ATYPICAL ULCERS
{ NOT REALLY }

BEING AN ACCOUNT OF ADVENTURE AND MISADVENTURE
ON THE
FRONTIER OF WOUND SCIENCE & PRACTICE

Including the Inspirational Saga of the Great Traverse
Through the Arid Desert of Autoimmunopathy
and Mesenchymal Pathology

With a Traveler's Guide to an Allegorical
SEVEN CITIES OF CIBOLA
of Wound Knowledge & Treasure

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arimedica.com
Phoenix, Arizona
2009

AUTOIMMUNOPATHY AND CONNECTIVE TISSUE DISORDERS

THE TRUE INTRINSIC DISEASES OF WOUND HEALING

A GUIDE TO UNDERSTANDING

CAP Wounds (Chronic and Pathological)

Coagulopathic & Micro-Occlusive Ulcers

Immunopathic & Auto-Immunopathic Ulcers

The Interconnections Between These Diseases

The Origins of Auto-Immunopathy & Soft Tissue Pathology

The Effects of Auto-Immunopathy on Wound Healing

Clinical Profiles of These Disorders

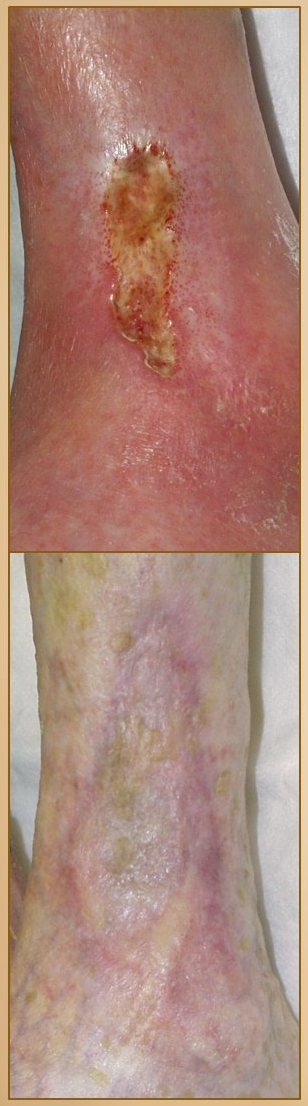
ARTERIAL

VENOUS

DIABETES

PRESSURE

NOT ARTERIAL - VENOUS - DIABETES - PRESSURE NOT







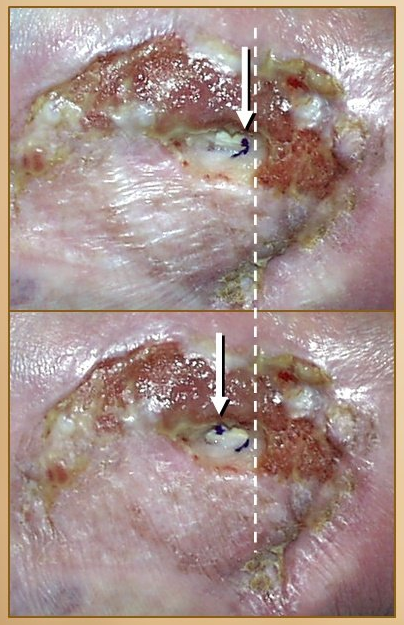








MECHANICAL ULCERS



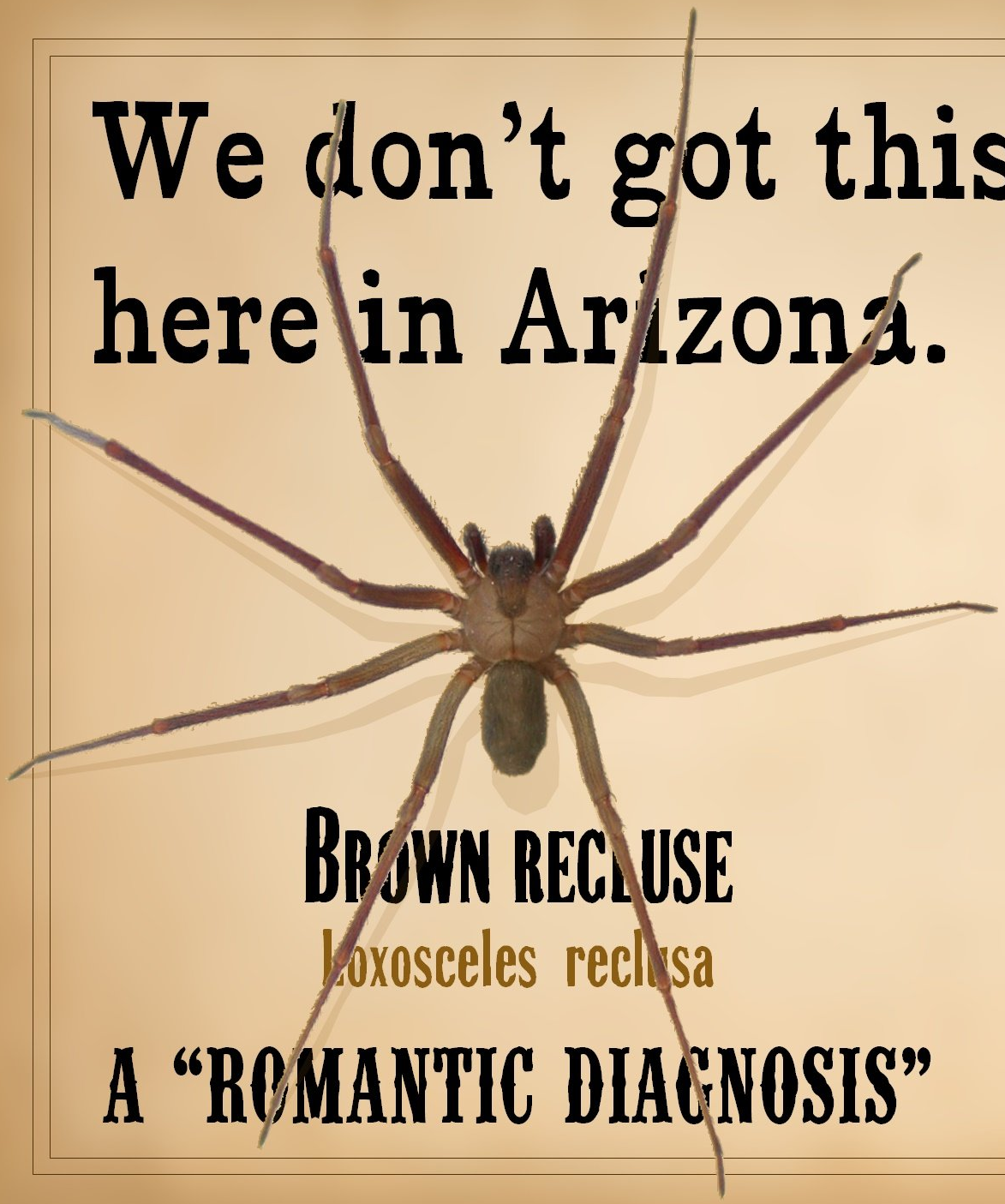
NOT ARTERIAL - VENOUS DIABETES - PRESSURE NOT


Regranex


inches
cm
T.M. 09/08/08


inches
T.M. 1/27/09

We don't got this varmint here in Arizona.



Brown recluse
Loxosceles reclusa

A "romantic diagnosis"

Arizona recluse
Loxosceles arizonica

Apache Recluse
Loxosceles apachea

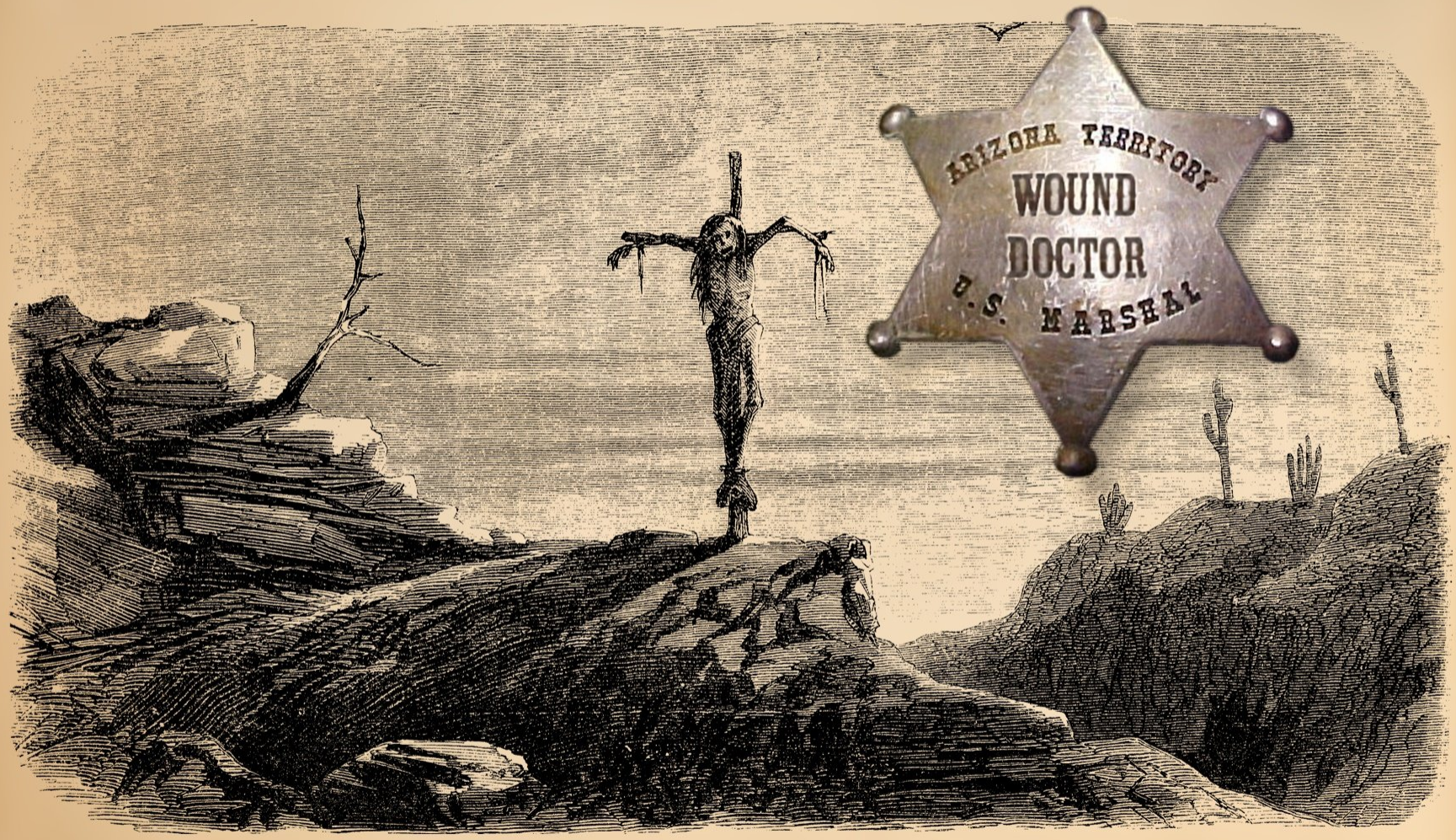
Desert Recluse
Loxosceles deserta

Tucson Recluse
Loxosceles sabina

Grand Canyon Recluse
Loxosceles kaiba

Vetter RS, Myth: idiopathic wounds are often due to brown recluse or other spider bites throughout the United States. Western Journal of Medicine 173:357-358, 2000.

ALL GOOD CARE STARTS WITH PROPER DIAGNOSIS



R.I.P. SQUARE PEG IN ROUND HOLE OF MISDIAGNOSIS

EDITORIAL ABOUT MODERN WOUND PRACTICE

1

Chronic and pathological wounds (CAP wounds)
represent a distinctive class of disease and clinical activity.

2

There is a non-expert legacy misunderstanding of wounds that focuses only on trauma and a few standard categories of CAP wounds - arterial, venous, pressure, diabetes.

3

Legitimate purveyors, professors, and practitioners of this specialty must have the professional level of knowledge required to master these diseases. Like all specialties, this starts with an understanding of the full spectrum of relevant pathologies.

4

What are often dismissed as "atypical wounds" are not atypical at all.
In fact, they are the core of chronic and pathological wounds, and they are far more abundant and significant than naives and non-experts perceive.

AN INTRODUCTION TO PATHOLOGICAL WOUNDS

DISORDERS AND DISEASES OF THE WOUND HEALING PROCESS

CAP WOUNDS

Chronic and Pathological

1 - Wounds caused by chronic illness or pathology.

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

WOUND DIAGNOSIS

CHRONIC WOUND CAUSES & PATHOLOGIES

Arterial
Micro-occlusive
Micro-angiopathies
Hemopathologies
Hypercoagulable
Venous
Immunopathies & CVD-CTD
Panniculopathies
Dermatoses
Diabetes
Neuropathy

Pressure
Mechanical
Metabolic
Toxic & chemical
Physical & energy
Cancer
Infectious
Genetic
Factitious & iatrogenic
Mixed diagnoses
Unknown

IF MOST WOUNDS HAVE AN EXTRINSIC CAUSE OR PATHOLOGY, WHAT THEN ARE THE INTRINSIC DISEASES OF WOUND HEALING?

CAP WOUNDS

MAJOR UNDERLYING PATHOLOGIES

ZEROING IN ON THE INTRINSIC DISEASES OF WOUND HEALING

THROMBO-INFARCTIVE

Micro-occlusive

Micro-angiopathies

Hemopathologies

Hypercoagulable / Coagulopathic

INFLAMMATORY-LYTIC

Autoimmune

Collagen Vascular Diseases

Connective Tissue Disorders

Lymphoreticular / Reticuloendothelial

X-A

BASIC REVIEW

HYPER COAGULABLE ULCERS

HYPERCOAGULOPATHY

NOMENCLATURE OF THROMBO- & MICRO-OCCLUSIVE DISORDERS

hemodynamic disorders	vessels, blood, & coagulation normal **fluid dynamics abnormal**	Examples: arteriovenous malformations vascular compression, atrial fibrillation
endo-vasculopathies	blood & coagulation normal **vessels abnormal**	Examples: small vessel atherosclerosis thromboangiitis, alloplastic implants
exo-vasculopathies	blood & coagulation normal **vessels abnormal**	Examples: calcium-phosphate disorders, immunopathies & connective tissue disorders
non-hypercoag hemopathologies	vessels & coagulation normal **blood abnormal**	Examples: red cell & platelet abnormalities, hemoglobinopathies, dys- & cryoproteinemias
hypercoagulability	vessels & blood normal **coagulation abnormal**	disorders of the coagulation system intrinsic: the prethrombotic disorders extrinsic: examples - estrogens, cancer

Key Syndromic Features

thrombotic - embolic events • miscarriages • wound pathergy

connective tissue disorder • family history

Prethrombotic Disorders

factor V Leiden
other f.V mutations
prothrombin mutation
antithrombin III
protein C
protein S
fibrinogen
plasminogen
warfarin

Related Disorders

antiphospholipid antibodies
anticardiolipin
lupus anticoagulant
homocysteine disorders
estrogens, pregnancy

Disease Associations

inflammation
connective tissue disorders
acute & chronic venous
cancer (Trousseau)
parox. noct. hemoglobinuria

Macrothrombosis

Acute Large Vessel

overt life-and-limb threatening events

cava-tibial venous thrombosis
aorto-tibial arterial thrombosis
other peripheral thrombosis
coronary artery thrombosis
cerebrovascular thrombosis
pulmonary embolism
intracardiac thrombosis
graft and valve 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)

Microthrombosis

Subacute, Chronic, Recurring

perplexing refractory problems of non-obvious origin

vascular occlusion not overt
secondary clinical events
underlying causes elusive

miscarriage
complications of trauma & surgery
non-healing ulcers
non-immune glomerulonephritis
primary pulmonary thrombosis
warfarin necrosis
complications of contraceptives

chronic, recurring
refractory to Rx
long history of failed Rx
young age
family history
warfarin resistance

HYPERCOAGULOPATHY RECOGNITION & DIAGNOSIS

HYPERCOAGULABLE ULCERS HAVE NO PATHOGNOMONIC FEATURES, BUT THEY DO HAVE A DISTINCTIVE APPEARANCE.

