Hemophilia B.*	Gene mutation, acq'd, not common. *Hypercoagulable when high or mut's.*	Not common cause, but in concept similar to f.VIII effects. 2nd tier test.
factor XI	•		65 – 150%	Aka plasma thromboplastin antecedent. *Defic. causes bleeding, Hemophilia C.*	Genetic?, acquired, not common. *Hypercoagulable when high.*	Not common cause, but in concept similar to f.VIII effects. 2nd tier test.
prothrombin mutation 20210G/A	•		normal non hetero- or homozygous		Causes hyperprothrombinemia. *Increases risk of thrombosis.*	2.3% general population heterozyg, higher fraction in those with dvt's.
prothrombin mutation 19911A/G			normal non hetero- or homozygous		Some studies show increased thrombotic risk, others do not. *Significant?*	Listed as example, more gene mut's will be found & test offered. 2nd tier.
factor V.Leiden R506Q	•		normal non hetero- or homozygous		Faulty V resists protein C, remains active, thrombin unbridled. *Clotting risk high, often with other triggers.*	Frequent, often found on post-clot eval. Thrombosis risk over normal: heterozyg 5-10x, homozyg 50-100x.
factor V HR2 Allele	•		normal non hetero- or homozygous		FV.Leiden coinheritance raises risk. *Thrombosis risk 3-4x fV.Leid alone.*	Another example, new gene mut's will be found & test offered. 2nd tier.
activated protein C resistance (APCR)		•	> 2.1 ratio test ÷ nl plasma	Errant f.V, mainly Leiden, resists APC, thrombin unbridled. *Hypercoagulable.*		This is a test of f.V, not prot. C&S. Low values abnormal, clotting risk.

Test	Variance from nl Low	Variance from nl High	Interpretation	Notes
Panel 1-a	**Quick screen for thrombosis**		**Simple screen to identify active thrombosis.** It implies a possible hypercoagulable ***state*** (chronic or sustained) but does not confirm. It does not identify category or species of a primary hypercoag ***disorder***, not even that there is one. *It is not relevant if there is active trauma, bleeding, known large thrombus, other obvious or acute events.*	
fibrinogen	•	•	Low due to consumption. High in hypercoagulable states.	Panel best used to identify disorders where thrombosis is suspected but not overt. **Fibrinogen & d-dimer** are inexpensive, performed by most hospital labs, **TAT** the opposite but sensitive. **PT-frags, & f.mono.** more sensitive than **fdp**, but not offered in small labs; the 3 are comparable, need only one for diagnosis. **Biopsy** gives high quality info – do not miss opportunity if safe to do.
d-dimer, or other fdp		•	Degrade products imply thrombus present, prior-recent.	
TAT complex		•	Sign thrombin generation, implies active-current thrombosis.	
prothrombin fragment 1, 2		•	*Indicates thrombin conversion, implies active thrombosis.*	
fibrin monomer		•	*Indicates active thrombin-fibrinogen, implies thrombosis.*	
			Order fibr'gen, d-dimer, & one from among the other 3.	
histology (tissue biopsy)			Direct visualization of old and new thrombus, & 2° effects.	
Panel 1-b	**Full screen for thrombosis**		**Thorough screen to identify active thrombosis.** Full Panel 1a plus the two items here (if offered by lab). These are all direct residues of thrombin and fibrin except nETP which is an indirect but potent indicator of thrombic potential.	
fibrinopeptide A		•	*Indicates fibrin conversion, implies thrombosis.*	Costly, but sensitive when diagnosis remains elusive. **FpA** similar to TAT et al, but few labs offer. **nETP** valuable for diagnosis & prognosis, but rarely offered.
thrombin generation (nETP)		•	*Indirect measure, marker of capacity to make thrombus.*	
			2nd tier. Order all 5 items from Panel 1a, plus these 2.	
Panel 2-a	**Quick screen for hypercoag state**		**Simple screen to identify a hypercoagulable state.** This implies not just signs of active or recent thrombosis, but evidence of heightened thrombic potential or of longer term compensatory adjustments to persistent coagulation. It tends to confirm a hypercoagulable ***state***, but it does not identify the underlying primary hypercoagulable ***disorder***.	
Panel 1-a			Fibrinogen, d-dimer, & TAT (or PT-frags or f-monomer).	**Panel 1** identifies that thrombosis has or is occurring. **Panel 2** identifies that coagulation has been chronic or ongoing, or that blood is in a hyperthrombotic state. **C**, **S**, & **AT-3** do not vary synchronously, so check all three for better diagnostic sensitivity. Plasminogen activator and inhibitor also useful but not as first line screen. **Bleeding time** easy, direct on the patient, meaningful if very rapid.
protein C		•	Endogenous anticoagulants, similar interpretation for all.	
protein S		•	Low causes thrombosis. **High** = upregulation in response	
antithrombin III		•	to ongoing thrombosis, markers of hypercoagulable state.	
plasminogen		•	Rises in thrombotic states, marker of ongoing thrombosis.	
bleeding time	•		Directly observe clotting rate, rapid implies hypercoag.	
			Order Panel 1-a and C, S, & AT-3, plasminogen.	
Panel 2-b	**Full screen for hypercoag state**		**Thorough screen to identify a hypercoagulable state.** Full Panel 1b & 2a plus the additional items here. The extra items have varied physiologies and can cause thrombosis, but all are markers of heightened ongoing thrombotic risk.	
Panel 1-a, b			Fibrinogen, d-dimer, TAT, PT-frags, f-mono, *f-peptide-A.*	Other than nETP, the additional items on this panel are generally available from reference labs. **Panel 1** identifies occurrence of thrombus. Readily available **Panel 2a** can identify a hypercoag state. **Panel 2b** tests additional species, thrombotic and vascular (ANCA's), for a more sensitive or thorough indication of heightened risk or sustained state of thrombosis, at macro or micro scales.
Panel 2-a			Protein C, protein S, antithrombin-3, plasminogen.	
tiss. plasminogen act'r (tPA)	•	•	Low causes clot. High = marker of hypercoag conditions.	
plasminogen act-inh (PAI-1)		•	High causes clot, & reflex marker of hypercoag conditions.	
ANCA's anti-PR-3, anti-MPO		•	Causes clots, but also indicate heightened thrombic state.	
thrombin generation (nETP)		•	Marker, capacity to make thrombus, high in hypercoag state.	
			Order Panels 1-b, 2-a, and tPA, PAI-1, ANCA's, & nETP.	
Panel 3-a	**Hypercoag scrn, thrombophilic dis.**		**Panel of tests to identify primary causes & hypercoag species, focus on the plasma coagulation system.** This panel derives from assay group 3a (thrombophilics), some of which are uncommon or less relevant. Listed here are the main items, balancing diagnostic & economic efficiency. For more precision, the others can be ordered as 2nd tier tests.	
factor VIII		•	Potent primary instigator of thrombosis. High causes clot.	High yield first tier test, readily available in clinical labs.
von Willebrand factor (vWF)		•	Potent thrombogen by f.VIII promotion et al. High = clot.	Not as freq., but 1st tier for potent effect & common test.
prothrombin mut. (20210G)		•	Hetero- or homozygous mutation = high thrombosis risk.	Both gene tests identify common root causes of clotting. Both are "send out" tests easily ordered, 2-3 wk reporting.
factor V Leiden (R506Q)		•	Hetero- or homozygous mutation = high thrombosis risk.	
activ. prot. C resist. (APCR)	•		Low value means that f.V resists protein C, promoting clot.	Test for F.V Leiden: indirect but readily available and quick.
protein C	•	•	Endogenous anticoagulants, similar interpretation for all.	**C**, **S**, & **AT-3**, listed in Panel 2 as hypercoag markers, are also potent thrombogens when low. Frequent. Not in synch, so order all three. The tests are readily available.
protein S	•	•	High values reflect a thrombotic state. **Low** = accelerated	
antithrombin III	•	•	thrombin conversion, potent causes of thrombosis.	
plasminogen	•	•	Low allows thrombus extension, (low & high mark clotting).	These 3 identify thrombosis from weak clot degradation, and offer multi insights into coagulation state. **Plasm'gen** test readily available, **tPA** & **PAI-1** unlikely in smaller labs.
tiss. plasm'gn activator (tPA)	•	•	Low activity equiv. to low plasminogen, propagates clot.	
plasminogen act-inh (PAI-1)		•	High implies low tPA activity impl. low plasmin impl. clot.	
			For quick workup, ignore gene tests and order APCR. For high yield, quick turnaround panel offered in all labs: **F.VIII, vWF, APCR, protC, protS, AT-3, plasminogen.**	**Panels 1, 2** identified hypercoag state, or do concurrently. For slower but more thorough diagnostic precision, order all items. Order 2nd tier tests if diagnosis remains elusive.
Second tier			*factor IX (hypercoagulable when high)* • *factor XI (high)* • *dysfibrinogenemia (rapid)* • *C4 binding protein (C4B, high)*	
Panel 3-b	**Hypercoag scrn, autoimmune dis.**		**Panel of tests to identify primary causes & hypercoag species, focus on immune procoagulants.** This panel derives from assay group 3b (immune), most relevant to a primary hypercoag workup. The few not listed here can be ordered as 2nd tier tests. Practical subsets for efficient screening are listed in the comprehensive or integrated panels below.	
ANA, w/reflex		•	ANA's mark the cvd-ctd's, generic ANA or misc subtypes.	Identify autoimm. state or dx (some cvd-ctd pts sero-neg).
inflam. screen: esr, crp, ldh		•	Non-specific markers, acute inflammation (& misc others).	Moot if infl. obvious. Useful for occult dx or track therapy.

Hypercoagulable Disorders

Key Points

Examples of patients, tests, and interpretation of results.

DIAGNOSIS & APPROACH TO THE HYPERCOAGULABLE DISORDERS

Interpretation of Common Hypercoagulable Tests

fibrinogen	Typically high, common final pathway.
d-dimer	Often high, reflecting persistent microthrombosis.
protein C **protein S** **AT-3**	If low, these are hypercoagulable entities. If high, they are upregulation of endogenous anticoagulants . . . reflecting chronic active microthrombosis.
f.VIII	If high, microthrombosis is occurring.
lupus anti-coag **anti-cardiolipin**	Imply an associated autoimmune disorder. Expect high ana, and possibly rf, ccp, ds-dna, or others.
f.V Leiden **prothrom. 20210G**	Genes, thus system roots, immutable evidence of pathology. These confirm a breeder disorder for cvd-ctd.

78F Sjögren's

fibrinogen	565	++
protein C	60	–

67F Rheumatoid Arthritis

F.V Leiden	heterozyg	+
fibrinogen	640	++
plasminogen	135	+
protein C	136	+

57M Cirrhosis

bili	2.1	+
alk phos	160	+
RF	44	+
ANA	1:80	+
AT-III	47	–
protein C	35	–
protein S	55	–

Hypercoagulable disorders & ulcers are NOT diagnoses of exclusion.
They can be made on specific criteria.

Diagnosis is often made by just:
patient history
family history
physical exam

If history and physical seem certain,
positive blood tests are confirmatory.

If history and physical are equivocal,
positive blood tests are confirmatory.
(Remember, tests were ordered for suspicion.)

If history & physical are certain,
then even if labs are negative,
the diagnosis is made.

The Hypercoagulable Syndrome

Tetrad – Pentad

Thrombotic or embolic event
Autoimmune cvd-ctd
Wound pathergy
Miscarriage
Family history of same

Highly correlated with lab findings and response to rx, the basis for ordering confirmatory lab tests.

Hypercoagulable Disorders

Key Points

Cases illustrating the extraordinary correlation of hypercoagulability and auto-immune disorders.

The connection is frequently established by personal and family history, and lab studies confirm that such patients have blood markers of both.

Of particular importance are the hypercoagulable genes, three readily ordered from clinical labs : :

factor V Leiden

prothrombin 20210G

MTHFR

If these are present, they are the roots of the pathology, and hypercoagulability is the breeder disease that caused the auto-immune state.