APPEARANCE
ischemic infarction
periwound stasis
active ulceration
edema absent
inflammation absent
mixed wound module

good pulses
no signs of other dx

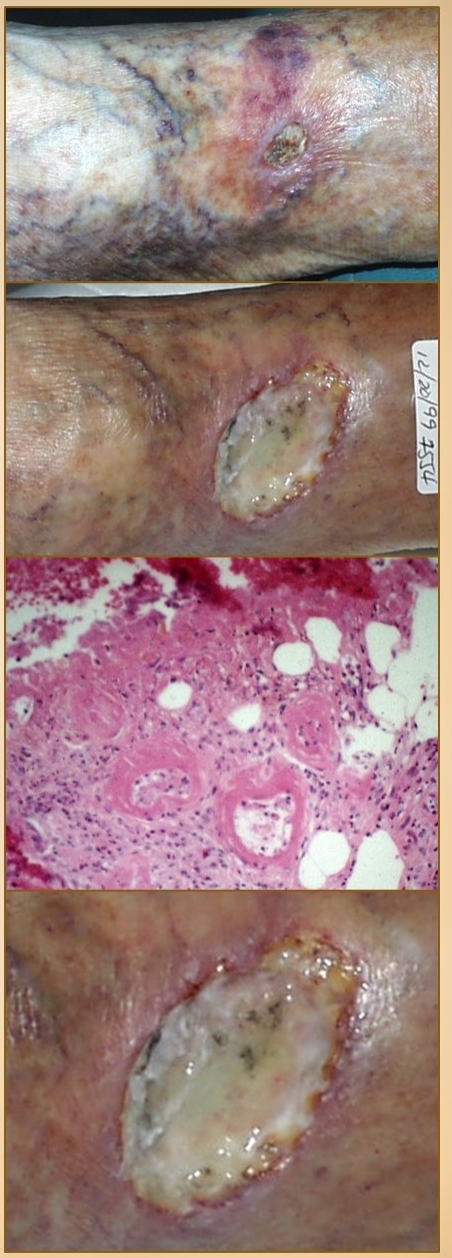
RESPONSE TO WRONG RX
pathergy
necrosis
dehiscence
failed response

DYNAMICAL BEHAVIOR
impaired wound
behavior characteristic
of severe ischemia

recalcitrant
continuously pathological
persistent active:
necrosis
pathergy
active ulceration

misbehavior over time

rapid evolution
slow resolution



RECOGNITION & DIAGNOSIS
- LABORATORY -

HYPERCOAGULABLE STUDIES

Factor V Leiden
prothrombin mutation
antithrombin III
protein C
protein S
fibrinogen
DIC screen
plasminogen
homocysteine
lupus anticoagulant
anticardiolipin
cryoglobulins
cryofibrinogen

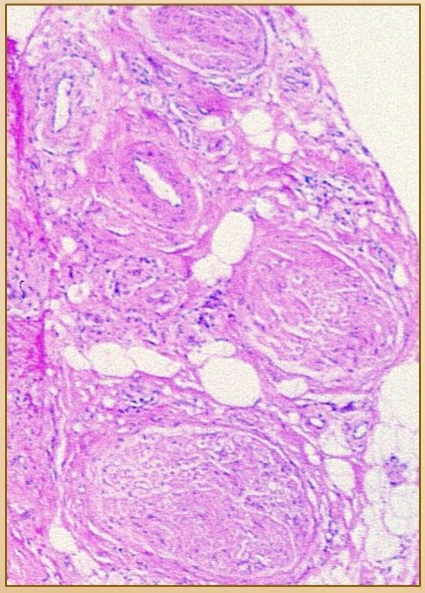
SCREEN FOR CONNECTIVE TISSUE DISORDERS

sedimentation rate
CRP
ANA
anti-DNA
rheumatoid factor

OTHER STUDIES

TcPO2
laser doppler

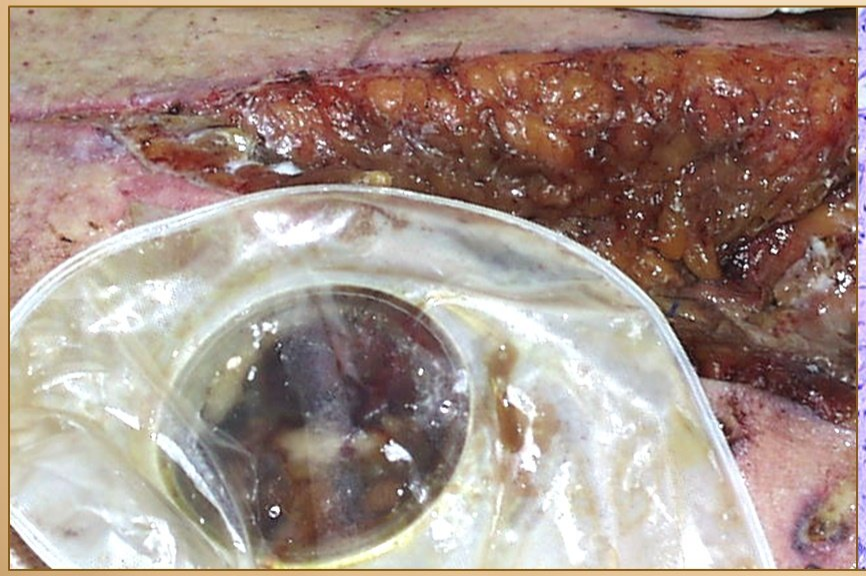
Biopsy and Histology
microthrombi
aggregates
minimum inflammation
microvasculopathies
vascular fibrosis
stenosis
vasculitis

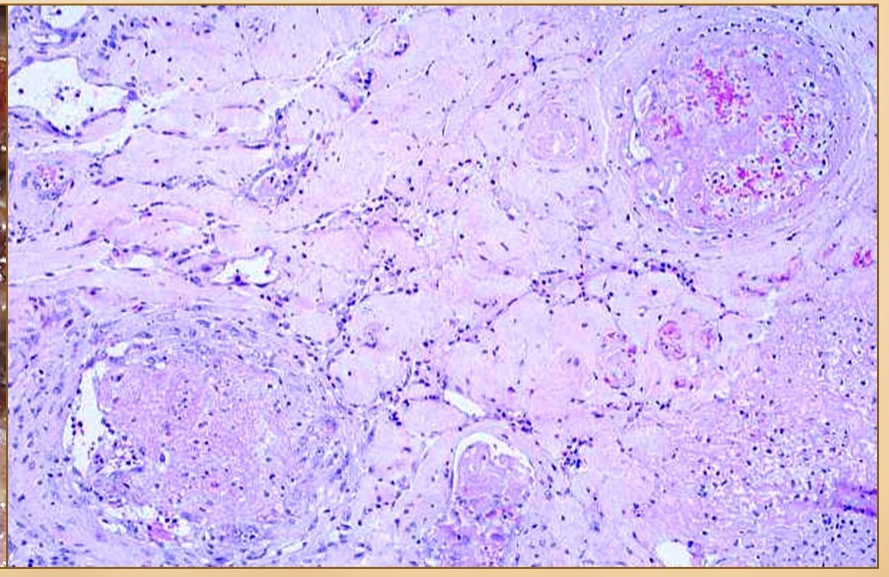


Hypercoagulable ulcers are NOT diagnoses of exclusion.

These diagnoses can be made on specific criteria.

HYPERCOAGULOPATHY
- BAD OUTCOMES -





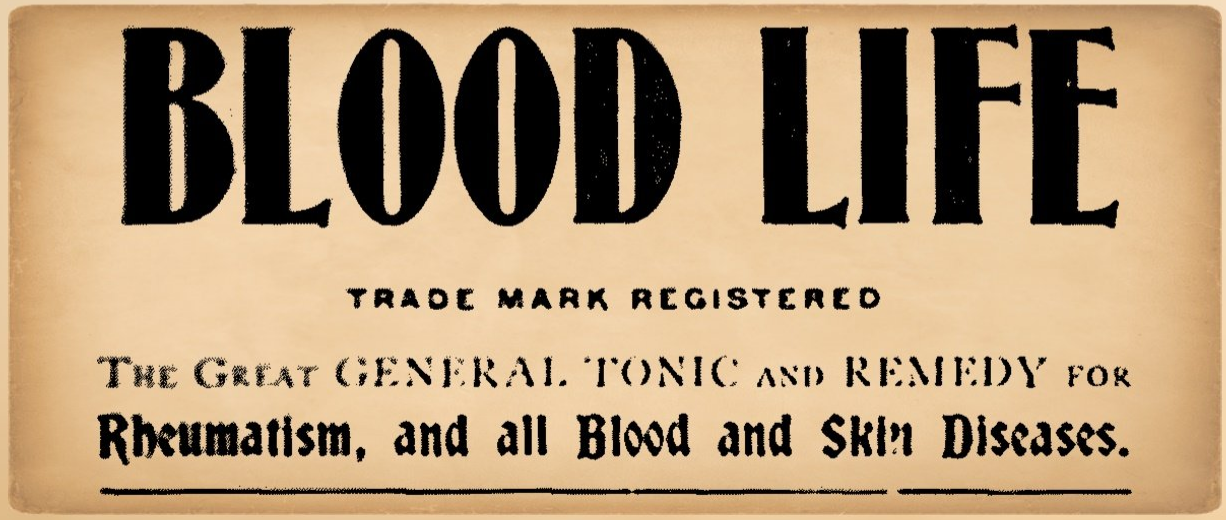
HYPERCOAGULOPATHY
- GOOD OUTCOMES -

KEY SYNDROMIC FEATURES

thrombotic - embolic events
miscarriages
wound pathergy
connective tissue disorder
family history

SUMMARY 1-A

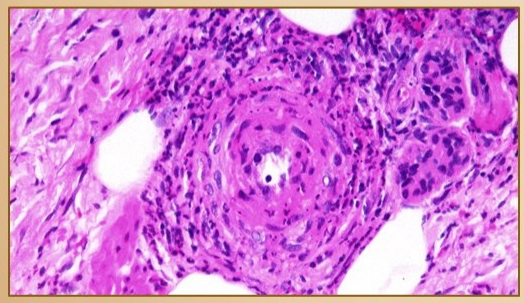
The hypercoagulable disorders and ulcers are a major category of chronic wounds and wound pathology, under appreciated, but overly important.

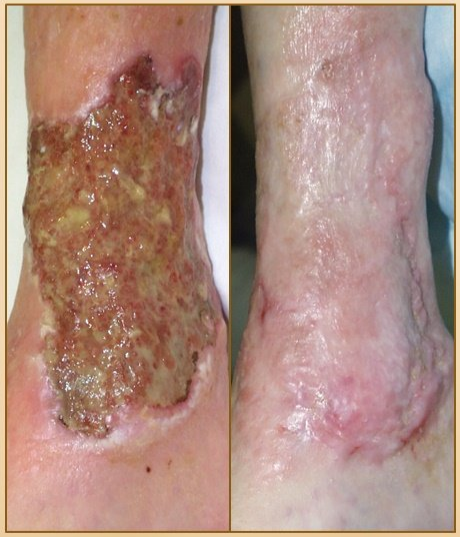


X-B

BASIC REVIEW

IMMUNE ULCERS & CLASSIC IMMUNE DISORDERS





Immunopathies, Spectrum of Disease

Connective Tissue Disorders

rheumatoid
lupus
sjögren's
scleroderma
polymyositis
mctd (mixed)
uctd (undiff'ed)
ank. spondylitis
behçet's
wegener's
sarcoidosis
fam. med. fever

Vasculitides

polyarteritis nod.
autoimmune
giant cell
hypersensitivity
thromboangiitis

Fasciitis & Panniculitis

weber-christian
nodular fasciitis
erythema nodosum
necrobiosis
lipoidica

Miscellaneous

crohn's
ulcerative colitis
others

Inflammatory Dermatoses

eczema
pyoderma
gangrenosum
erythema nodosum
pemphigus / -goid

Immunopathies, Features and Findings

General and Common Findings	Findings by System	Distinctive and Unique Findings
arthropathies rashes ulcers neurological abnormal serology	musculoskeletal renal & pulmonary cardiac & vascular blood & immune cns & eye	crst sicca pathergy necrotizing synovitis necrotizing vasculitis
Findings by Disease	**Disease Associations**	**Other Tip-Offs**
rheumatoid lupus scleroderma sjogren's polymyositis	hypercoagulability venous arterial disease neuro-psych many misdiagnoses	multiple allergies drug hypersensitivity photosensitivity malar rash nasal perforation

Immunopathic Ulceration . . . Physical Findings

Pre-Ulcerative

inflammation
edema
dermatitis
panniculitis

vascular stasis
congestion
infarction

systemic sx
malaise
athralgias, etc.
pain

distribution
focal
multifocal

Immunopathic Ulceration . . . Physical Findings

Acute & Early Ulcers

necrosis & ulceration

focal vs. multifocal

immune lysis vs. microthrombotic infarction

inflammed vs. bland

vasculitis & synovitis

general

inflammation
dermatitis
panniculitis
vascular stasis
systemic sx
pain

Immunopathic Ulceration . . . Physical Findings

Late & Chronic Ulcers

persistent inflammation

progressive ulceration

retarded wound module

chaotic behavior

pain & symptoms

Immunopathic Ulceration . . . Physical Findings

Other Distinctive Findings

ulceration
along tendons

unstable scars
lysis & ulceration

not just gaiter
not just leg

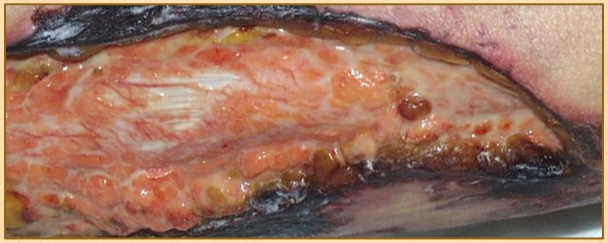
skin atrophy
skin sclerosis

post-op & -injury
pathergy

features of
each disease

Immunopathic Ulceration . . . Physical Findings

What is NOT There



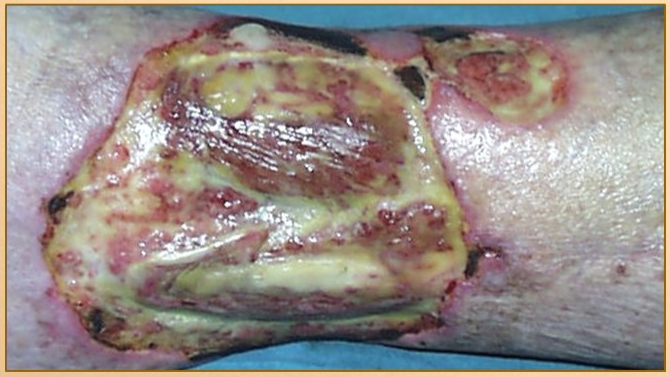
no venous

no arterial

no eschar

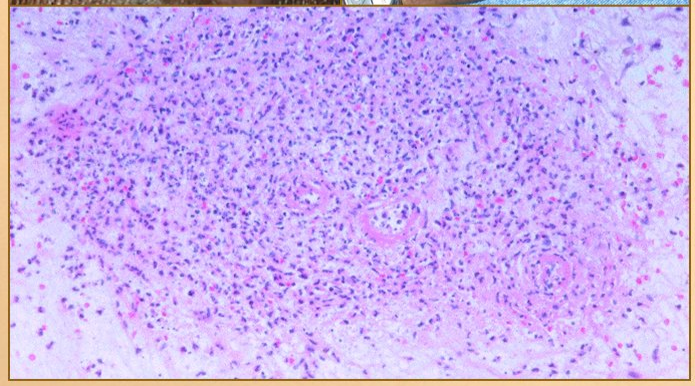
no wound module

age & risks



Immunopathic Ulceration . . . Physical Findings

General Exam & History



general physical exam

common signs of immunopathy

inflammatory state

arthropathies

neurolepsy & neurological

malaise & systemic

laboratory histology

history & system review

disease history
family hx
Rx history

steroids lowered

complications of trauma or surgery

disease associations

vasculopathies
hypercoagulopathy
neurological
renal
pulmonary

Immunopathic Ulceration . . . Physical Findings

Treatment History

no response
failed Rx
multiple failed Rx
surgery failures

adverse response
disease flare-up
surg. complication
atopic dermatitis
atopic vasculitis

correct response
steroids
anti-immune
anti-inflammatory

contrary response
cytokines

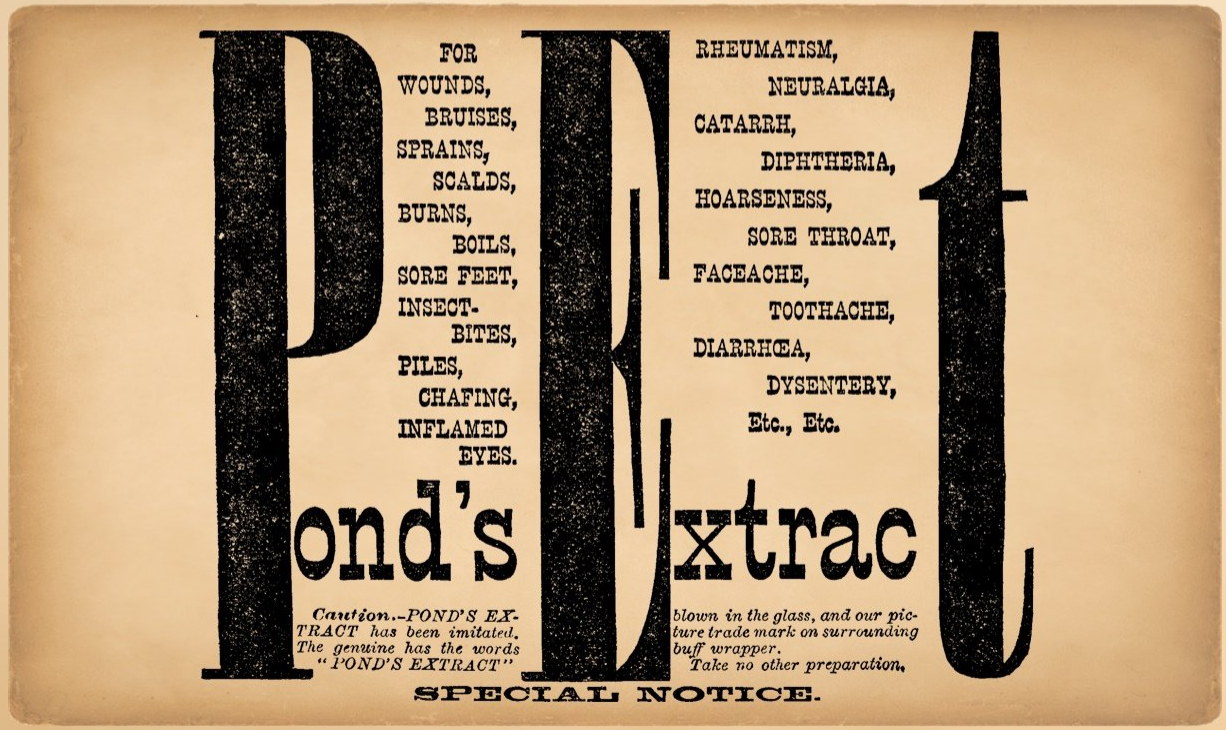
SUMMARY I-B

The "rheumatoid" and immunopathic ulcers are a major category of chronic wounds and wound pathology, under appreciated, but overly important.

I-C

- BASIC REVIEW -

THE COMMONALITY OF THE CONNECTIVE TISSUE DISORDERS



THE DIAGNOSIS AND MISDIAGNOSIS OF WOUNDS

AUTO-IMMUNOPATHY & THE CONNECTIVE TISSUE DISORDERS

RHEUMATOID WOUNDS

THE DIAGNOSIS AND MISDIAGNOSIS OF WOUNDS

AUTO-IMMUNOPATHY & NON-RHEUMATOLOGY DISORDERS

DERMATOSES AND PANNICULOPATHIES



15 g

NDC 51672-1270-1

Desoximetasone Cream USP, 0.25%

FOR EXTERNAL USE ONLY.
NOT FOR OPHTHALMIC USE.

CAUTION: **Federal law prohibits dispensing without prescription.**
Keep this and all medication out of the reach of children.

Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.

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Hawthorne, NY 10532

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ULCERATIVE DERMATOSES AND PANNICULOPATHIES

ULCERATIVE DISORDERS and WOUNDS

SKIN DISEASES and DERMATOLOGICAL PRACTICE

Inflammatory, suppurative, necrotizing, & ulcerative disorders of the skin and adipose fascias, mostly immunopathic in origin.

Dermatoses
- Eczema
- Pyoderma
- Pemphigus
- Pemphigoid
- Sweet's

Panniculitis
- Weber-Christian
- Erythema nodosum
- Necrobiosis lipoidica
- Eosinophilic

CTD-CVD
- Lupus
- Poly-dermatomysositis
- RA / granuloma annulare
- Scleroderma / CRST
- Behcet's
- Crohn's

Vasculitis
- Leukocytoclastic
- Polyarteritis

Miscellaneous
- Uncategorized
- Drug eruptions

. . . AND MANY MORE . . .

Spectrum of severity
Steroid responsive
Anti-inflammatory rx
Anti-immune rx

Autoimmune Disorders

Classic connective tissue disorders
Synovitis & arthropathies
Dermatoses & panniculopathies
Inflammatory bowel disease
Bowel-dermatosis-arthritis (badas)
Autoimmune hepatitis & biliary
Autoimmune thyroiditis
Autoimmune aspects of diabetes
Rheumatic carditis
Autoimmune neuropathies
Autoimmune myopathies
Myasthenia gravis
Multiple sclerosis
Sarcoidosis
Granulomatous disorders
Autoimmune arteritides
Venous vasculitis
Autoimmune sialoadenitis
Autoimmune nephritis
Polyserositis
MCTD
NCTD

**Rheumatology, Dermatology,
Allergy & Immunology, Hematology
Gastroenterology, Neurology, Nephrology,
Endocrinology, Cardiology, Pulmonary**

Concept of a common autoimmune disease

MCTD

Mixed connective tissue disorder

NCTD

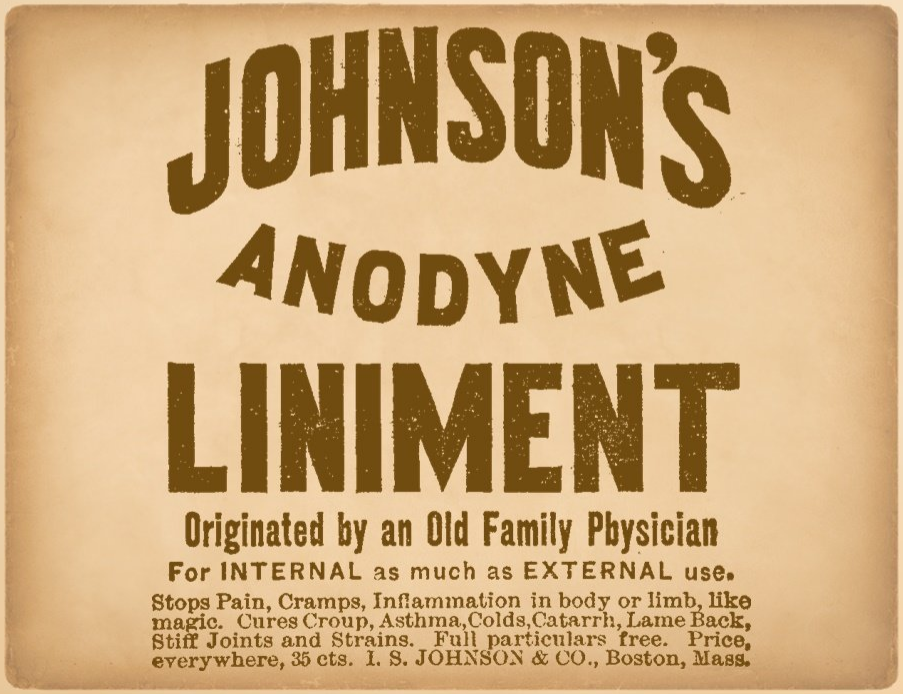
Non-specific connective tissue disorder

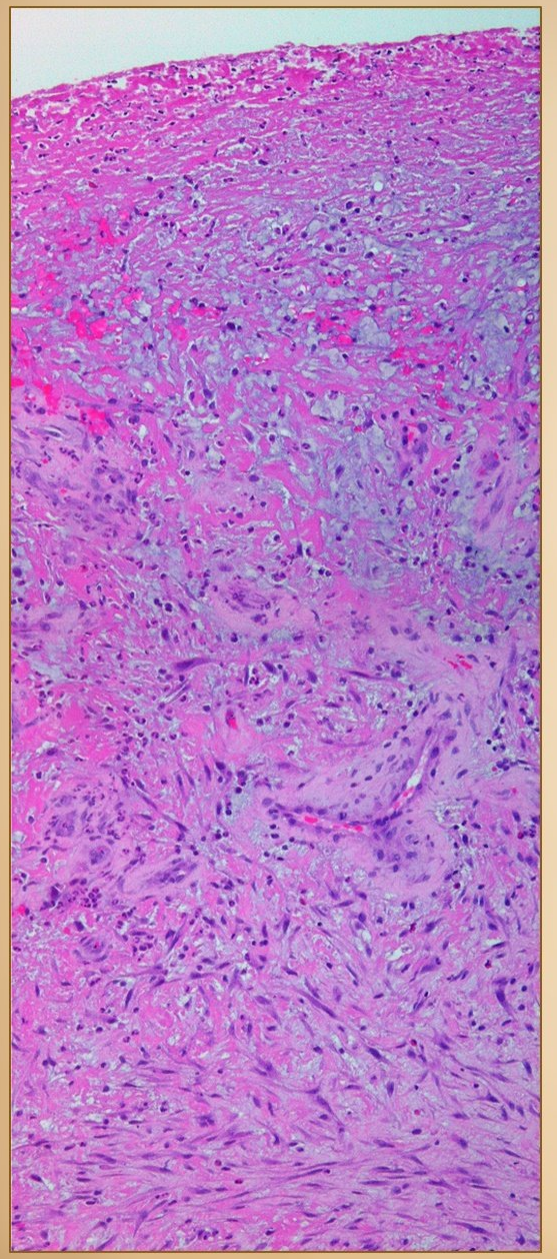
SUMMARY 1-C

Autoimmune disorders are manifest in a variety of distinctive syndromic patterns. They are thus classified by an accepted nosological nomenclature, but this is artifice.

They are in many ways a single disease, and all can be considered MCTD - NCTD.