54M No prior diagnosis

F.V Leiden	heterozyg	+
ANA	1:80-spkl	+
lupus anticoag	pos	+
cardiolipin IgA	15	+
cardiolipin IgG	>150	+++
cardiolipin IgM	20	+
protein C	60	-
protein S	56	-
homocysteine	14.6	+

66F Scleroderma / MCTD

rheumatoid factor	35	+
ANA	1:1280-centro	++
protein S	62	–
fibrinogen	499	+

81F Leg ulcer

ANA	1:1280-homo	++
rheumatoid factor	27	+
lupus anticoag	pos	+
cardiolipin IgM	51	+
fibrinogen	429	+
homocysteine	19.3	+
protein C	142	+

76F Scleroderma

sed rate	56	+
C-reactive protein	7.4	+
ANA	1:1280	++
cardiolipin IgM	134	++
fibrinogen	477	+
protein S	58	-
plasminogen	>150	+

69F Rheumatoid

F.V Leiden	heterozyg	+
protein C	51	–
protein S	52	–

72F Polycythemia Vera

ANA	1:160	+
cardiolipin IgM	80	++
protein S	53	–

75M Anemia / Cythemia

rheumatoid factor	2780	++
cardiolipin IgM	70	+
protein C	65	-
cryoglobulin	pos	+

80F Leg ulcers, brain infarct

fibrinogen	386	+
protein C	12	- - -
protein S	43	-

Hypercoagulable Disorders

Key Points

Principles of management are shown, related to general and acute care, management of the affected wounds and tissues, and long term management.

TREATMENT & MANAGEMENT OF THE HYPERCOAGULABLE DISORDERS

4-A • Management - General

Major thrombotic events
urgent management as required
thrombolysis, target specific
thrombolysis, optional general

Associated risks and diseases
treat each accordingly
workup & treat immunopathies

After w/u and confirmed diagnosis
start anticoagulation
option heparins / inhibitors short term
warfarin, heparins, inhibitors long term
optional steroids for inflammation
regulate and monitor warfarin

of uncertain relevance:
anti-platelet drugs
rheologicals

Without a correct diagnosis or treatment, hypercoagulable ulcers are prolonged, persistent, frustrating, refractory, and resistant to care.

4-B • Management - Wounds & Tissues

Basic wound care and control
wound hygiene
debridement *(manage to avoid pathergy)*
topicals *(those for acute control)*
edema control

Problem specific management
for associated or derivative disorders:
other hematological
arterial, venous
immunopathic

Management for closure
basics *(topical care, natural contraction)*
repair, grafts, flaps as required
regenerative biomatrices
hyperbaric oxygen *(selective)*

Once a correct diagnosis is made and anti-coagulants are started, the wounds are usually easy to resolve, at times by anticoagulation alone, or with other necessary treatment.

4-C • Management - Long Term

General
manage underlying diagnoses
control associated risks & triggers

Wound support and prevention
compression and edema control
general skin care
topical steroids for dermatoses

Anticoagulation
until healed, plus 3-6 months
limited use for antiplatelet drugs
long term or lifetime anticoagulation,
(depending on diagnosis and risks)

PROPHYLAXIS FOR PROCEDURES

Principles of Anticoagulation
Restoration of Normal Profile

Different than ordinary anticoagulation.
You are not "thinning" normal blood.
You are restoring "sticky" blood to normal.
For warfarin, high INR required, 3.0 - 3.5 (or higher)

After adequate anticoagulation, necrosis stops, tissues start to revascularize, and wound healing resumes.

Hypercoagulable Disorders

Key Points

Clinical examples.

Emphasis is that : :

1 - Correct diagnoses can be made.

2 - Once made, treatment with anticoagulants corrects the abnormal effects and allows wounds to heal.

29 M

Multiple leg ulcers, many years.
Suspicious history.

Otherwise healthy.
No other illness or explanation.

Family history multiple miscarriages.
Family history.

Lab: high anticardiolipins.
Confirmatory blood tests.

Healed, 14 weeks after warfarin start,
8 weeks after PT-INR stable 2.5 – 3.5.
Healed with anticoagulation only.

Dx: Antiphospholipid antibodies

43 F **Dx: Proteins C & S deficiency**

Refractory leg ulcers, many years.
Multiple DVT & PE. (Otherwise healthy.)
No venous reflux or hypertension.
Suspicious history. No other illness or explanation.

Lab: low Protein C & S, low skin TcpO2.
Confirmatory lab tests.

Healed after high-INR warfarin (& *regenerative biomatrix*).
Recurrence after lapsed warfarin.
Characteristic response to anticoagulation.

61 F **Dx: Protein S deficiency**

Refractory leg ulcer, many years.
Multiple DVT & PE. (Otherwise healthy.)
No venous reflux or hypertension.
Suspicious history. No other illness or explanation.

Lab: low Protein S.
Histology shows old and recanalizing thrombi.
Confirmatory lab tests.

Healed after high-INR warfarin (& *regenerative biomatrix*).
Recurrence after INR drop to 2.5 – 3.0.
Rehealed after INR restored to 3.5 – 4.0.
Characteristic response to anticoagulation.

Hypercoagulable Disorders

Key Points

More clinical examples.

67 F **Dx: Factor V Leiden**

Back wound necrosis after spine surgery.
Family hx strong for DVT & leg ulcers.
Suspicious history.
Thrombo-infarctive, vascular stasis.
Confirmatory exam.
Lab: Factor V Leiden, fibrinogen high.
plasminogen & protein C high.
Healed: warfarin, then surgery.

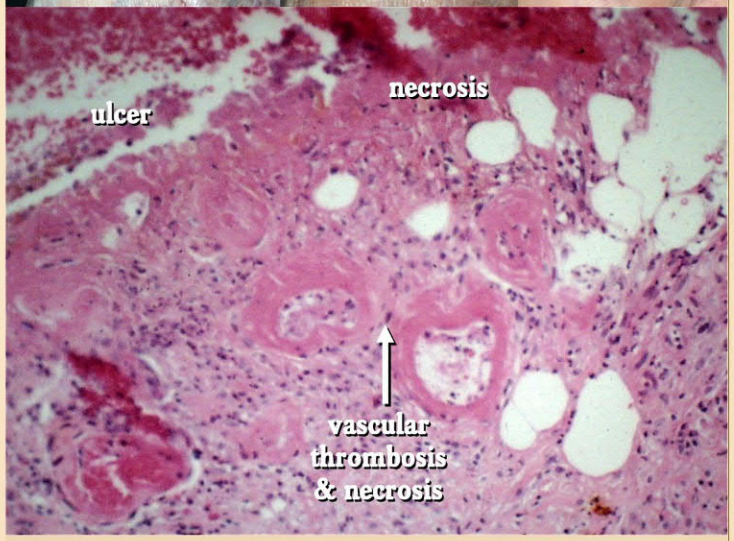
53 F **Dx: C & S deficiency**

Wound infarct after dogbite injury, u.e.
Multiple failed surgery. Rheumatoid.
Suspicious history.
Lab: protein C low, protein S low.
histology - thrombus, organization.
Confirmatory tests.
Healed: warfarin, biomatrix.
Late re-ulceration after warfarin stop.
Proper wound behavior only after warfarin.

46 F

Refractory active ulcers.
Multiple miscarriages.
Suspicious history.
Mixed but mainly thrombo-infarctive pattern.
Good pulses in feet.
Confirmatory exam.
Lab: prothrombin 20210G mutation.
homocysteine very high.
p-anca & anti-mpo high.
Confirmatory blood tests.
Healed: warfarin, etc.
Healing on anticoagulation.

Dx: Primary hypercoagulopathy
Secondary immunopathy



69 F **Dx: mixed coag**

Spontaneous skin ulcer.
Venous perforator thrombosis.
Wound pathergy after biopsy.
Suspicious history and exam.
No prior illness or explanation.
Lab: protein C low.
cryoglobulins present.
Confirmatory tests.
Healed: warfarin, biomatrix.
Proper behavior only after warfarin.

Hypercoagulable Disorders

Key Points

These examples demonstrate that long-recognized clinical syndromes, such as chronic venous disease, often have an underlying hypercoagulable disorder (but not all do).

This has a variety of implications for short term care, future risks, and duration of anticoagulation. Venous patients should be worked up for the underlying cause.

42 M

Refractory leg ulcer, many years.
Multiple DVT.
Mother has same hx.
Suspicious history.
Wound edge infarcts.
Confirmatory exam.
Healed: warfarin, compression.
Healed with warfarin.

Lab:
protein C & AT-3 low.
anticardiolipins high.
homocysteine high.
f.V Leiden heterozygous.
Confirmatory blood tests.

Dx: Multi-factorial hypercoagulopathy

38 M **mixed hypercoag**

Refractory leg ulcer, many years.
DVT.
Suspicious history.
Lab: fibrinogen high.
protein C & AT-3 low.
f.V Leiden heterozygous.
Confirmatory blood tests.

33 M **venous disease**

Refractory leg ulcer, many years.
DVT after femur fx, age 9.
Suspicious history.
Lab: f.V Leiden heterozygous.
Confirmatory blood tests.

Young men with chronic Venous Disease.

Venous hypertension, panniculitis & dermatitis, ulceration.

Classical clinical syndromes yield to new understanding.

"Venous disease", when presenting with complications or refractory sequelae, has greater cause and implications than simple "post-phlebitis", both for origin of the illness, and effectiveness of care.

42 M **venous disease**

Chronic venous hypertension, recurrent panniculitis & dermatitis.
Suspicious history.
Lab: f.V Leiden heterozygous.
Confirmatory blood tests.

(Top, active before rx; bottom, 1 year later.)

Hypercoagulable Disorders

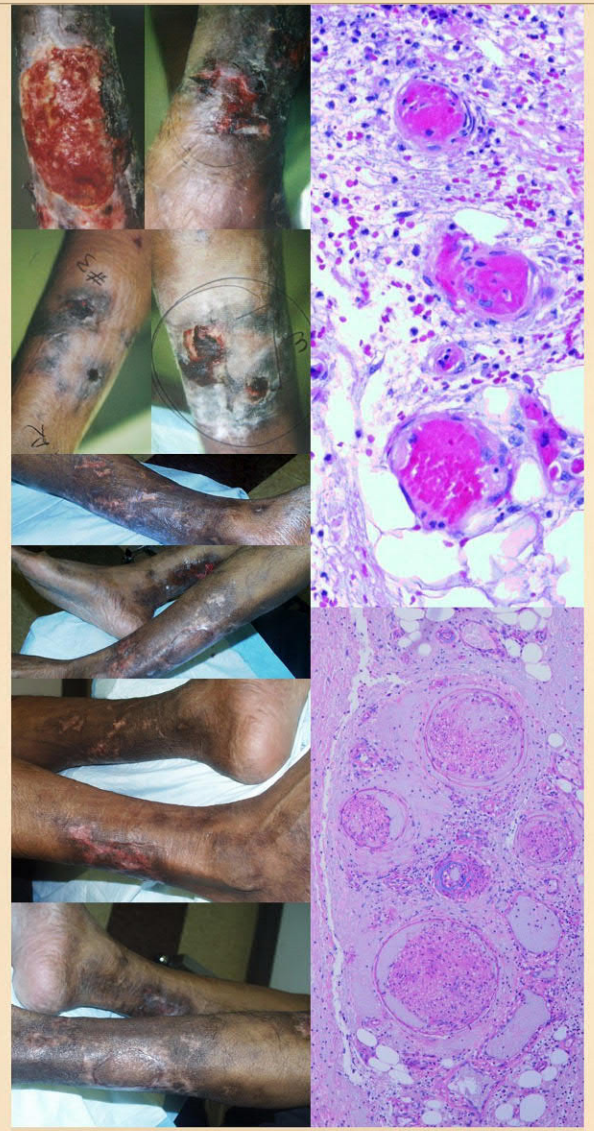
Key Points

More clinical examples, emphasis that long standing “refractory” wounds heal quickly once missed diagnosis is made and anticoagulant treatment is started.

57 F **Factor V Leiden Hetero**

Acute leg & ankle skin infarcts & ulcers.

Healed by warfarin only (& basic topicals).



43 M **Very low Proteins C & S**

Acute spontaneous vascular stasis and skin infarcts.
Diffuse micro-thrombosis.
Healed by warfarin only (& basic topicals).

38 F **Lupus, APL syndrome**

Acute skin infarcts of leg.
Ischemia and ulcers, hands.
Protein S low, Anti-cardiolipins high
Healed by warfarin only (& basic topicals).

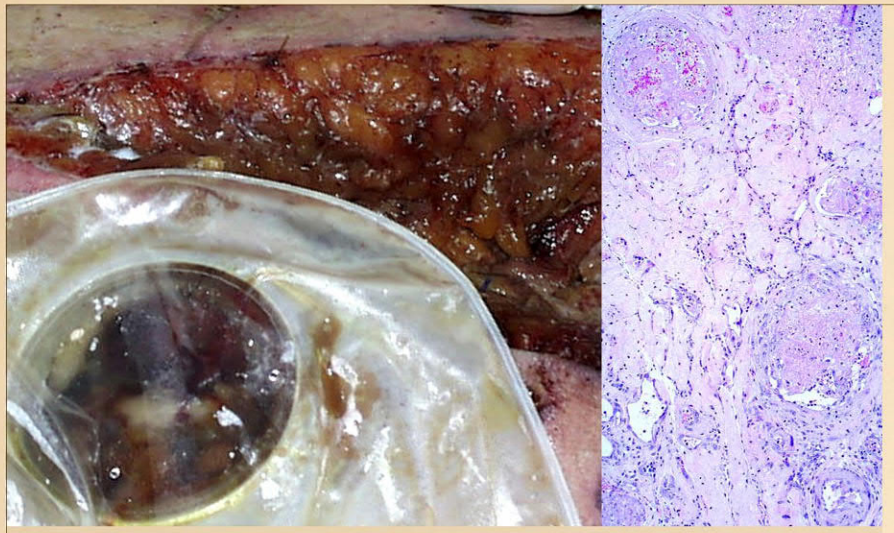
Note the potency of anticoagulants alone to restore normal wound healing, allowing eligible wounds to heal by natural contraction.

Hypercoagulable Disorders

Key Points

More clinical examples, emphasis that wound pathergy and the hypercoagulable complications of surgery - trauma can be dramatic and highly morbid, including death or unrecoverable damage such as blindness and paraplegia.

Hypercoagulable Disorders – Implications for Wound Pathergy, Acute Wounds, Chronic Ulcers, Trauma, and Surgery.

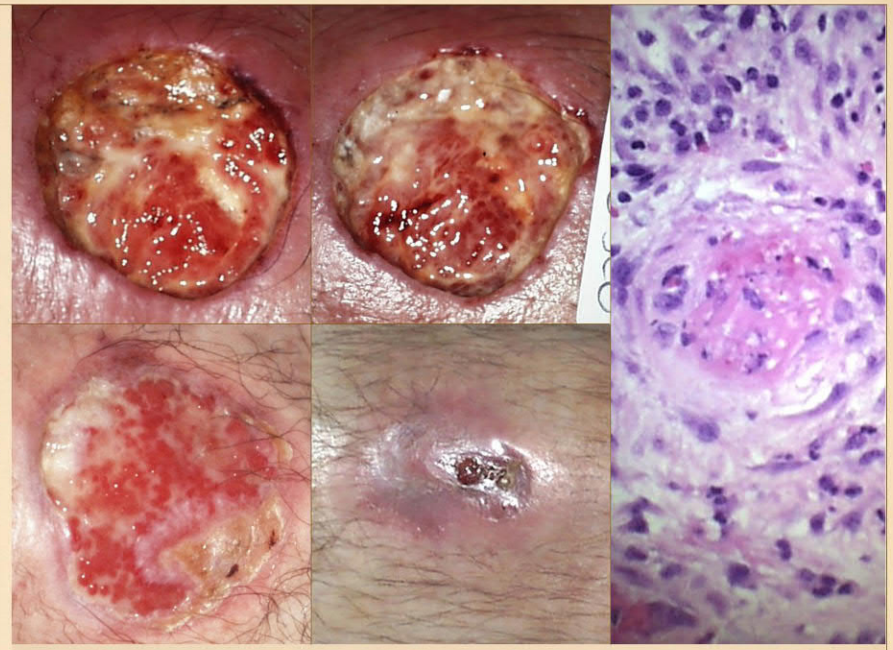


62 M **Dx: APC resistance, probable factor V Leiden**

Diverticular colo-vesical fistula.
Wound pathergy, then multiple infarcts and complications after surgery.
Bowel necrosis, abdominal wall necrosis.
Hx DVT - PE.
Hx finger necrosis after minor trauma.
Suspicious history.

Lab: APC resistance high.
Confirmatory tests.

Died before anticoagulation and diagnosis-specific Rx.



34 M **Dx: Lupus, Antiphospholipid antibody syndrome**

Wound pathergy, then multiple failed surgery after trivial hand trauma.
Multiple subsequent wounds from failed grafts and flaps.
Second set of wounds after elective hip replacement (for lupus arthritis).
Suspicious history.

Lab: anticardiolipins high.
Confirmatory tests.

Healed by warfarin only (& basic topicals).
Proper wound behavior only after warfarin.

Later: mva, abdominal trauma, abdominal wall infarct with wounds & colon fistula.
Later: home fall, minor non-skeletal back injury, tardive 2° cord infarct, paraplegia.

39 M **Dx: Factor V Leiden**

Tardive paraplegia from non-skeletal non-cord back injury

Minor fall without spine injury or neuro deficit, then paraplegia in coming days.
Recurrent infarctive wounds of feet from minor wheelchair trauma or pressure.

Lab: factor V Leiden, histology - diffuse thrombosis.

When trauma and surgery interact with the hypercoagulable disorders, the results can be extremely morbid, often fatal.

Hypercoagulable Disorders

Key Points

More clinical examples, emphasis on surgical cure of hypercoagulable wounds.

Many hypercoagulable wounds heal with anticoagulants alone, supported by basic topical wound care.

For those that need surgery, risks are substantially reduced by anticoagulants, but there are still risks to wounds, flaps, grafts, and final outcome.

Risks can be obviated, and reconstructive success with healed wounds assured by triad of : :

Anticoagulants

Hyperbaric oxygen

(in peri-operative period, typically one week in advance, two weeks after surgery).

Closure with regenerative matrices.

Note the importance of the "hypercoagulable therapeutic triad" – anticoagulants, hyperbaric oxygen, regenerative biomatrices.

67 F

Acute skin necrosis.
Suspicious history.

No prior risks or history.
Good pulses in feet.
No other illness or explanation.

Pure thrombo-infarctive pattern.
Confirmatory exam.

Lab: anti-thrombin-3 deficiency.
Confirmatory blood tests.

Healed: warfarin, hbo, regenerative biomatrix.
No recurrence on anticoagulation.

Dx: Anti-thrombin-3 deficiency

44 F **Dx: APL syndrome**

Achilles rupture, multiple failed surgery.
Blind from retinal artery occlusion.
Suspicious history.

Otherwise healthy.
No other illness or explanation.

Lab: anticardiolipins high.
fibrinogen high.
periwound TcpO2 low.
Confirmatory tests.

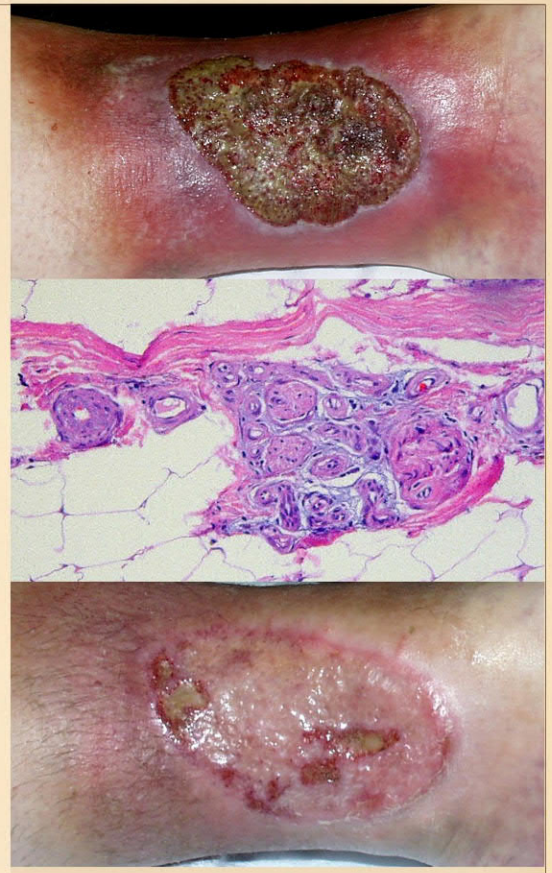
Healed: warfarin, hbo, biomatrix.
Proper wound behavior only after warfarin.

The "hypercoagulable therapeutic triad".

Anticoagulants
Hyperbaric Oxygen
Regenerative Biomatrices

Each has its role to

Arrest pathology.
Restore physiological deficits.
Allow healing without risk of wound pathergy.



30 F **Dx: Mixed coagulopathy**

Refractory active ulcers. Severe ischemic pain.
History miscarriage.
Suspicious history.

Wound surface "granulation tissue" infarcts.
Confirmatory exam.

Lab: protein C deficiency, lupus anticoagulant.
Low skin TcpO2, with normal pulses.
Histology shows old and recanalizing thrombi.
Confirmatory tests.

Healed: warfarin (hard to regulate), hbo, matrix.
No recurrence on anticoagulation.

Hypercoagulable Disorders

Key Points

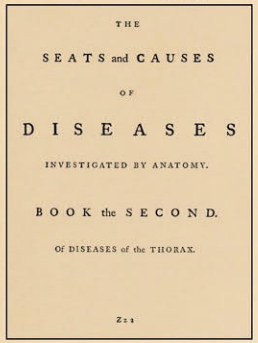
More examples of old, “classical”, long recognized syndromes or diseases that can now be attributed to underlying hypercoagulable states.

Keep an open eye and mind to situations of unexpected, unexplained, diffuse, recurrent, thrombosis, infarction, non-inflammatory ulceration, dropout of organ or physiological functions, etc., and look for a hypercoagulable state or disorder.

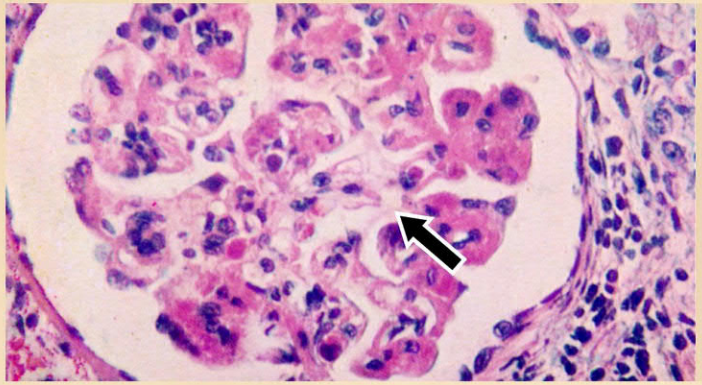
Look for secondary auto-immunity.

In conditions of “auto-immunity first” where such diagnoses have already been made, look for a primary breeder disorder, such as hypercoagulable diseases.

WHAT HAVE WE BEEN MISSING?