- BASIC REVIEW -
WOUND HEALING BIOLOGY





THE WOUND MODULE

OF PROLIFERATIVE REPAIR

and the

CLINICAL SIGNS OF WOUND HEALING

0
injury
inflammation

1
inflammation
subsides

2
macrophages,
eschar separation,
cytokines

3
ground substance,
mucus

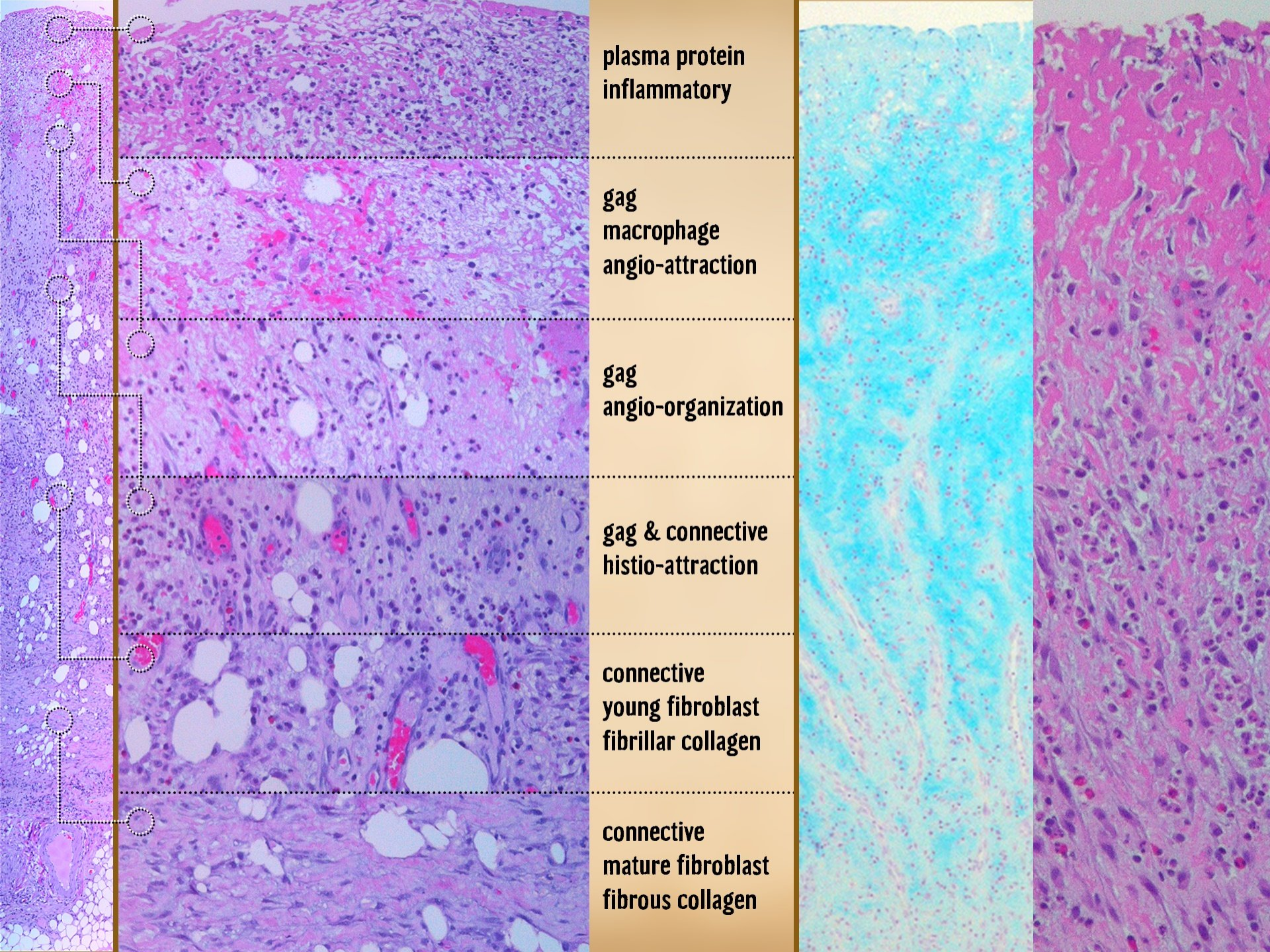
4
"granulation"
angiogenesis

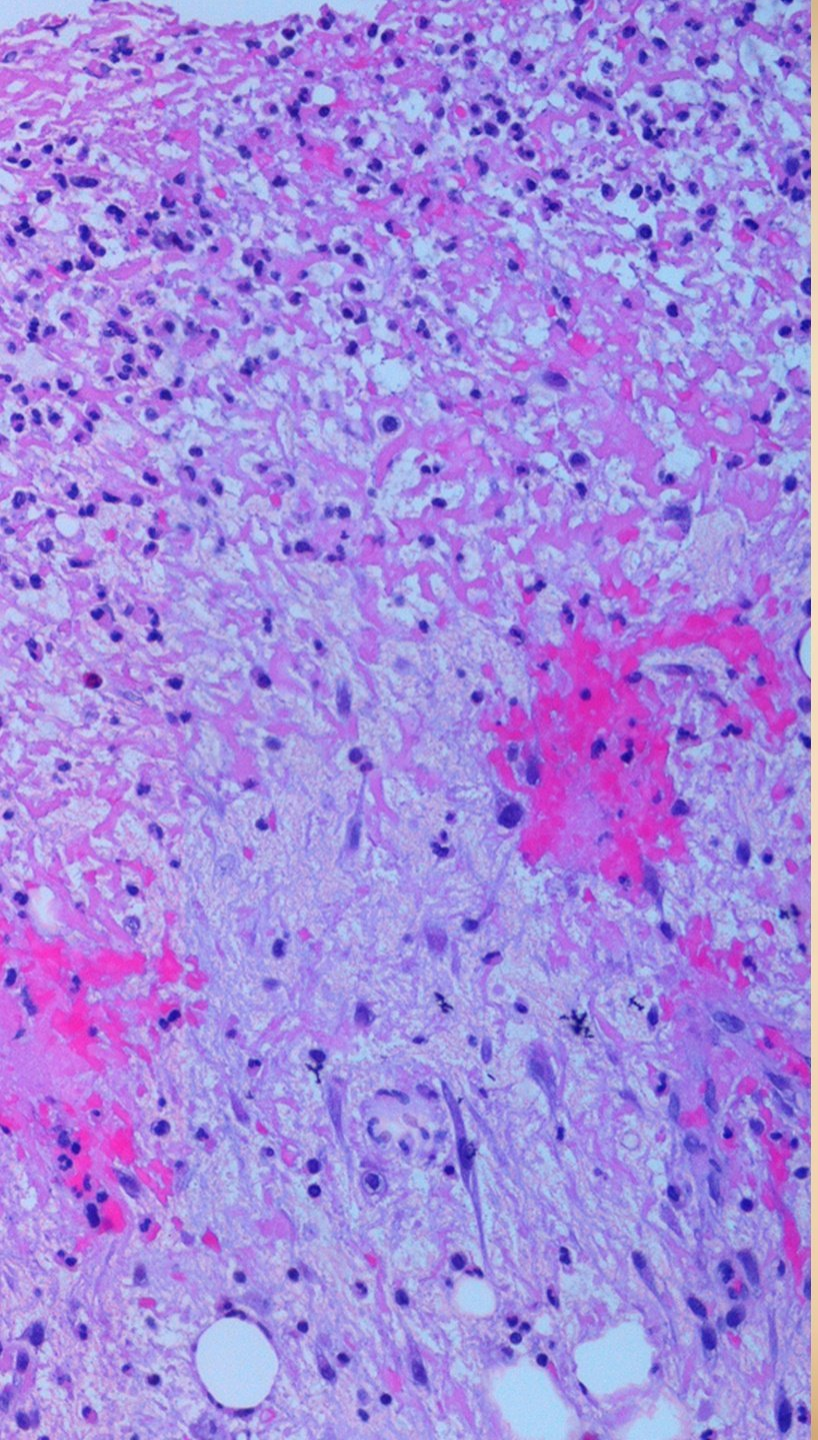
5
histioblasts, fibroblasts,
fibroplasia

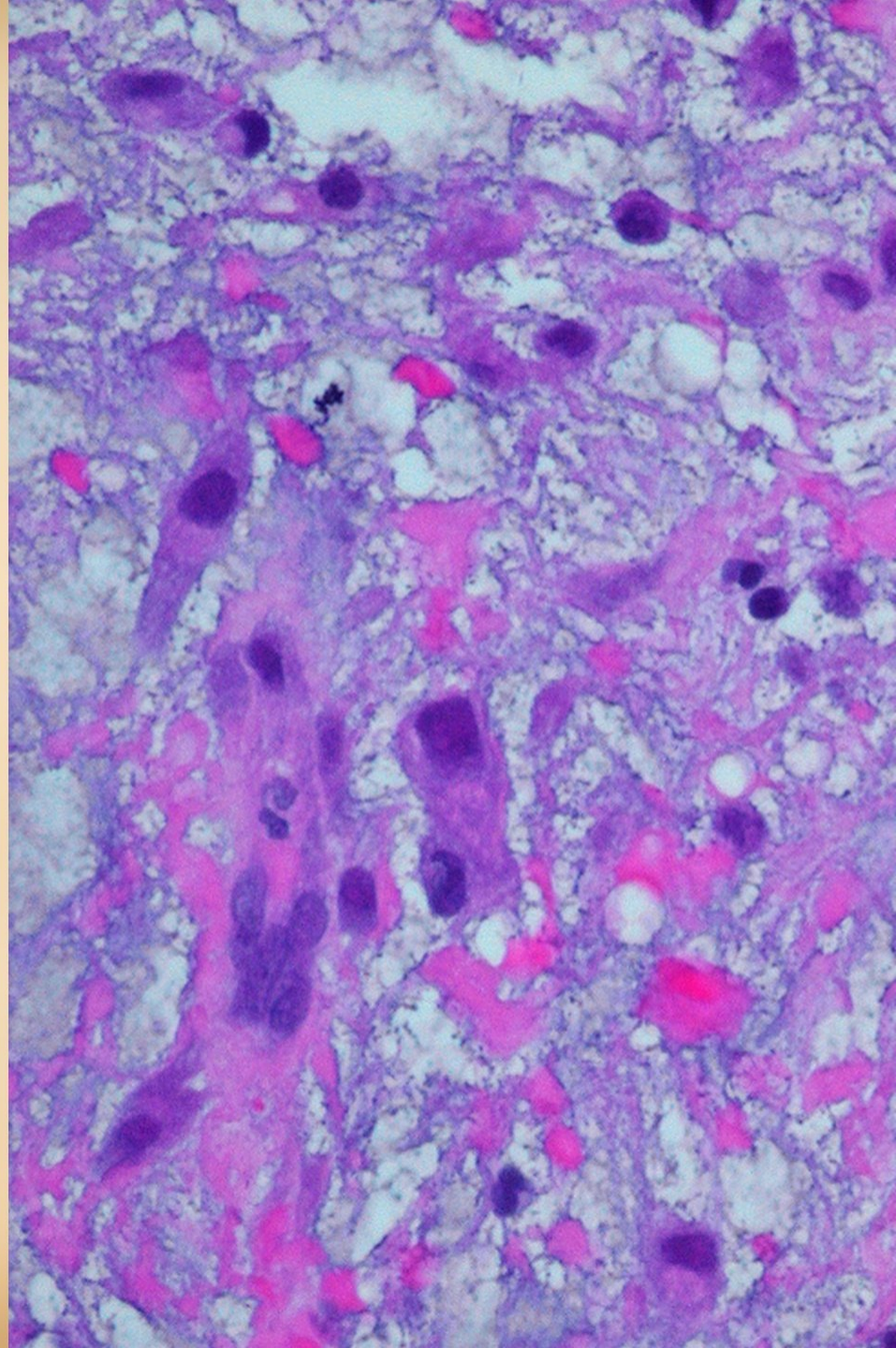
6
myofibroblasts
contraction

7
epithelialization

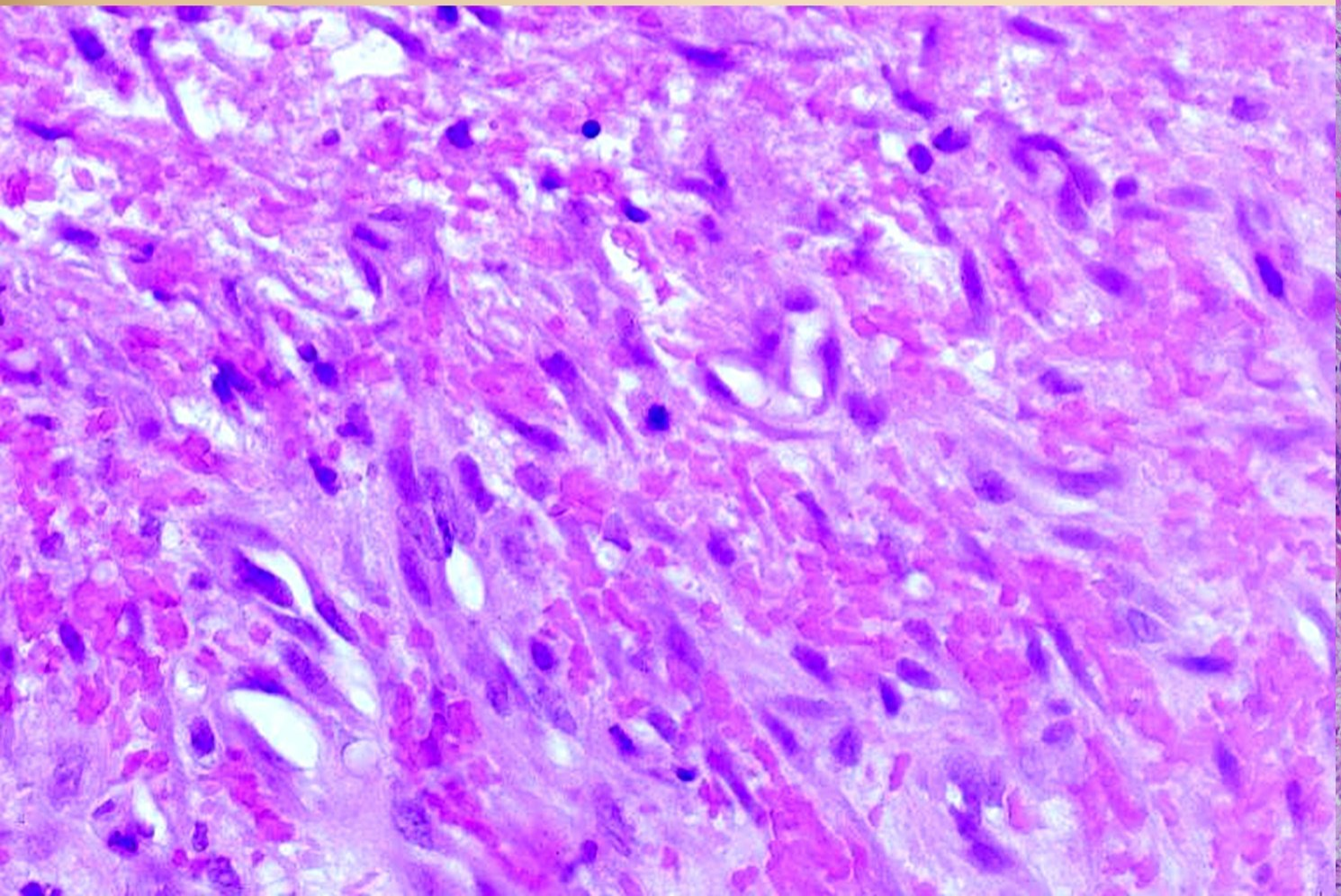
8
maturation

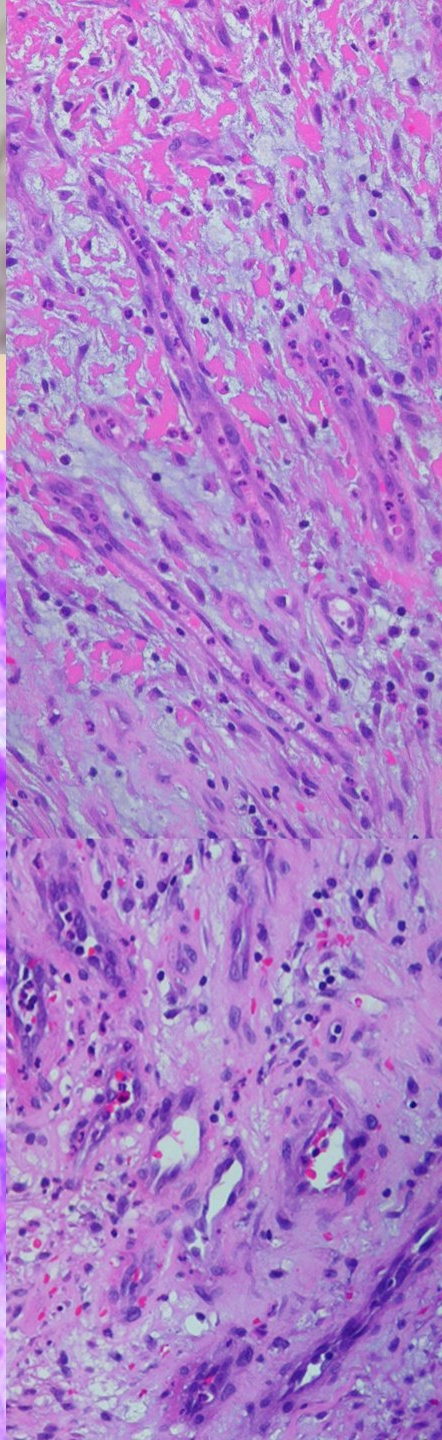

plasma protein
inflammatory
gag
macrophage
angio-attraction
gag
angio-organization
gag & connective
histio-attraction
connective
young fibroblast
fibrillar collagen
connective
mature fibroblast
fibrous collagen

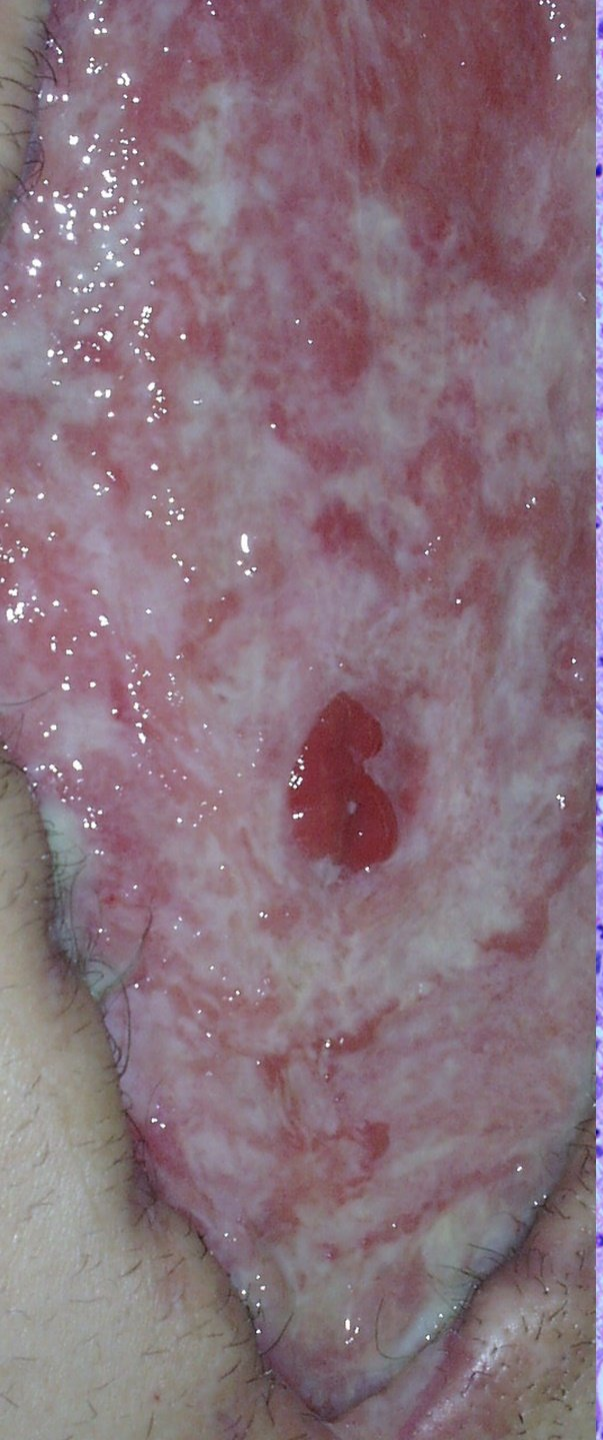
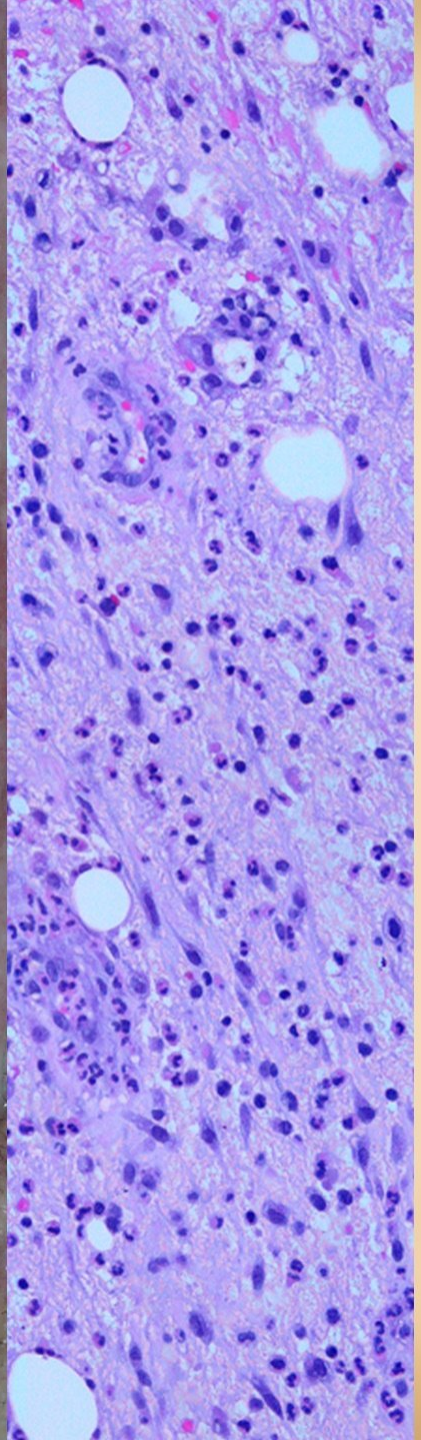
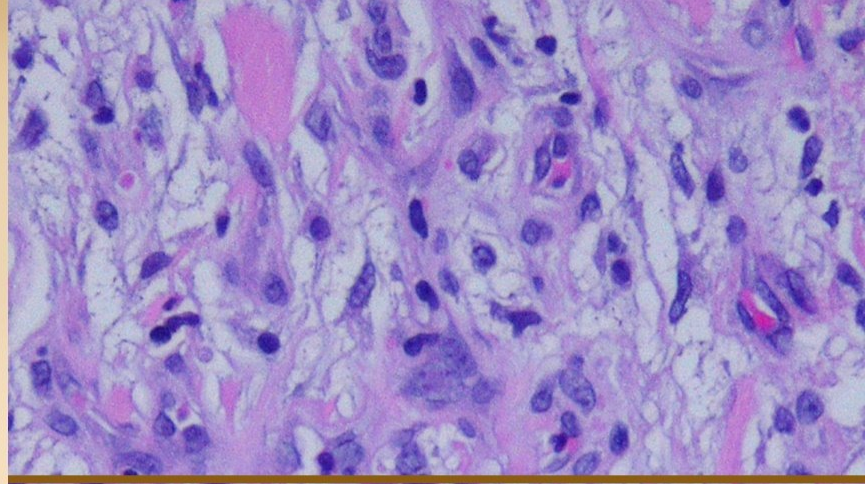
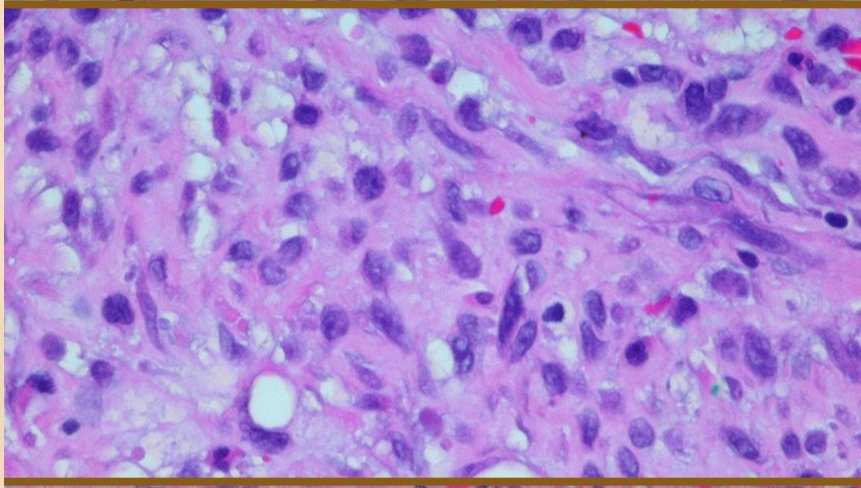
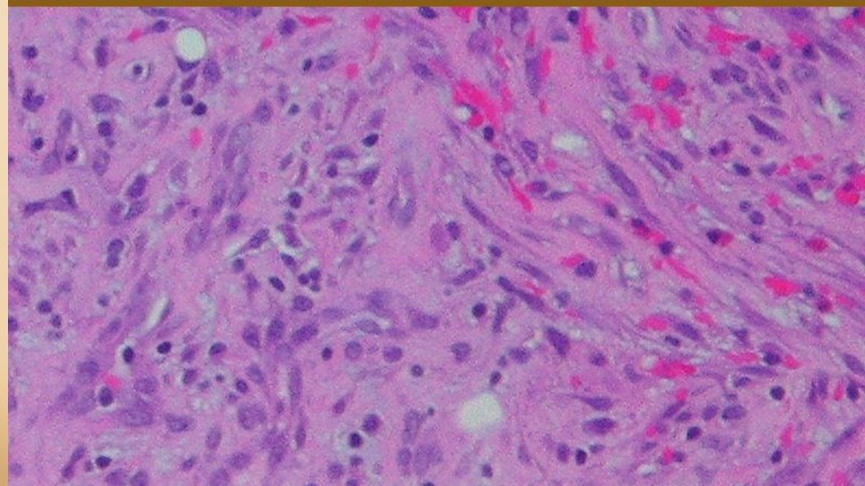


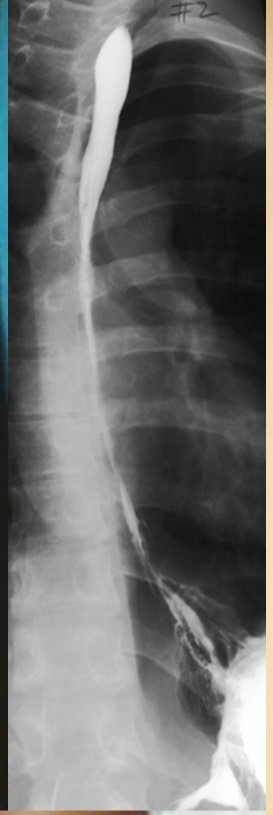


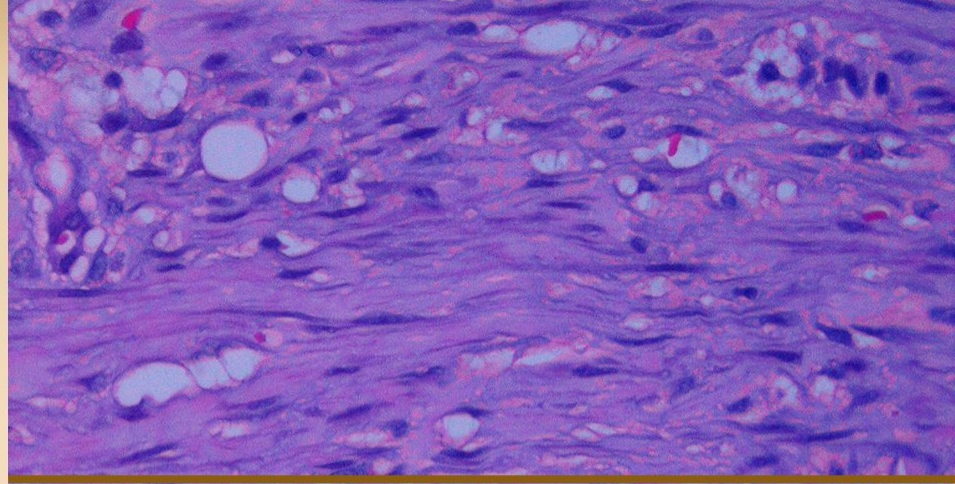
Focus on 2 cell types: *angiocytes & fibroblasts*

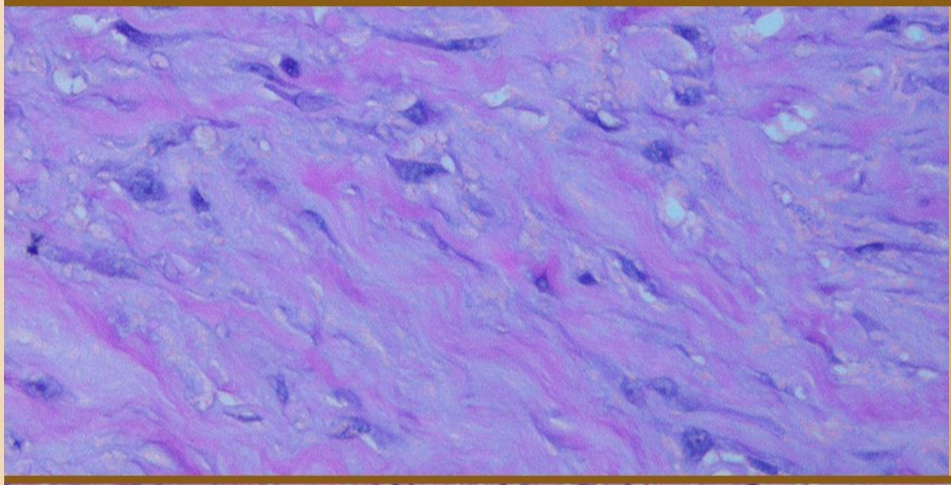


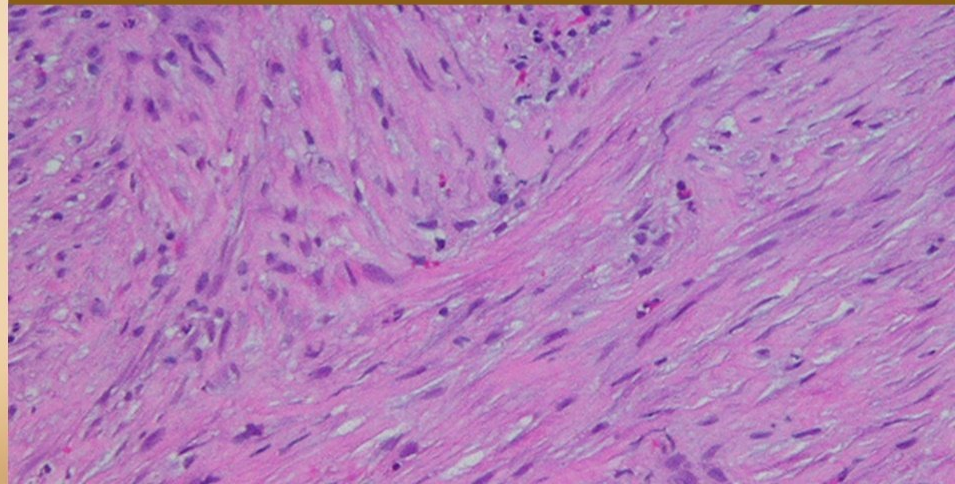


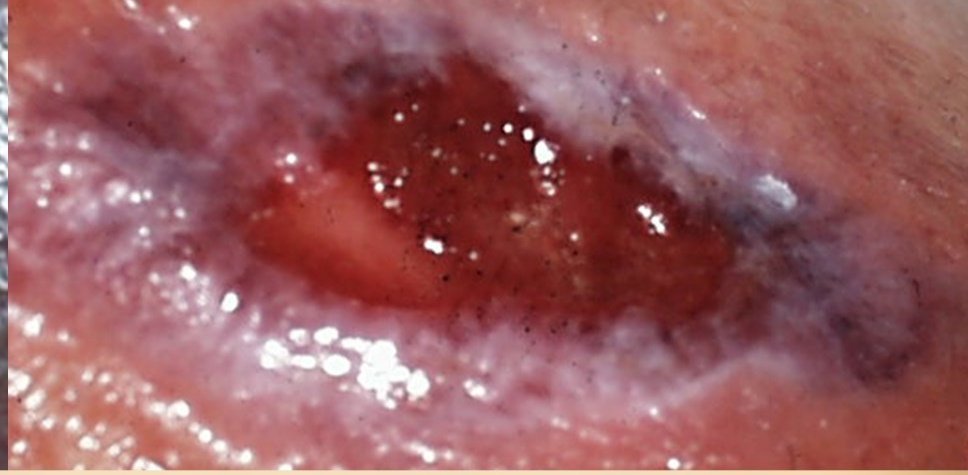
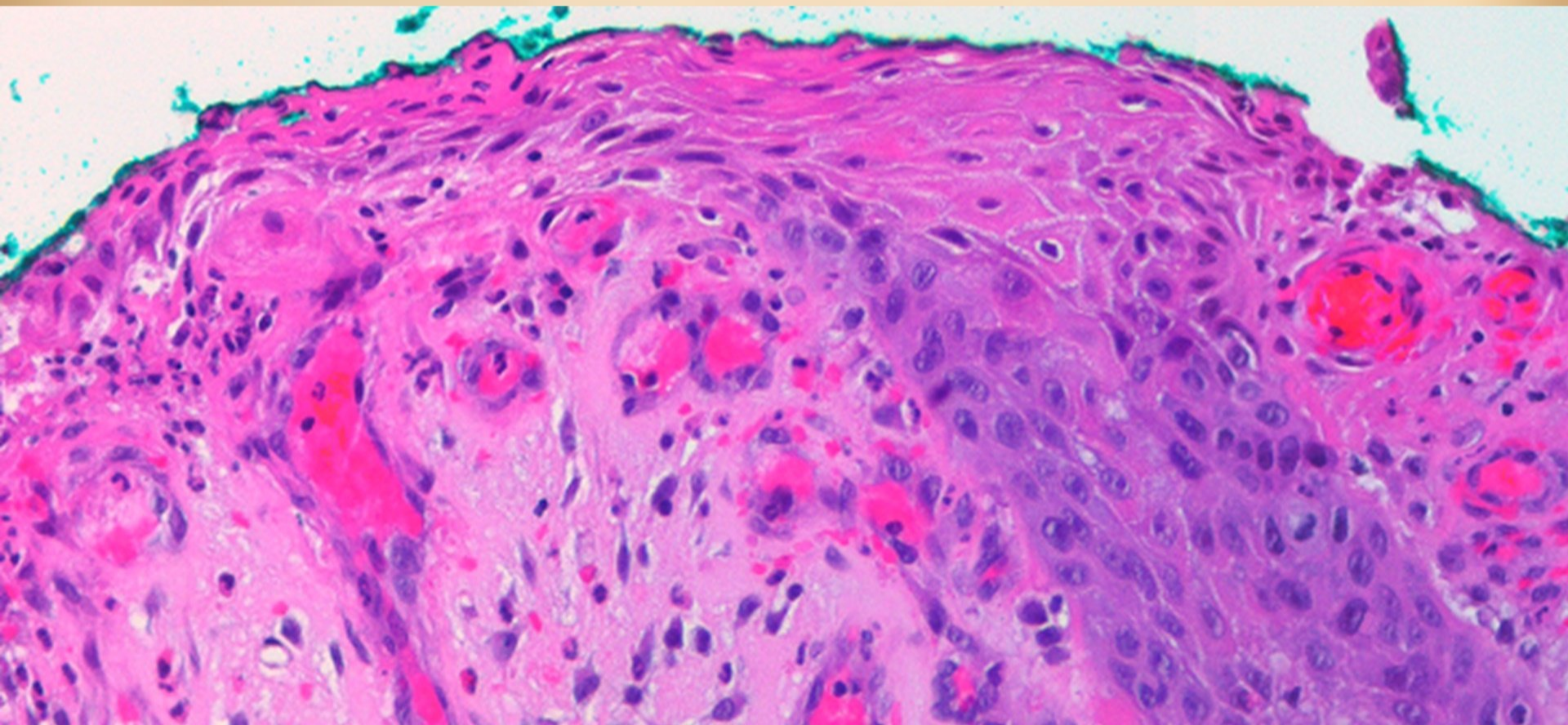