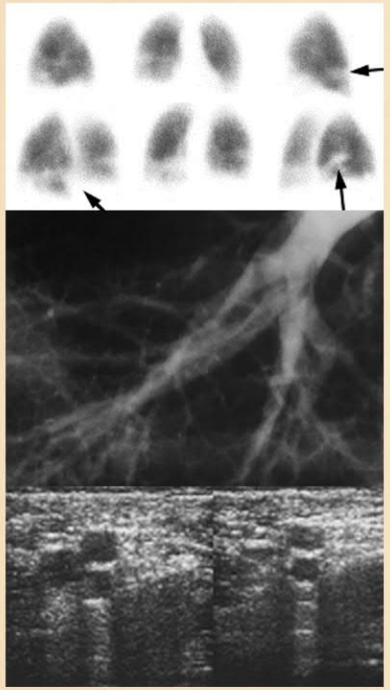
THE
SEATS and CAUSES
OF
DISEASES
INVESTIGATED BY ANATOMY.
BOOK the SECOND.
Of DISEASES of the THORAX.



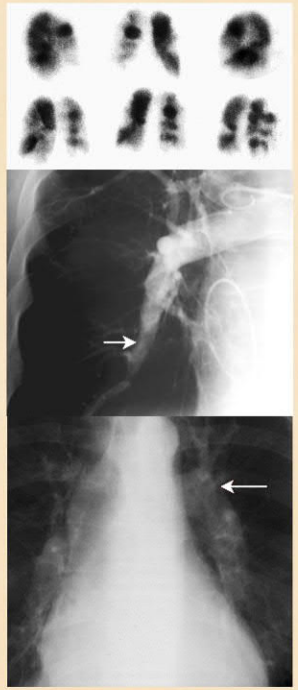
lupus glomerulonephritis
focal thrombotic glomerulonephritis
rapidly progressive glomerulonephritis
glomerulonephritis of chronic liver disease

fibrin thrombi

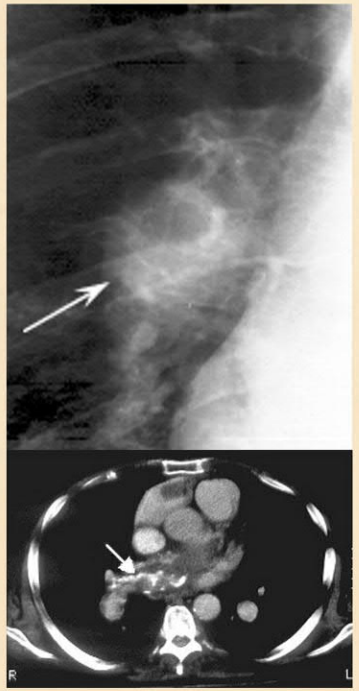
RETHINKING
the cause, diagnosis, & treatment of classical syndromes and clinical disorders.
PATHOGENESIS
RECOGNITION
APPROACH



34 f, healthy
subacute respiratory symptoms
multifocal pulmonary flow voids
pulmonary artery thrombus
clean iliofemoral veins



57 m, healthy
1 year progressive dyspnea
multifocal flow voids
pulmonary artery thrombus
pulmonary hypertension



57 m, scleroderma
1 year progressive dyspnea
pulmonary hypertension
calcified mural thrombus
pulmonary angiopathy

20f, healthy
dyspnea after starting oral contraceptives
multifocal flow voids
pulmonary thrombi

PPT
primary pulmonary thrombosis

ISPAT
in situ pulmonary artery thrombosis

CTEPH
chronic thrombo-embolic pulmonary hypertension

Hypercoagulable Disorders

Key Points

Summary. Hypercoagulable disorders can be diagnosed with high accuracy.

The tetrad-pentad hypercoagulable syndrome is the core of taking a history.

Hypercoagulable disorders versus states is an important distinction. When clinical trouble starts, it is often self-sustaining.

Patients are prone to wound pathergy and infarcts after trauma - surgery. Do not err by more indiscriminate surgery until diagnosis is made, anticoagulants started.

Principles of anticoagulation have some distinctive differences compared to usual non-hypercoag anti-coagulation.

For prophylaxis and long term, you are not thinning normal blood, rather restoring sticky blood to normal, typically around ptt-inr ≈ 2.0 - 2.5. For active or acute rx, target inr typically ≈ 3.0 - 3.5, sometimes a bit higher. Use anticoagulants to protect surgery. Use steroids if there is a companion ai-cvd-ctd.

SUMMARY OF THROMBO- & MICRO-OCCLUSIVE & HYPERCOAGULABLE DISORDERS, and THEIR IMPLICATIONS FOR WOUNDS & SURGERY

DE HIRUDINE. LIB. IV. 431

Stercus Lacertæ confert albugini, & pruritui oculorum, visum acuit, coloremque bonum efficit, inquit Avicenna.

Oleum in quo Lacerta viva cocta sit, cum vino, tamdiu donec illud absumatur, adinodùm probatur in alphis; sic refert Felix Platerus.

CAPVT XVIII.

DE HIRVDINE, SIVE SANGVISVGA.

HIRUDO alio nomine Sanguisuga dicitur, vermis aquatilis est, & nudæ cuti aquam ingressi, vel extrà eam debitè applicata, mordicùs adhæret;

Guillaume van den Bossche
Historia Medica 1639

Hypercoagulability

A modern discovery and concept.

They are common, but all too often under-appreciated, unrecognized, and overlooked.

Positive Diagnosis

They can be diagnosed on specific criteria.

Hypercoagulable disorders & ulcers are NOT diagnoses of exclusion.

In patient history, recognize unusual and unexpected infarcts and complications.

For wounds, recognize thrombo-infarctive pattern (vs inflammatory-lytic).

Recognize the tetrad-pentad syndrome.

Hypercoagulable Syndrome

Thrombotic or embolic event
Autoimmune cvd-ctd
Wound pathergy
Miscarriage
Family history of same

Pathophysiology & Triggers

Complex multi-control system, NLD.

Affected pt's are not always coagulopathic.

When hypercoagulable dynamics start, they can "lock in" to a persistent state.

Be cognizant of interplay of coagulation and inflammation, & of Virchow's Triad.

Wounds, Trauma, & Surgery

Hypercoagulable patients & states are prone to wound pathergy and infarction.

In face of odd, unexpected, repetitive wound complications, suspect hypercoagulability.

These are prime situations for principle of "do not do too much, too soon, too often".

Anticoagulation

Anticoagulation is foundation of treatment, to prevent blood from clotting inside vessels.

You are not thinning normal blood, rather restoring "thick" blood to normality.

Treatment parameters are different than "thinning" normal blood.

Anticoag. Rx restores normal wound healing.

Comprehensive Treatment

Acute & chronic. Treat acute events to stop progression, restore flow, limit infarction.

Anticoagulation, treat related disease (e.g. steroids), avoid extra injury, wound care.

Wounds: consistent good results from triad anticoagulation, hbo, regenerative biomatrices.

Managing Surgery

Start anticoagulation as soon as possible, pre-op when possible (& steroids as needed).

Run anticoagulants during surgery.

Continue anticoagulants until wounds heal, then 3 - 6 months (or longer) as they mature.

Mathematics & Engineering

Materials & Mechanics

Elasticity-Plasticity

Scar-tissue mechanics, Wolff

NLD (wounds, vessels, Wolff, etc.)

Quickies

LaPlace's Law

Surface-volume-compliance

Flap geometry

Flapology – brownout - blackout

Pressure

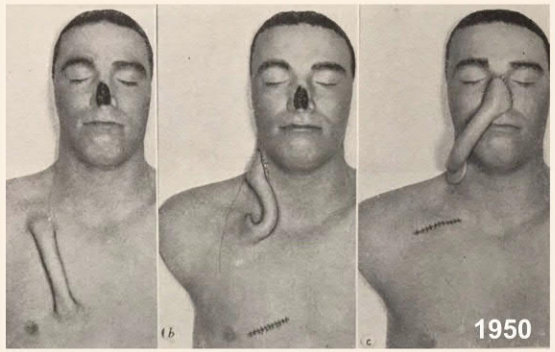
Quickies 1

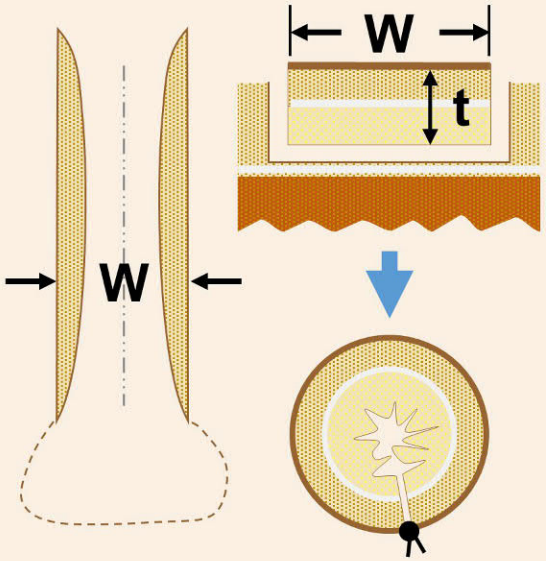
Tubing a flap

For a given flap thickness, how wide is the flap

(thickness typically means skin plus both of the adipose-areolar fascias, Camper's - Scarpa's)

?

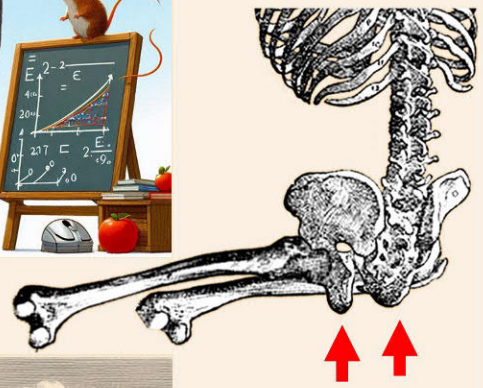


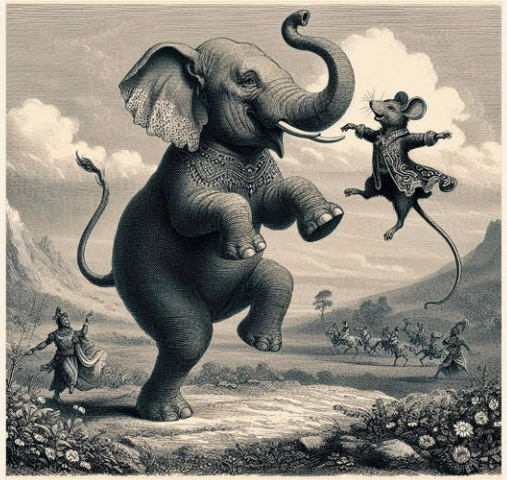


Quickies 2

Why don't little kids get ischial pressure sores ?

Spina bifida, CP, etc. – only at puberty.



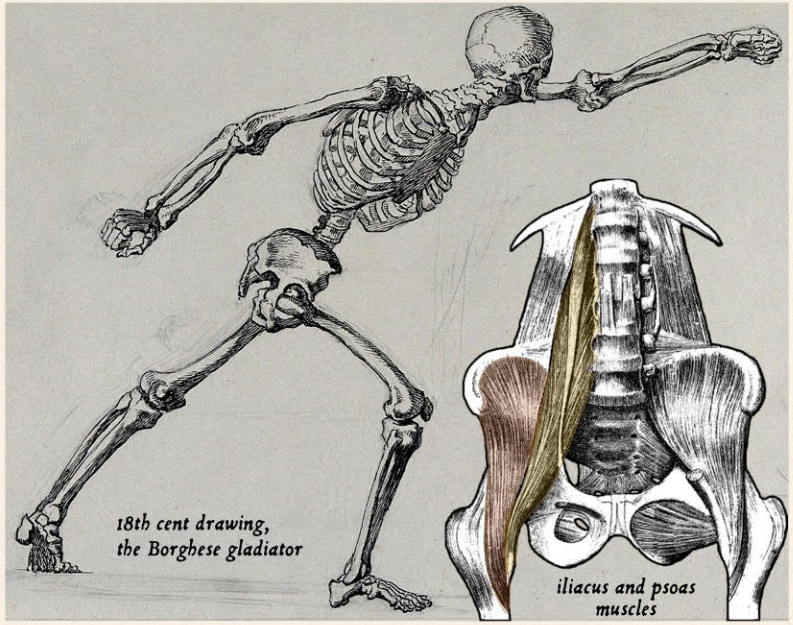


sitting = ischia

Quickies 3

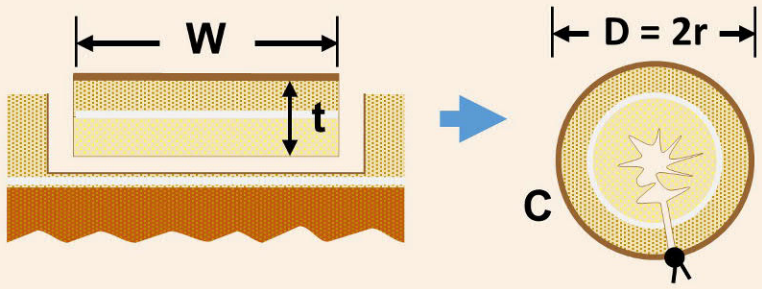
Why do AKA patients get ischial pressure sores ?