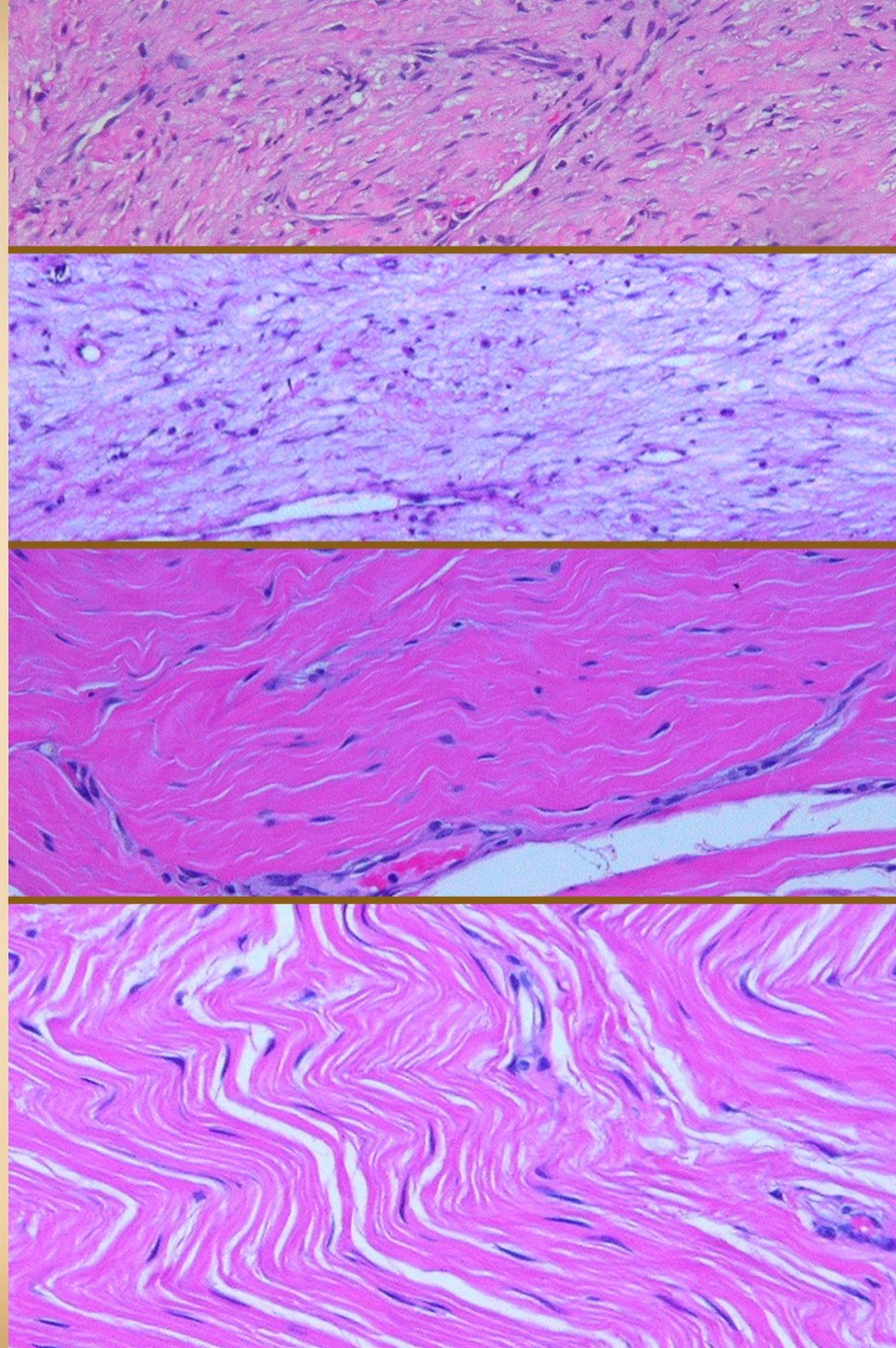










SUMMARY I-D

The mesenchymal component of normal wound healing is the proliferative *wound module* of post-inflammatory repair.

This process depends on just 2 types of cells:
***histio-fibroblasts* & *vascular angiocytes*,**
which create the vascular and connective structures which constitute the new stromal tissue.

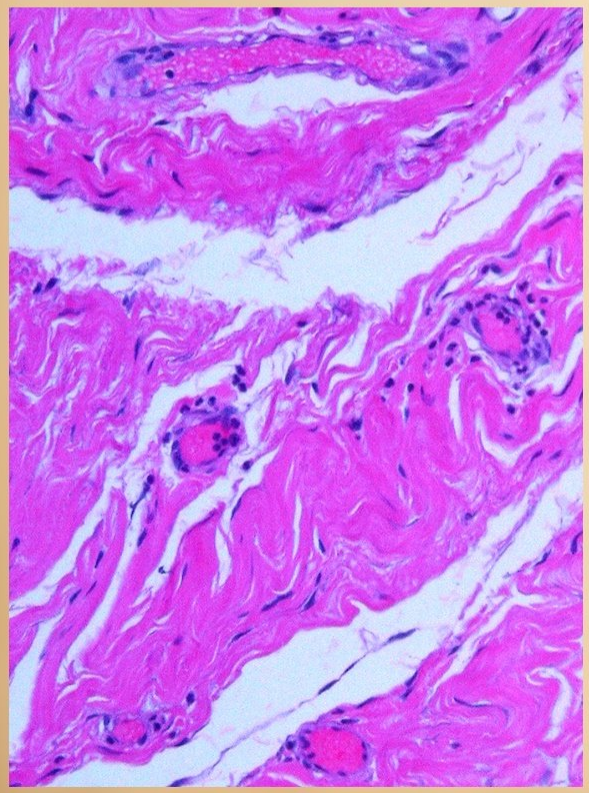
2-A

- AUTOIMMUNITY -

&

Collagen Vascular - Connective Tissue PATHOLOGY

WHY ARE THESE CALLED "COLLAGEN-VASCULAR DISEASES" "CONNECTIVE TISSUE DISORDERS"

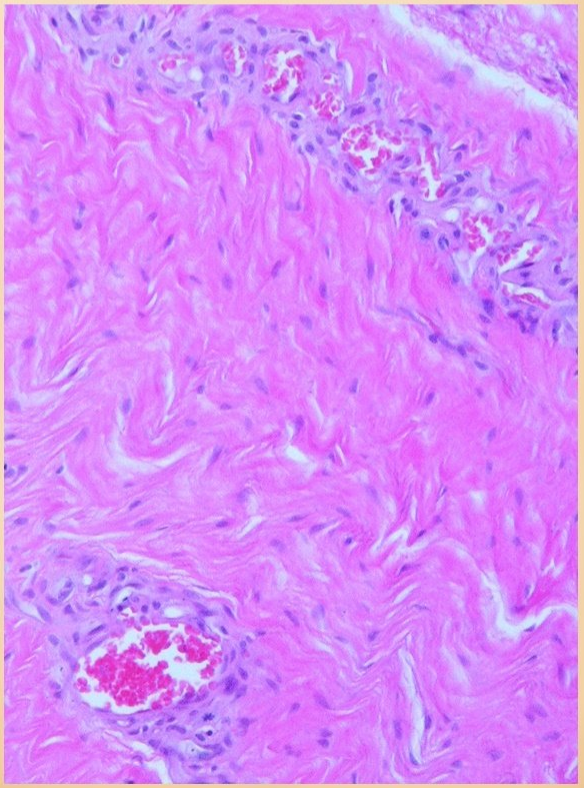


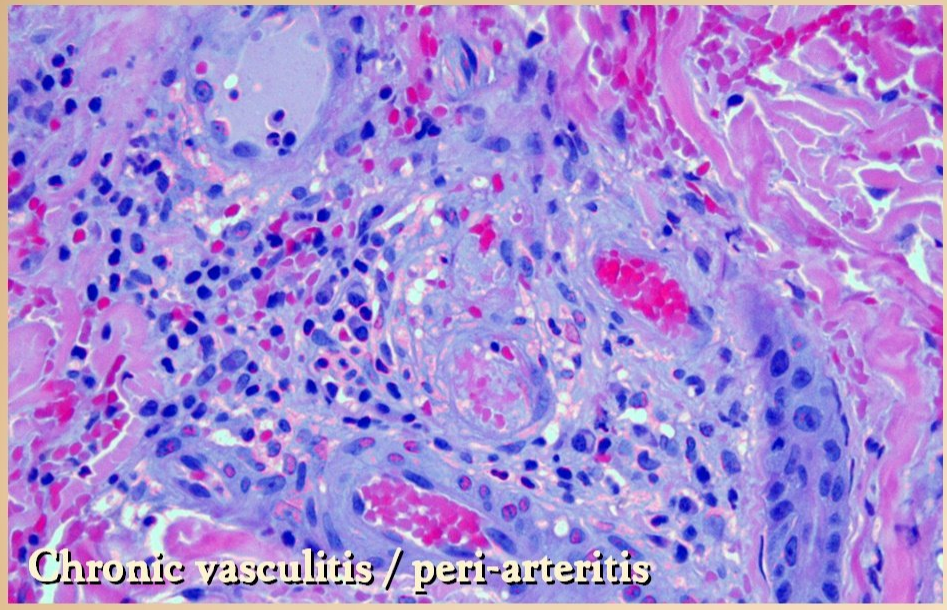
Mesoderm
Mesenchyme

Soft Tissue
Stroma

Histioblasts
Fibroblasts
Angiocytes

Connective tissue (collagen)
Blood vessels (vascular)

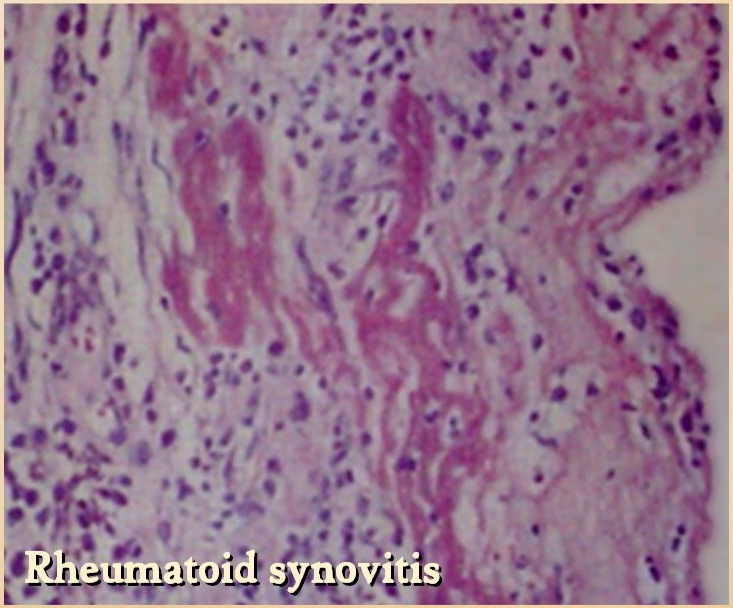



Chronic vasculitis / peri-arteritis

The stromal tissues, engineered by the mesenchymal cells of the mesoderm, predominantly histioblasts-fibroblasts and angiocytes, are composed of collagen and connective proteins, traversed by blood vessels and vascular structures.

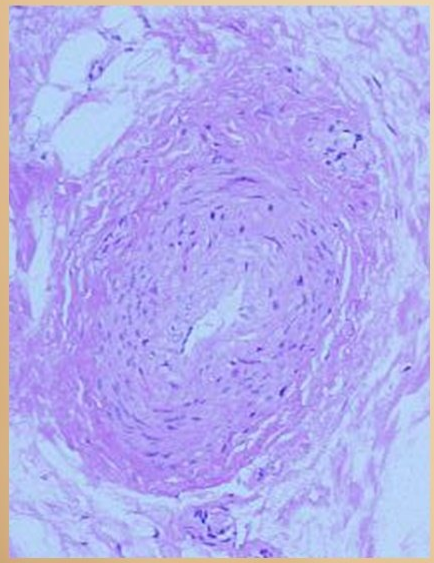
These cells, structures, and tissues are often the target of the autoimmune disorders and immunopathies.


Acute leukocytoclastic vasculitis


Rheumatoid synovitis




Acute and chronic damage to mesenchymal, musculoskeletal, and stromal structures.




TARGET TISSUES & EFFECTS

OF THE AUTO-IMMUNE CONNECTIVE TISSUE DISORDERS

Mesoderm
Mesenchyme

Soft Tissue
Stroma

Histioblasts
Fibroblasts
Angiocytes

Connective tissue
(collagen)

Blood vessels
(vascular)

From the Mesoderm / Mesenchyme

Synovium (RA)
Scar (Lupus complications)
Panniculitis (Sjogren's, Weber-Christian)
Polyserositis (Lupus, Weber-Christian)
Muscle (Polymyositis, PMR,CREST)
Ligament & tendon (RA, MCTD)
Vessels (Vasculitis)

Dermis, sclerosis (Scleroderma)
Dermis, lysis (Ulcer)

WOUNDS

Targets Against Ento-Ectoderm

(liver, kidney, adenoid, epidermis, etc.)

SUMMARY 2-A

Why are these called "Collagen-Vascular Diseases" and "Connective Tissue Disorders" ?

. . .

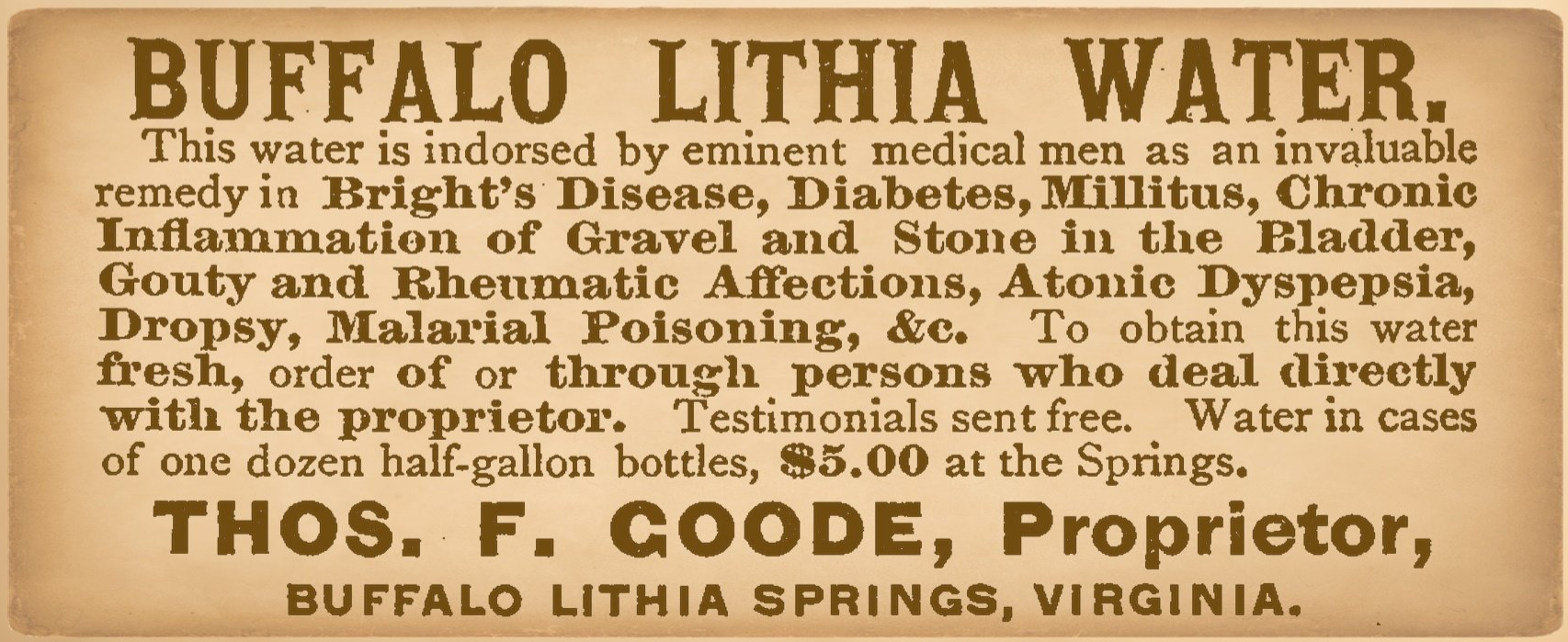
Because the immune events and targets affect the mesenchymal cells which constitute the stroma of all tissues, the connective tissues and blood vessels, composed predominantly of fibroblasts & angiocytes.