Especially old, infirm, and arteriopaths.



Tubing a flap

For a given thickness, how wide must a tubed flap be ?



Cross-section area **A**
$A = W\,t$

When tubed, the cylinder-circle has :
radius **r**, diameter **D**, circumference **C**

$$W\,t = A = \pi r^2$$

$$C = \pi D = \pi\, 2\, r \quad ; \quad r = C / 2\pi$$

$$W\,t = \pi\,(C / 2\pi)^2 = C^2 / 4\pi$$

For flap excessively wide, skin width W > C, tube is loose, non-cylindrical, good for circulation and flap safety, but may be impractical to take a wide flap.

For flap is too narrow W < C, skin-epithelium will not cover entire tube, defeating the purpose of tubing the flap.

For flap ideal W = C, just enough skin to cover the tube without unnecessary excess, but no deficiency that must be stretched causing elastic tension and pressure inside, then :

$$W = C$$

$$W\,t = C^2 / 4\pi = W^2 / 4\pi$$

$$\mathbf{t = W / 4\pi \quad ; \quad W = t\ 4\pi}$$

Width must be 4 · pi ≈ 12 times thickness of the fascias.

Quickies 1

Tubing a flap

For a given flap thickness, how wide is the flap

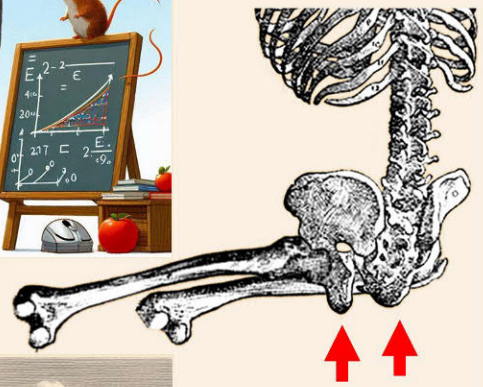
(thickness typically means skin plus both of the adipose-areolar fascias, Camper's - Scarpa's)

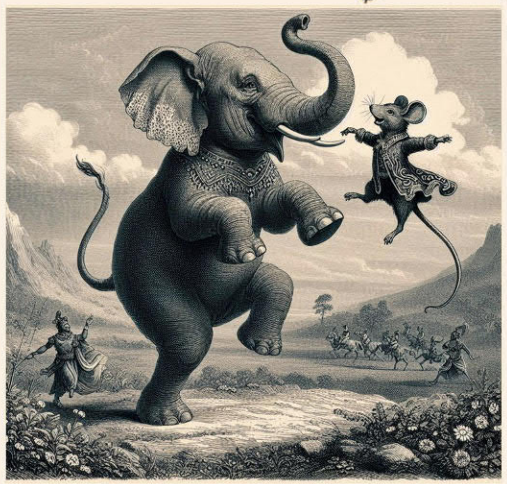
?

Quickies 2

Why don't little kids get ischial pressure sores ?

Spina bifida, CP, etc. – only at puberty.





sitting = ischia

Quickies 3

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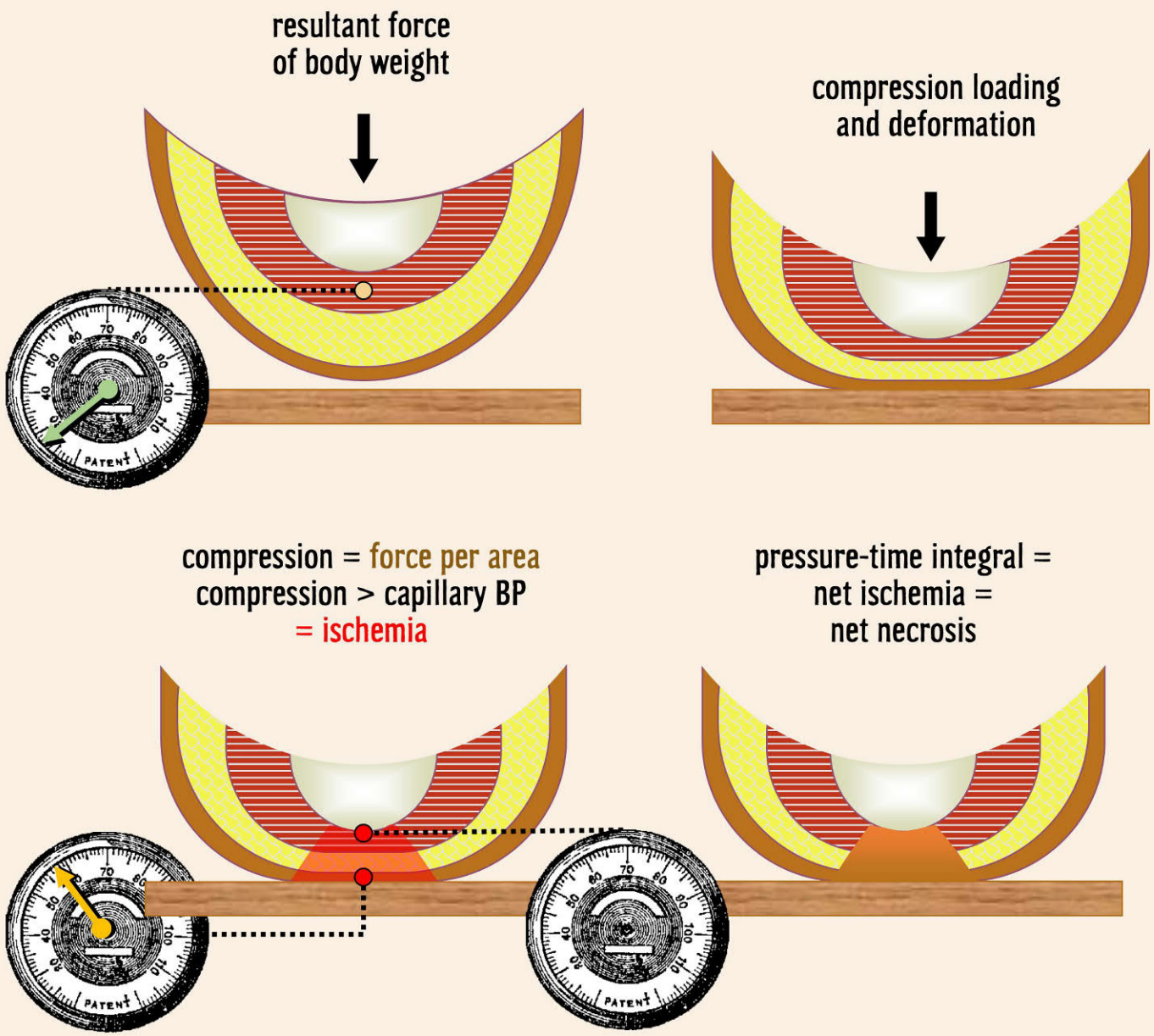
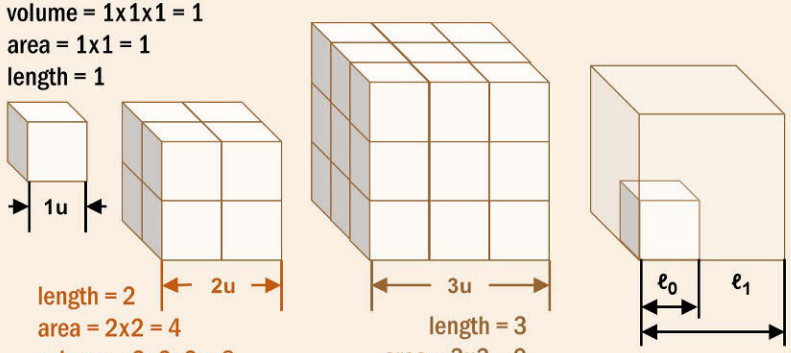
Especially old, infirm, and arteriopaths.



Why don't pre-pubertal kids get ischial pressure sores ?

The Physics of Scale.

volume = 1x1x1 = 1
area = 1x1 = 1
length = 1



length = 2
area = 2x2 = 4
volume = 2x2x2 = 8

length = 3
area = 3x3 = 9
volume = 3x3x3 = 27

$\ell_1 = S \cdot \ell_0$

S = L_1 / L_0 = linear scaling ratio.

Pressure = force / area = mass x g / area

For pt in wheelchair, assume upper body = 2/3's total mass; Approx. values :

age	height cm	pelvis+upper body, kg	w.c. contact area, cm²	bi-ischial area, cm²	skin press. torr	bi-ischial press., torr
10	140	15	400	4x1 x 2	28	1400
12	145	18	430	4.5x1 x 2	31	1500
14	160	25	530	5x1.1 x 2	35	1700

For growth with a linear increase of factor **S** :
any surface or cross section (area) scales by S^2,
any volume scales by S^3.
Pressure is force / area, $P = F / A$.
Assuming consistent density, force ≡ mass ≡ volume.

So, $\delta P \equiv \delta F / \delta A \equiv S^3 / S^2 = S$. $\delta P = S$.

Contact pressures increase proportional to linear scaling S.

Before puberty, contact pressures on wheelchair, under ischia, are approximately arteriolar-capillary.

After puberty and growth spurt, they exceed those pressures.

Quickies 1

Tubing a flap

For a given flap thickness, how wide is the flap

(thickness typically means skin plus both of the adipose-areolar fascias, Camper's - Scarpa's)

?

Quickies 2

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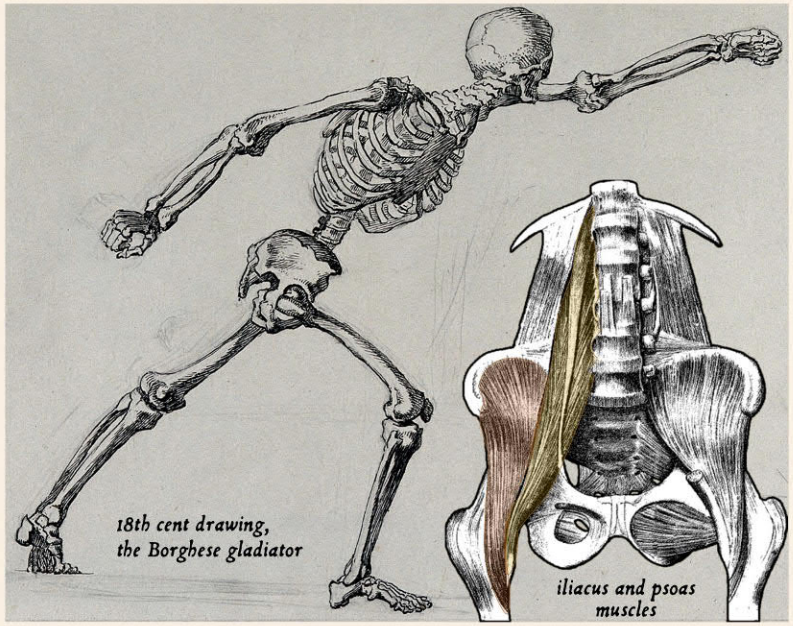
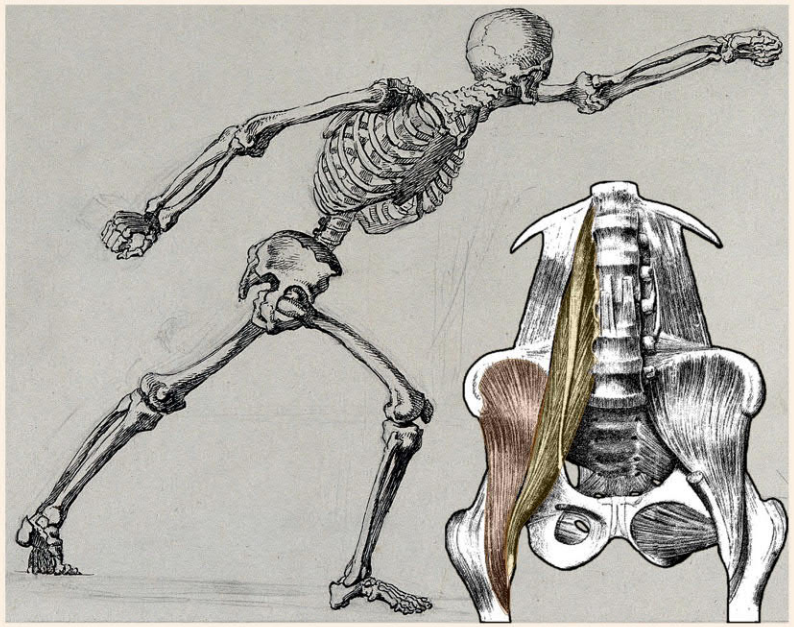
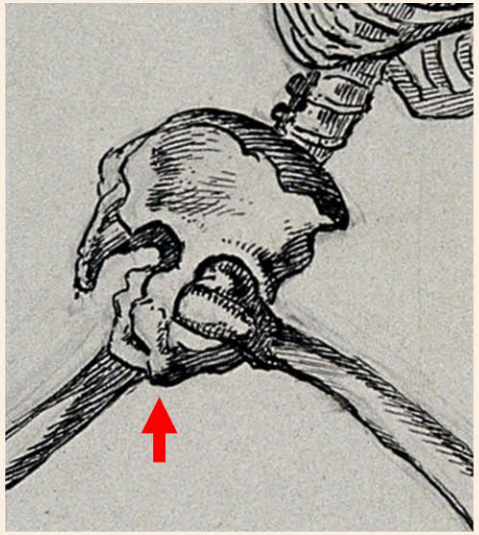
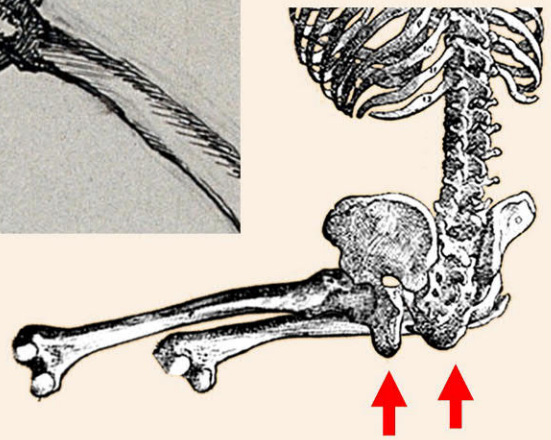
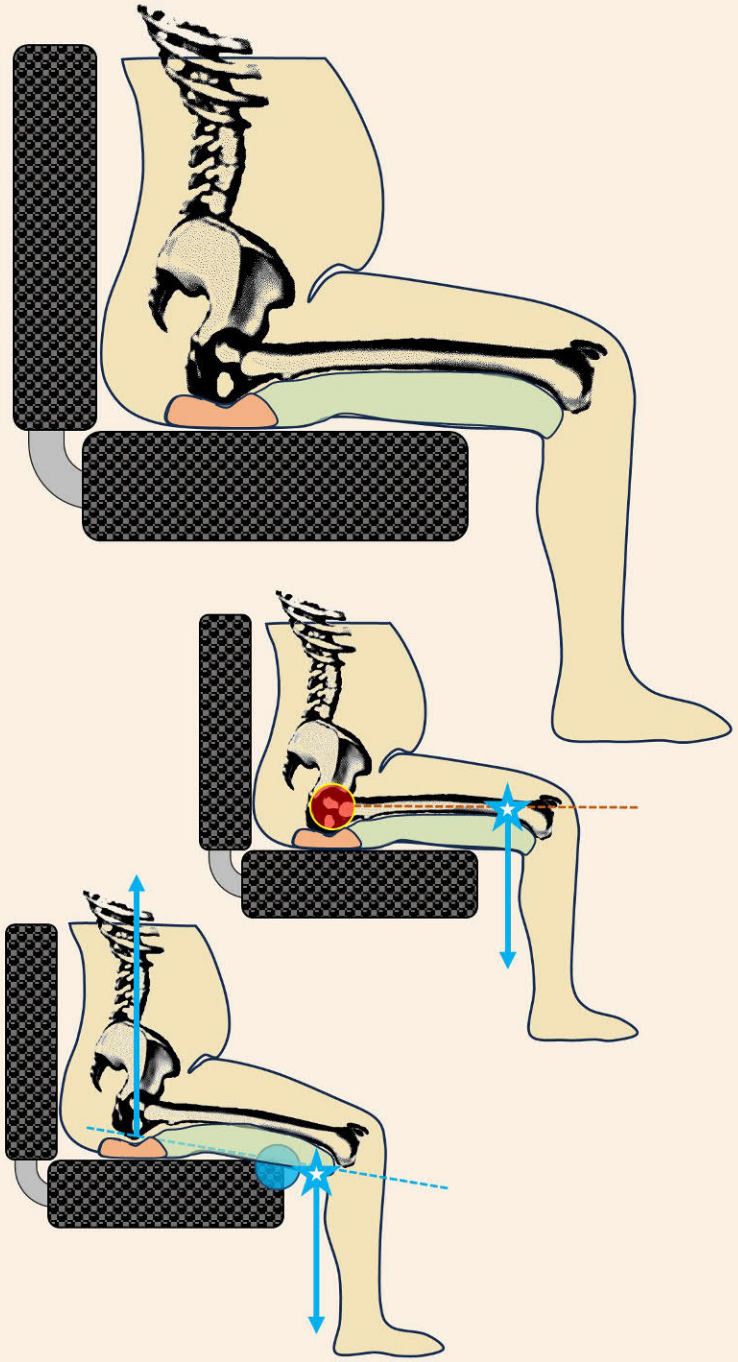




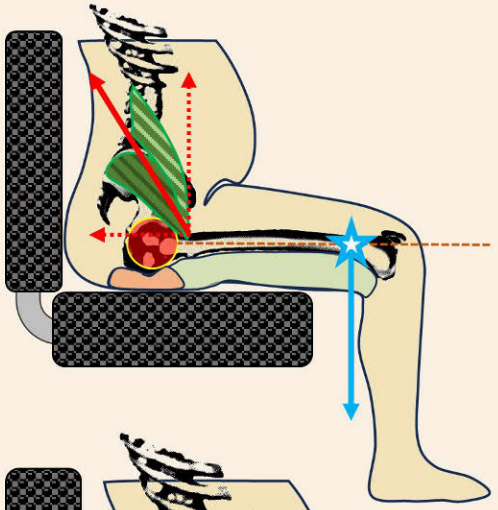




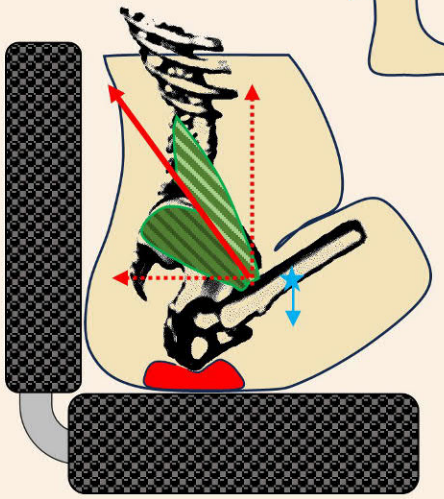


Why do AKA patients get ischial pressure sores ?

Especially old, infirm, and arteriopaths.



With a full lower extremity, limb center-of-gravity creates extension torque around hip to balance flexion of iliopsoas muscles.



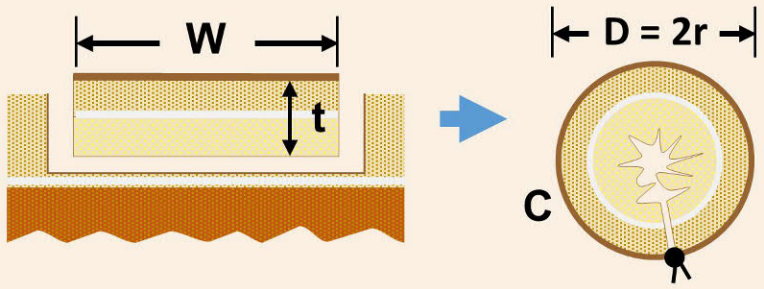
Thigh contributes to body-mass load-bearing and dissipation of sitting pressures.

With lower extremity removed, mass is reduced, center-of-gravity moves far proximal, extension torque drops.

Flexion torque from iliopsoas is unopposed, thigh swings up, and contact surface disappears except focus under ischium = pressure ulcer.

Tubing a flap

For a given thickness, how wide must a tubed flap be ?



Cross-section area **A**
A = W t

When tubed, the cylinder-circle has :
radius **r**, diameter **D**, circumference **C**

$W\,t = A = \pi r^2$

$C = \pi D = \pi\, 2 r \quad ; \quad r = C / 2\pi$

$W\,t = \pi (C / 2\pi)^2 = C^2 / 4\pi$

For flap excessively wide, skin width W > C, tube is loose, non-cylindrical, good for circulation and flap safety, but may be impractical to take a wide flap.

For flap is too narrow W < C, skin-epithelium will not cover entire tube, defeating the purpose of tubing the flap.

For flap ideal W = C, just enough skin to cover the tube without unnecessary excess, but no deficiency that must be stretched causing elastic tension and pressure inside, then :

$W = C$

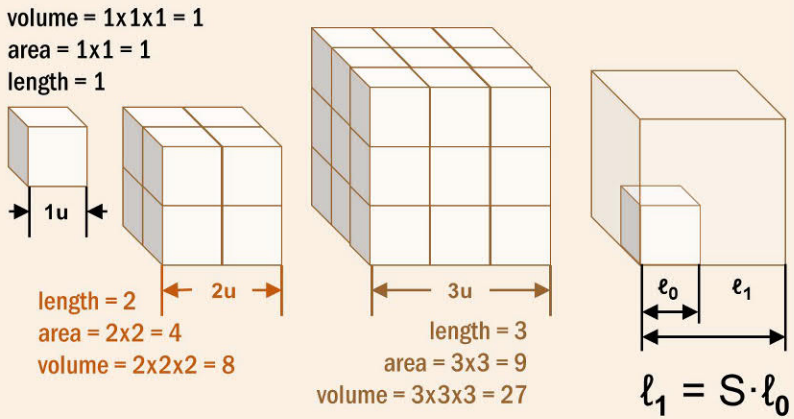
$W\,t = C^2 / 4\pi = W^2 / 4\pi$

$\mathbf{t = W / 4\pi \quad ; \quad W = t\, 4\pi}$

Width must be 4 · pi ≈ 12 times thickness of the fascias.

Why don't pre-pubertal kids get ischial pressure sores ?

The Physics of Scale.



S = L_1 / L_0 = linear scaling ratio.