2-B

- AUTOIMMUNITY -

& ORIGINS OF

Collagen Vascular - Connective Tissue DISEASE



Theories About the Origins of Autoimmunization & Autoimmune States

Antigen Exposure & Auto-Sensitization

c.f. extrinsic antigen cross reactivity
e.g. rheumatic carditis
e.g. spina bifida latex allergies

direct intrinsic sensitization
importance of anti-nuclear antibodies
antibodies against other chemicals

chronic inflammatory states
of multiple causes

antigen exposure
e.g. acnes
e.g. uveitis

Rheumatic and Related Disease Screening

Table 1. Systemic Lupus Erythematosus (SLE) and 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	-	-	+

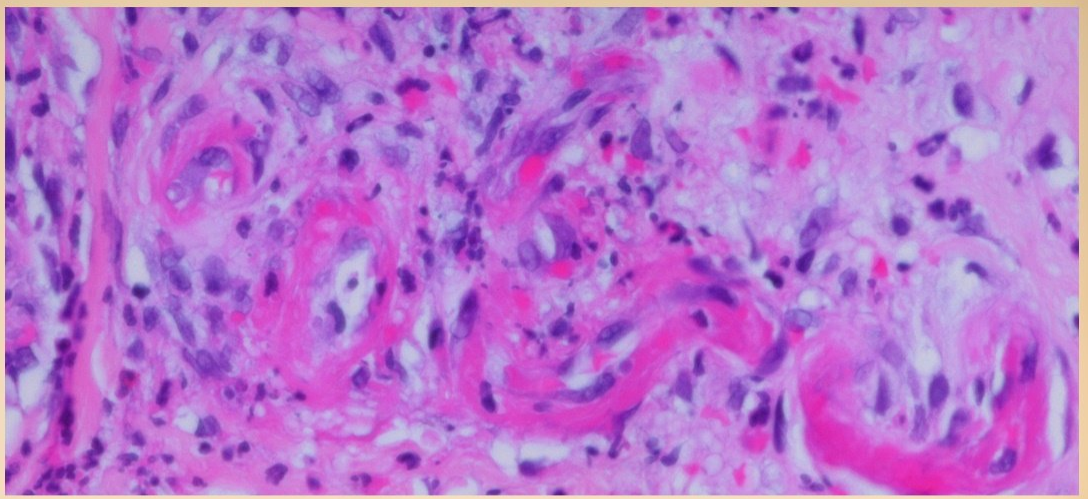
Table 3. CREST Syndrome and Neurologic SLE

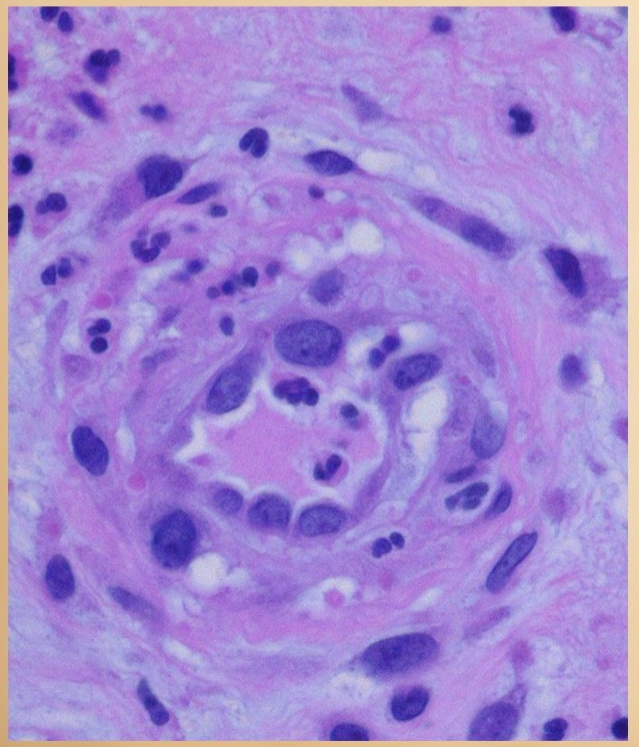
Test	CREST Syndrome	Neurologic SLE
Centromere antibody	+	-
Ribosomal P antibody	-	+

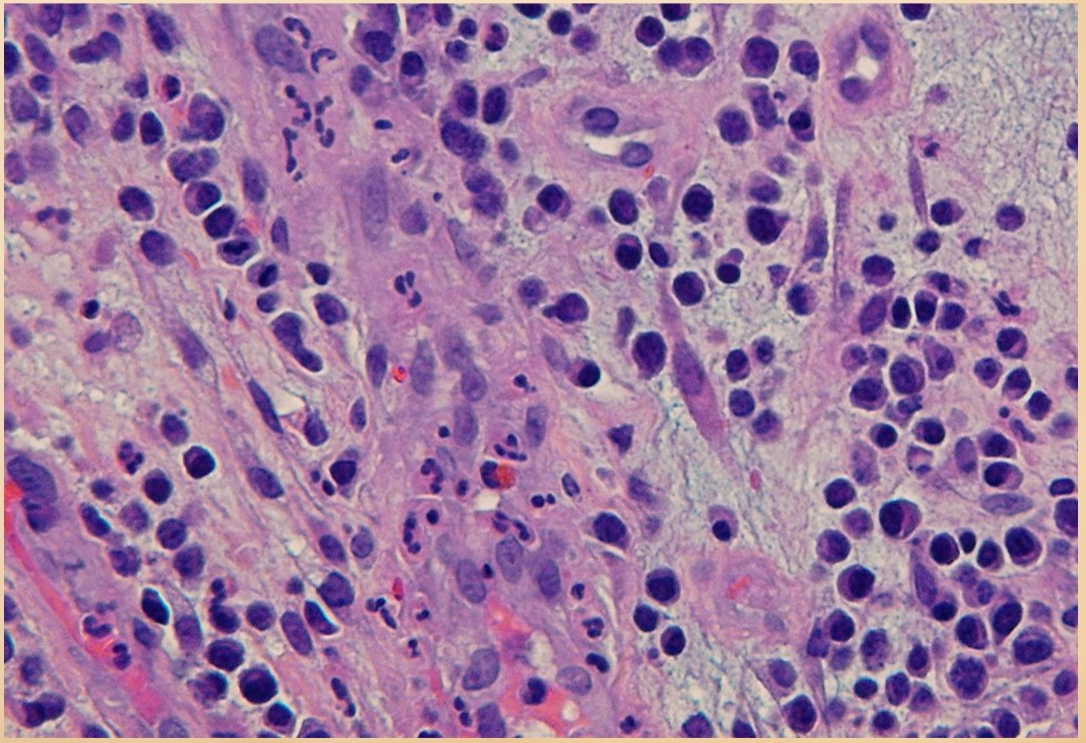
SLE, systemic lupus erythematosus.

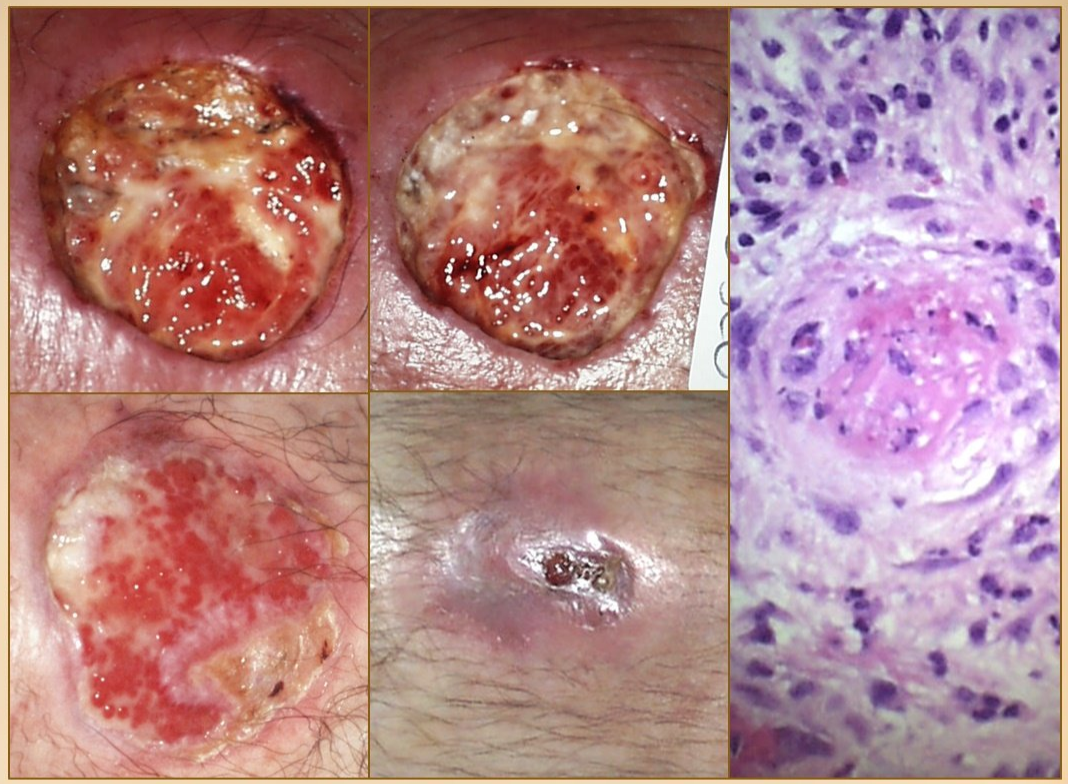
The origins of anti-nuclear antibodies

nuclear debris
poly dust









TOMBSTONE CLINICAL LABORATORY

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

34M, lupus, trauma wounds

pathergy, multiple wound failure: hand, groin, leg

multiple failed operations, refractory to all care

antiphospholipid antibodies

healed with warfarin

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	+

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	+

69F **Rheumatoid Arthritis**

FactorV Leiden	heterozyg	+
protein C	51	-
protein S	52	-

81F **Leg ulcer**

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

66F **Scleroderma / MCTD**

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

78F **Sjögren's**

protein C	60	-
fibrinogen	565	++

67F **Rheumatoid Arthritis**

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

67 & 176

1 & 3

$TcPO_2$

air & O_2

57M **Cirrhosis**

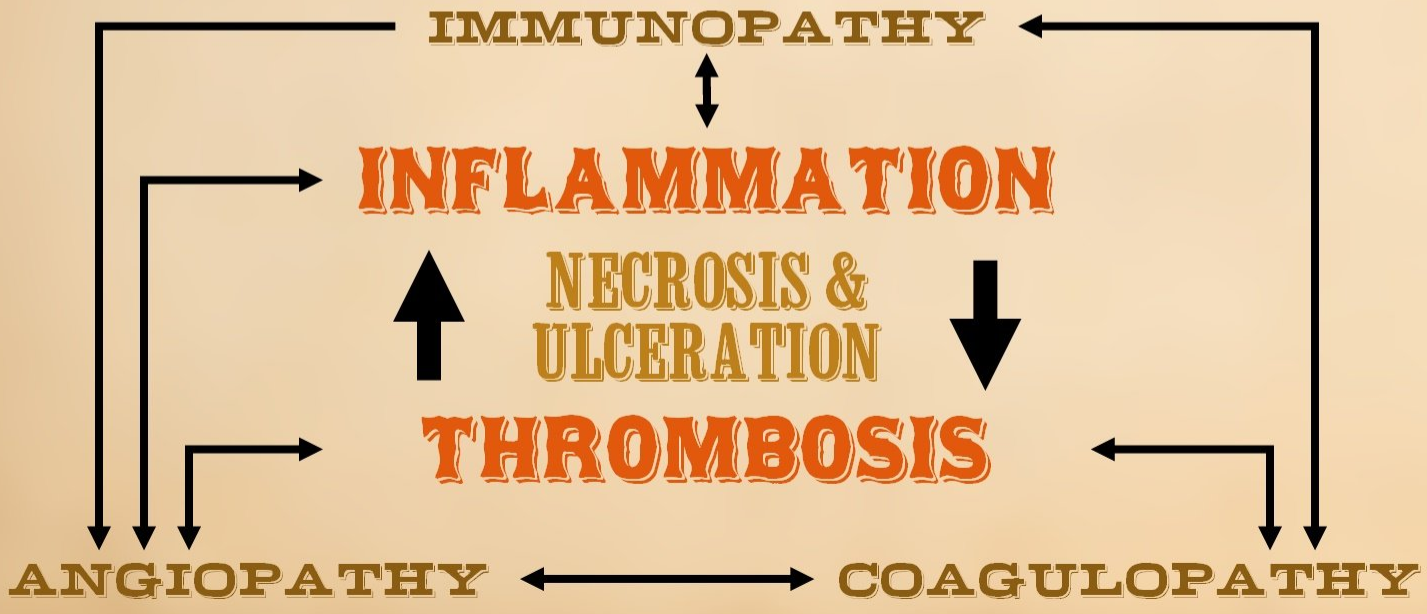
Bili	2.1	+
AlkPhos	160	+
RF	44	+
ANA	1:80	+
AT-III	47	-
ProtC	35	-
ProtS	55	-