Pressure = force / area = mass x g / area

For pt in wheelchair, assume upper body = 2/3's total mass; Approx. values :

age	height cm	pelvis+upper body, kg	w.c. contact area, cm²	bi-ischial area, cm²	skin press. torr	bi-ischial press., torr
10	140	15	400	4x1 x 2	28	1400
12	145	18	430	4.5x1 x 2	31	1500
14	160	25	530	5x1.1 x 2	35	1700

For growth with a linear increase of factor **S** :
any surface or cross section (area) scales by S^2,
any volume scales by S^3.
Pressure is force / area, P = F / A .
Assuming consistent density, force ≡ mass ≡ volume.

So, $\delta P \equiv \delta F / \delta A \equiv S^3 / S^2 = S$. $\mathbf{\delta P = S}$.

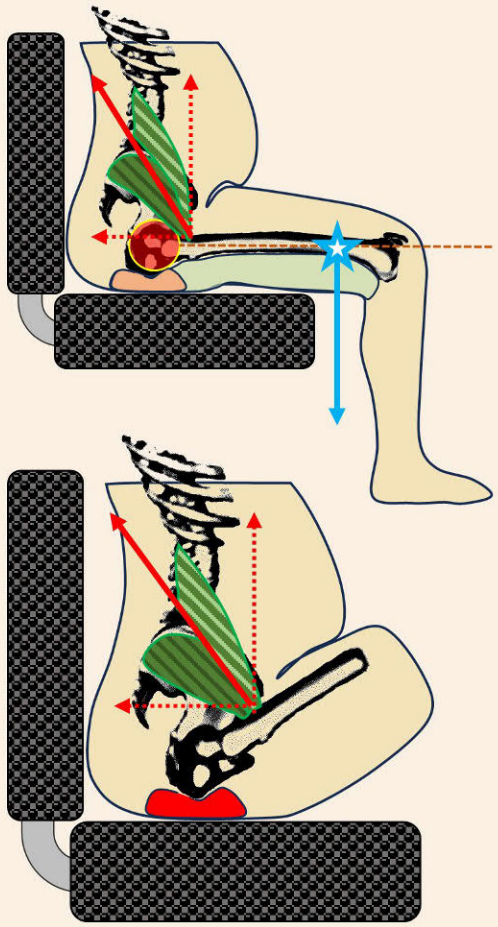
Contact pressures increase proportional to linear scaling S.

Before puberty, contact pressures on wheelchair, under ischia, are approximately arteriolar-capillary.

After puberty and growth spurt, they exceed those pressures.

Why do AKA patients get ischial pressure sores ?

Especially old, infirm, and arteriopaths.



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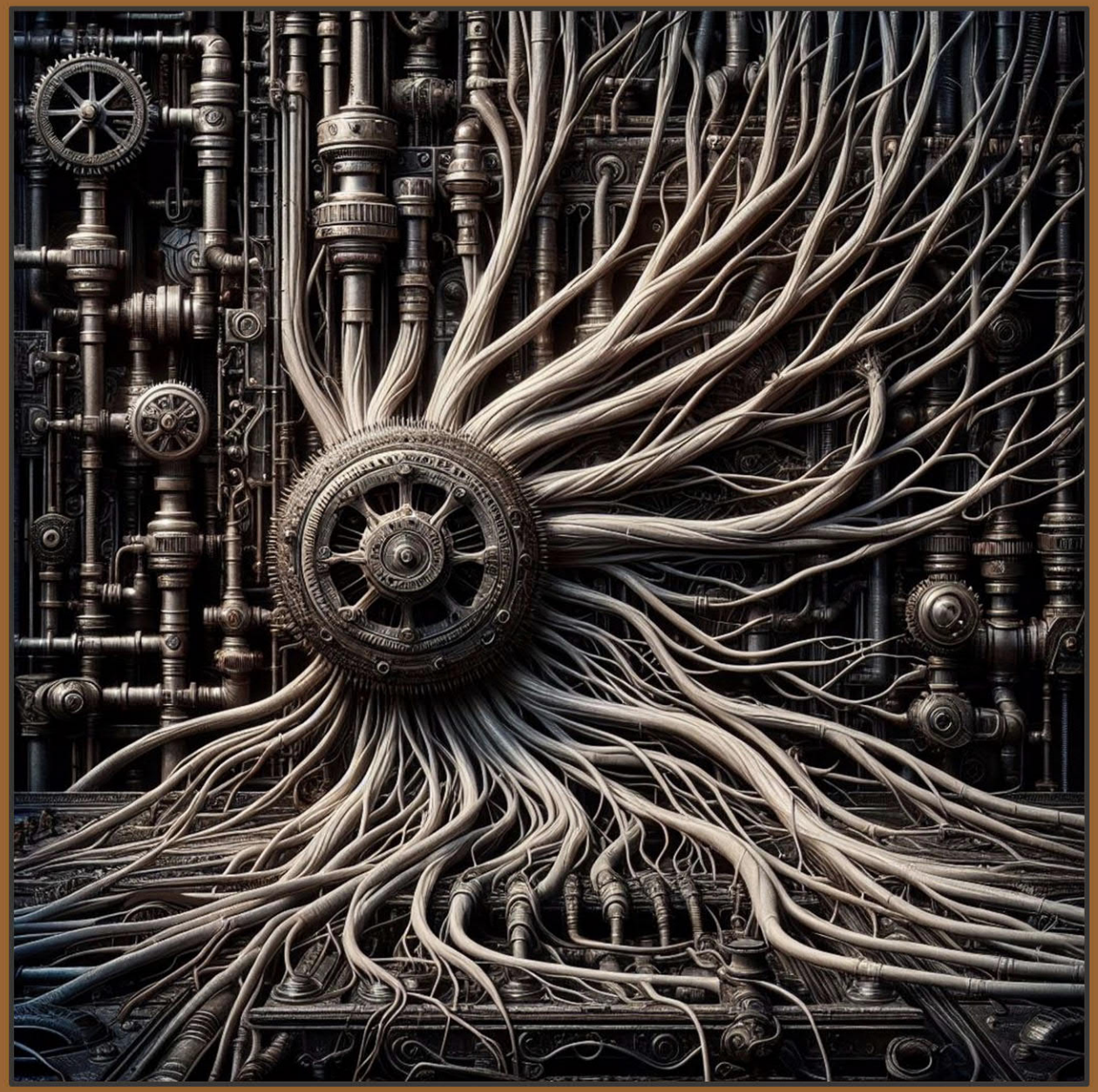
Mathematics & Engineering



LaPlace's Law

Surface-volume-compliance

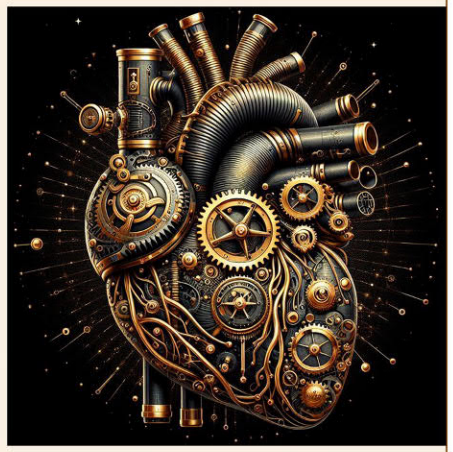
Flap geometry

Flapology – brownout - blackout

LaPlace's Law

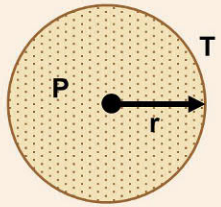
Equating pressure, mural tension, and radius in a pressure vessel or contained fluid.

Pierre-Simon LaPlace
1749-1827

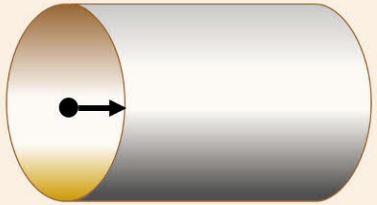


At the start of the Steam Age and Industrial Revolution.

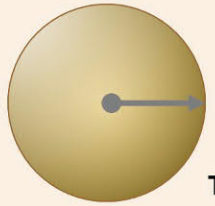
circle T = P r



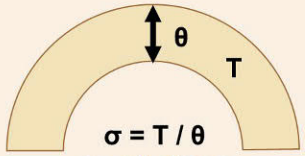
cylinder T = P r



T = tension
P = pressure
r = radius



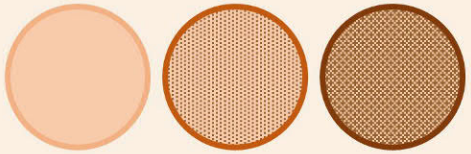
sphere
T = P r / 2



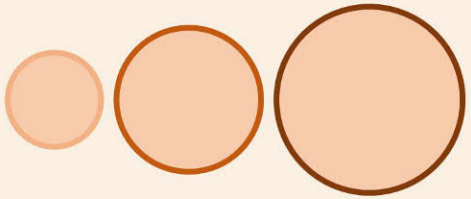
σ = T / θ
mural stress

θ = thickness

T = P r



For a given radius, T varies with P.
As pressure increases, mural tension increases.



For a given pressure, T varies with r.
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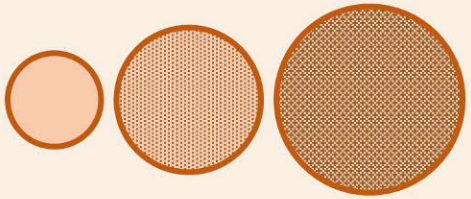


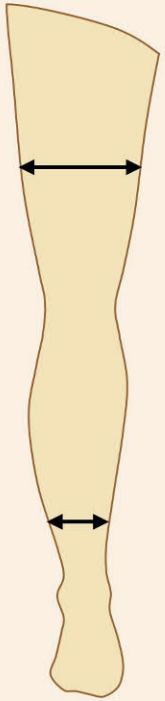
For a given tension, P varies with r.
As radius increases, pressure increases.

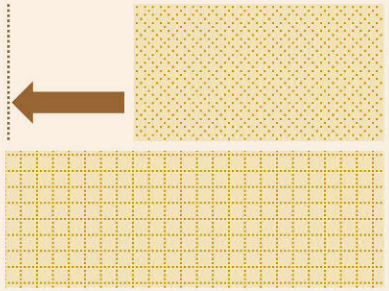
When tension only is pertinent, mural thickness and stress can be ignored. If mural stress and shell thickness are important, thicker material decreases mural stress for a given T = P r .

Pertinent Applications

Pulmonary physiology
Alveolar inflation - atelectasis
Mechanical ventilation
Cardiodynamics
Heart failure
Dilated cardiomyopathy
Reduction cardioplasty
Aneurysm development
Hernia development
Bowel obstruction - perforation
Bowel ileus
Bladder retention
Reduction cystoplasty
Anesthesia circuitry
ET tube design
Compartment syndromes
Hydrocephalus
Edema-stasis disorders
Vascular anatomy-mechanics
Wound mechanics
Wrapping an extremity
et al

Wrapping an extremity





If elastic bandage is stretched to a certain "feel" of tension, i.e. tension T constant, then :

For a small diameter,
(e.g. ordinary ankle), pressure is high.
! CAUTION, pressure injury is common; foot ischemia possible in a vasculopath.

For a large diameter,
(e.g. ordinary thigh), pressure is low.
! ATTENTION, stretch tighter to get desired pressure, or apply multiple layers to thicken θ, multiply tension.

Wrap looser at ankle, graduated firmer going higher.

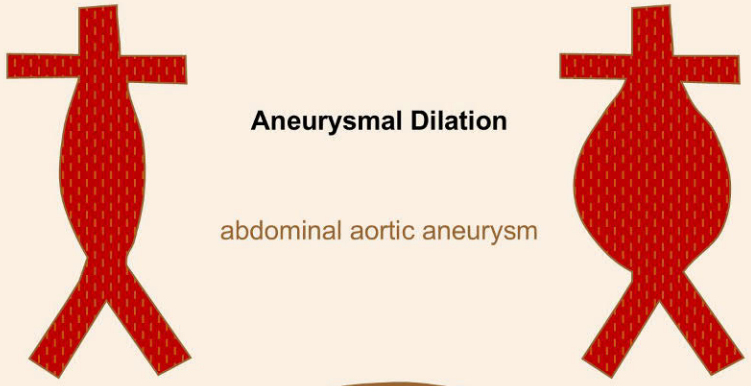
** For edema conditions (larger diameters), wrap tighter, more layers.

** For dermatoliposclerosis, rigid shell, wrap even tighter and more layers (or pumps).

** For arteriopaths (higher pressures disallowed), wrap looser and lighter.

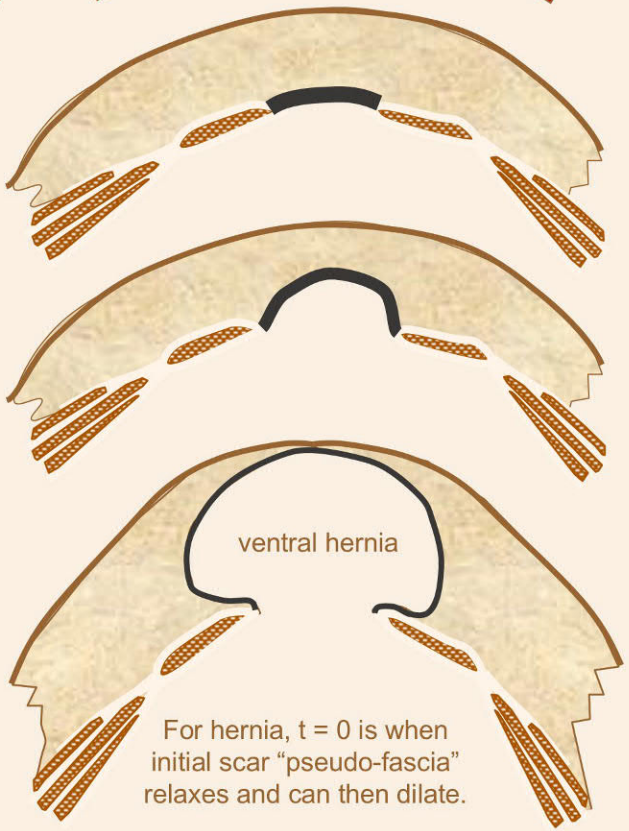
LaPlace's Law

Equating pressure, mural tension, and radius in a pressure vessel or contained fluid.



Aneurysmal Dilation

abdominal aortic aneurysm



For hernia, t = 0 is when initial scar "pseudo-fascia" relaxes and can then dilate.

Aneurysmal Dilation

Progressive increase in size of a pressurized cylindrical or spherical shell.

Because of LaPlace's law, rate of expansion is proportional to its current state, thus "first order kinetics", exponential strain rate.

At what rate does circumference of aneurysm or sac increase?
$dC / dt = ???$

Wall is increasing length – a strain or motion of the circumference – meaning there must be a force or stress to induce it.
The stress is the intra-luminal pressure.

Assumption : the rate of expansion is proportional to the inducing force, thus rate of change of circumference is proportional to the mural tension – an assumption, but a good one based on general biology and physics.

Then :

$dC / dt = k N$	(k = conversion coefficient ; N = tension, in lieu of T, not to confuse t = time)
$dC = k N dt$	But, **$N = P r$** (La Place)
$dC = k P r dt$	Here, blood pressure P is long time-base average pressure, effectively a constant.
$dC = kP (C/2\pi) dt$	(because $C = 2\pi r$.)
$dC = \{kP/2\pi\} C dt$	Constants can be rolled up into $K = kP/2\pi$.
$dC = K C dt$	
$dC / C = K dt$	

$\int (dC / C) |(C_0,C_t) = \int (K dt) |(0,t)$ Definite integral, domain & range

$\ln (C) |(C_0,C_t) = Kt |(0,t)$

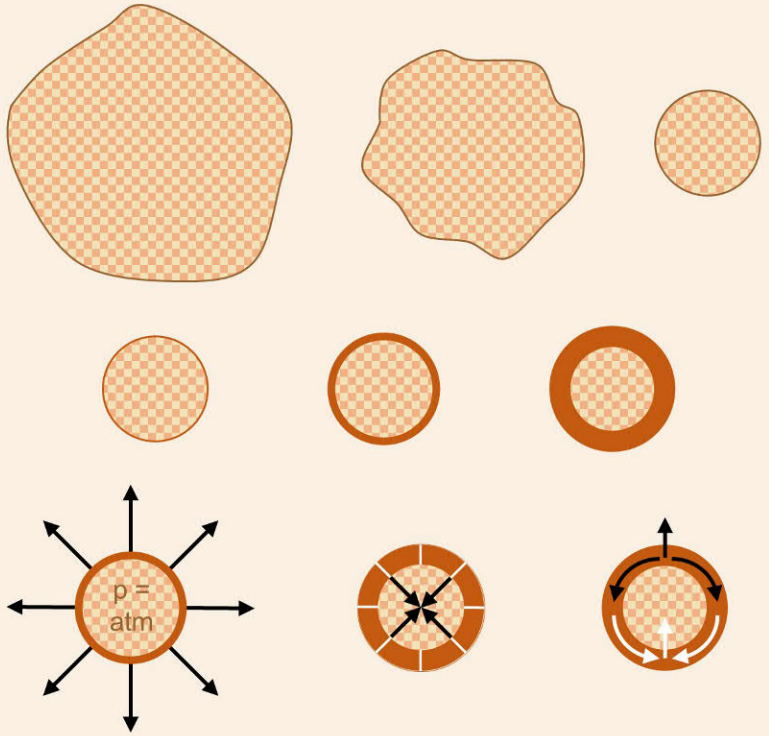
$\ln(C_t) - \ln(C_0) = Kt - 0$

$\ln(C_t / C_0) = Kt$

$C_t / C_0 = e \wedge (Kt)$

$C_t = C_0 e^{Kt}$ Circumference increases exponential rate.

Certain wounds that do not close.



normal stress = **negative** (host elasticity)

mural stress = **tensile** (LaPlace)

constant mural stress **resisted** (Wolff-Davis)

reactive scar (Wolff) creates self-sustaining arches resisting contraction at base

wound is in a Newtonian stand-off : high intra-scar tensions, but no net normal forces to move wound edges.

A little basic math can solve or explain a variety of everyday situations in plastic surgery.

As basic physical laws, they preempt a lot of clinical pseudo-science mumbo-jumbo.

Flapology –
brownout - blackout

Source inflow = 65u/min
Healthy flow = 10u/vox/min
Marginal critical flow = 8u/vox/min
10 vox healthy flow = 10x10 = 100u/min
10 vox marginal flow = 10x8 = 80u/min
10 vox actual flow = 65u/min

Sacrifice and expendability for the greater good.

Source inflow = 65u/min
Healthy flow = 10u/vox/min
Marginal critical flow = 8u/vox/min
8 vox healthy flow = 10x8 = 80u/min
8 vox marginal flow = 8x8 = 64u/min
8 vox actual flow = 65u/min

BROWNOUT :: THIN YOUR FLAP

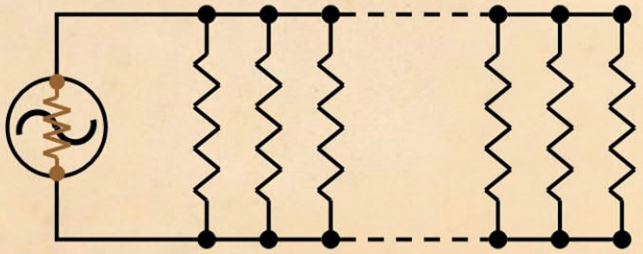
Compare a brownout to a rolling blackout.

V = voltage (pressure)
I = current (flow)
R = resistance

Ohm's Law $\mathbf{I = V/R}$ $\mathbf{V = I \cdot R}$

For parallel loads:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \cdots + \frac{1}{R_n}$$



Generator or input impedance:
If current is limited,
voltage decreases as load increases.

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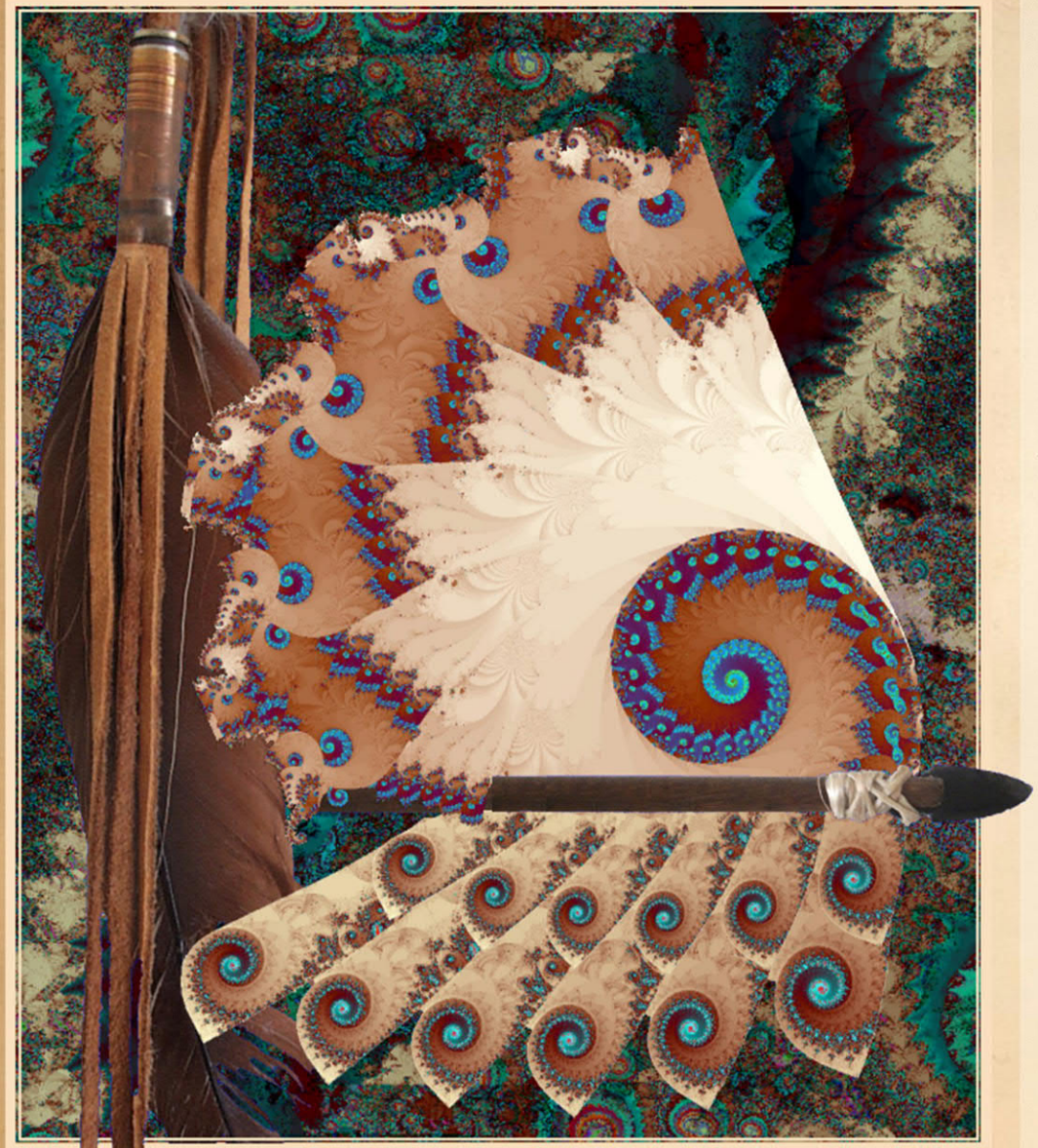
Marc E. Gottlieb, MD, FACS
Phoenix, AZ



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