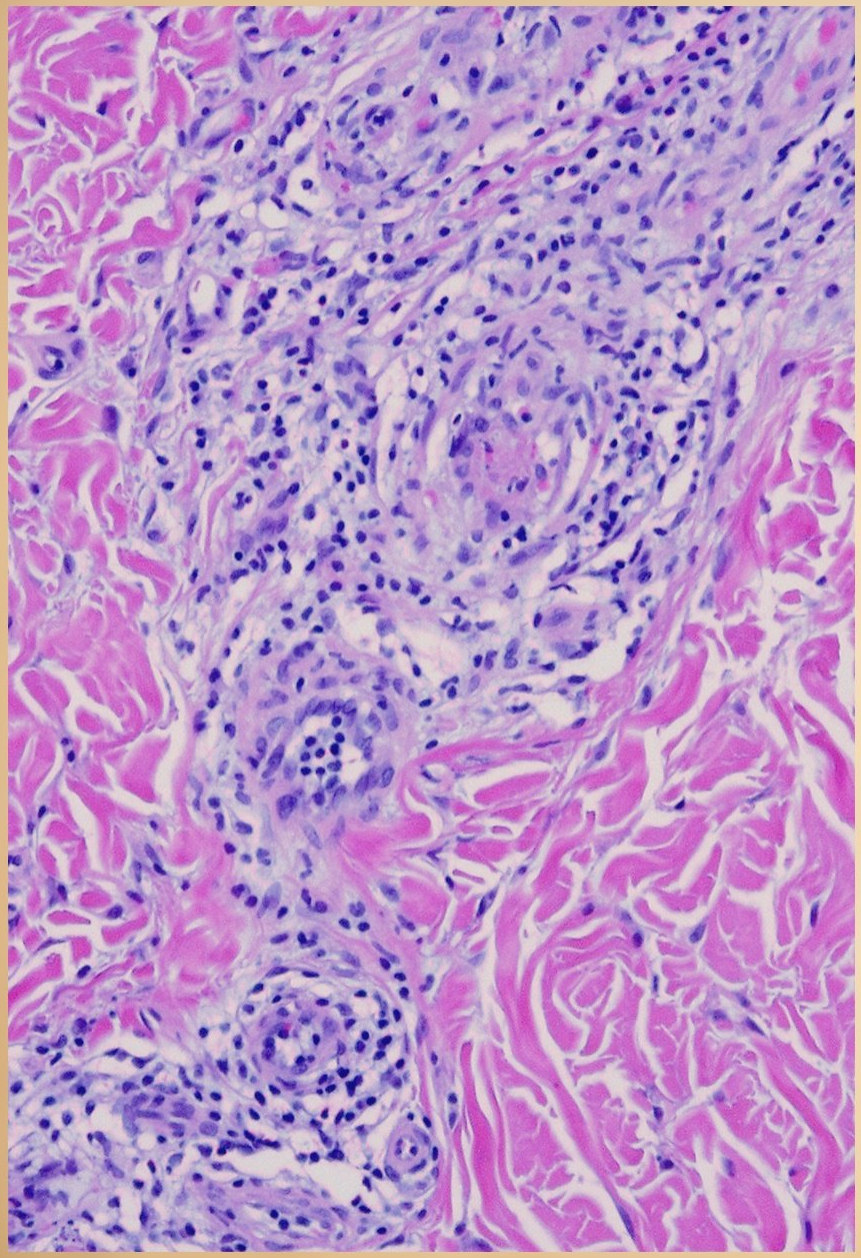
INTER-CONNECTIONS

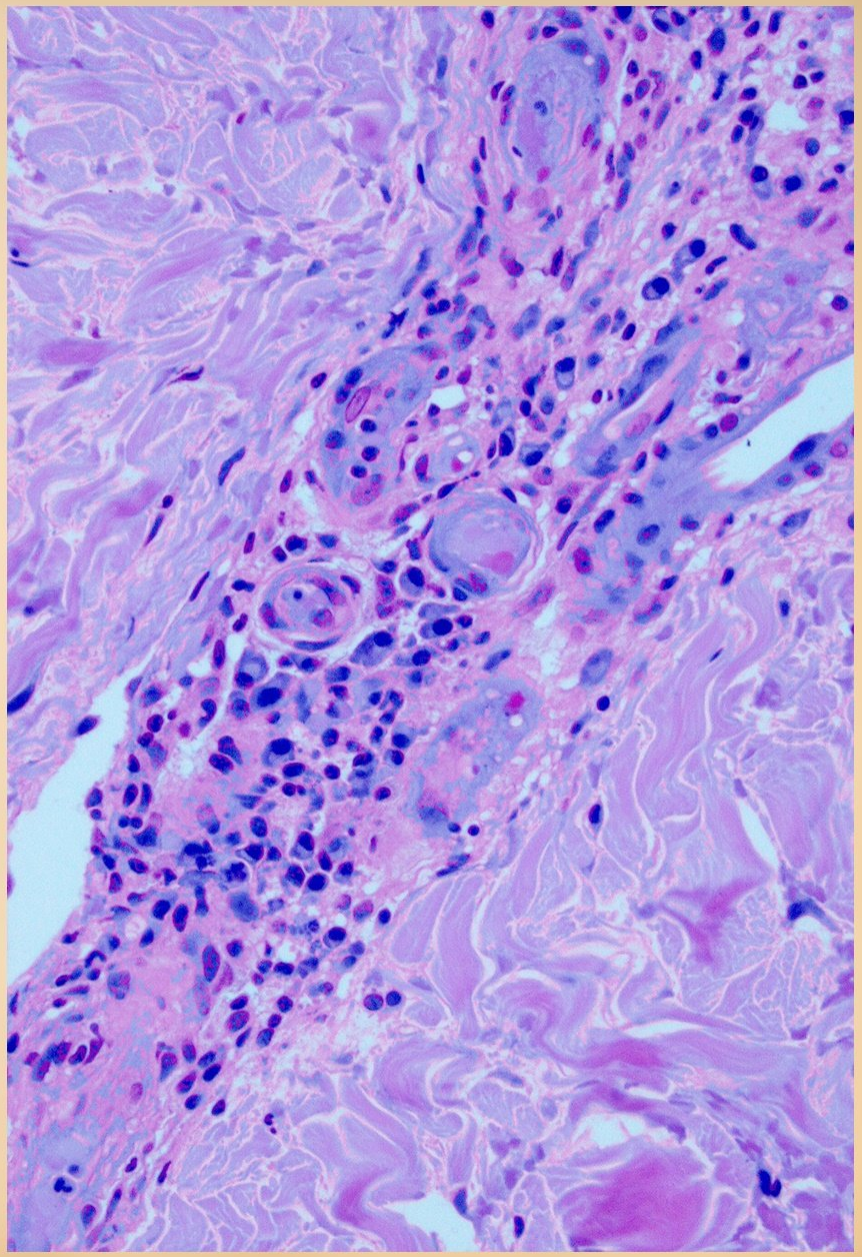
Wound & soft tissue pathology is governed by several highly interconnected events and responses:

injury - thrombosis - inflammation
pathergy - necrosis - ulceration
inflammation-immunity
coagulopathy - immunopathy - angiopathy - panniculopathy

Patients with pathological wounds have aberrations of these chains, and they frequently have multiple such abnormalities, e.g. auto-immunopathy generally accompanies hypercoagulable disorders.







OBSERVATIONS FROM WOUNDS AND SOFT TISSUES

What will cause the perfect storm of nuclear debris, exposed sequestered antigens, and a party where both macrophages and lymphocytes attend and get rowdy?

chronic reactive inflammation

chronic induced inflammation

chronic thrombotic state

chronic infections

allergenic states

immune states

genetic predispositions (e.g. HLA-B27, HLA-B51)

Any chronic inflammatory state.

Example: 49f, chronic severe hidradenitis, secondary rheumatoid arthritis

SUMMARY 2-B

Autoimmunity occurs when the immune system "sees" endo-cellular or other sequestered antigens that it should never have seen. Once auto-immunized, protean clinical sequelae ensue.

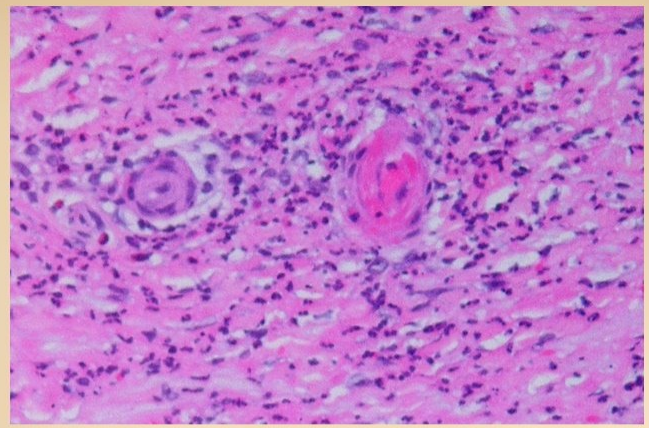
The auto-immunization can occur from chronic inflammatory processes which unmask and present these sequestered antigens.

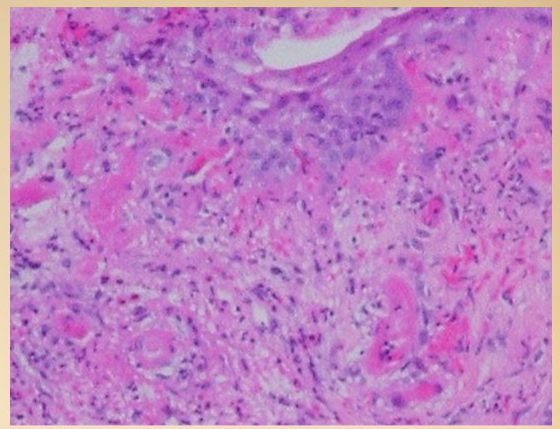
Angiocyte and fibroblast antigens are prominent in this sensitization, immunizing the patient to the connective tissue and vascular cells which constitute the stroma of all tissues.

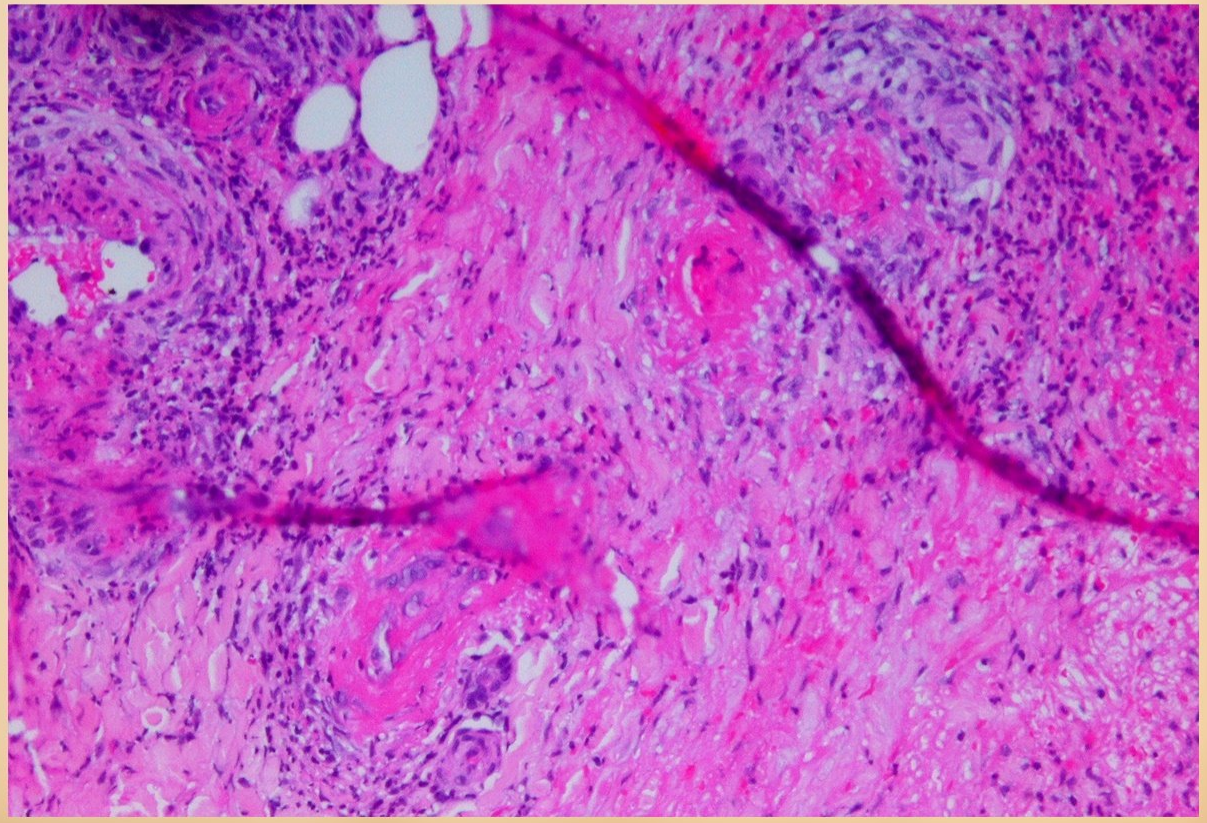
3-A

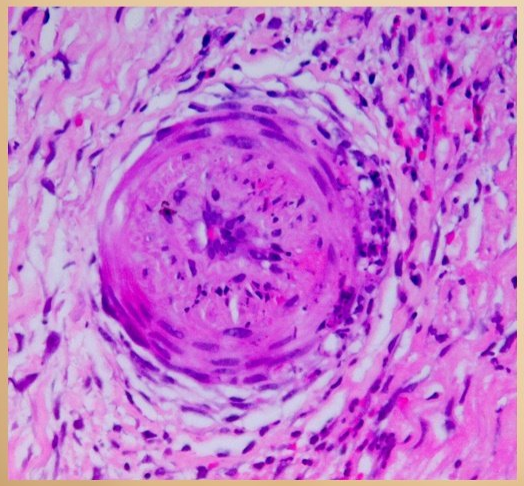
- CONNECTIONS -

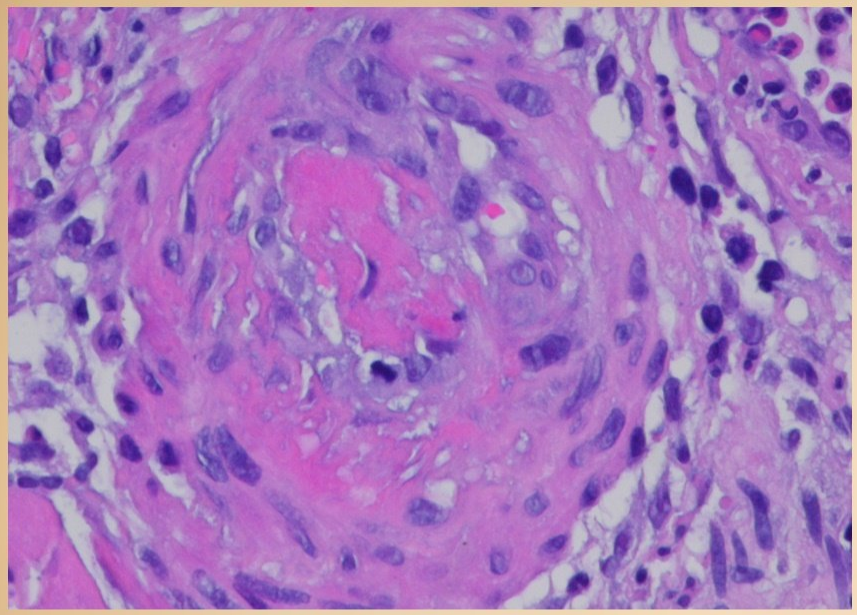
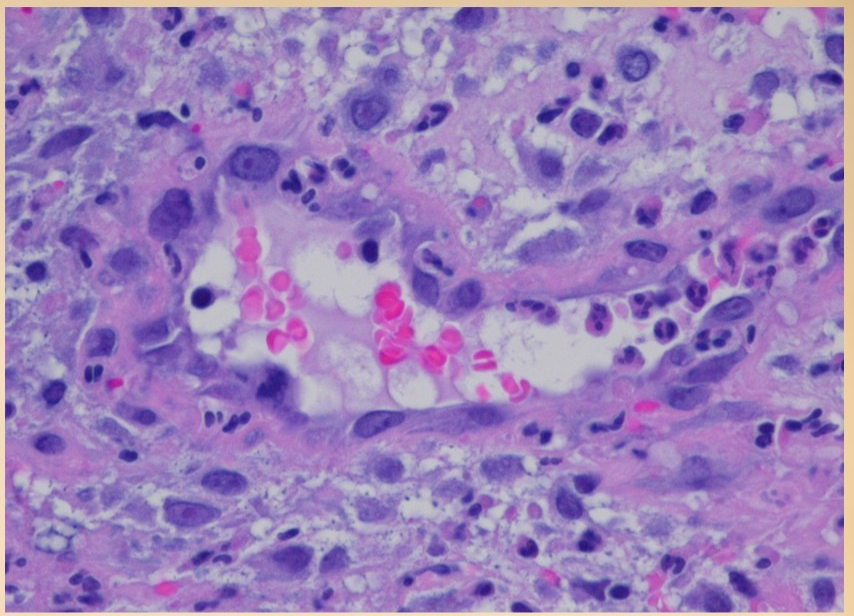
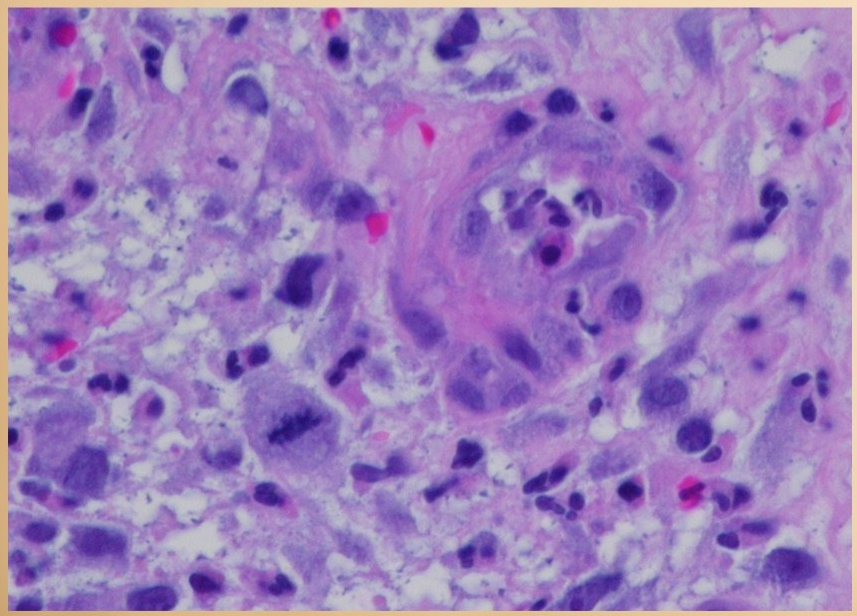
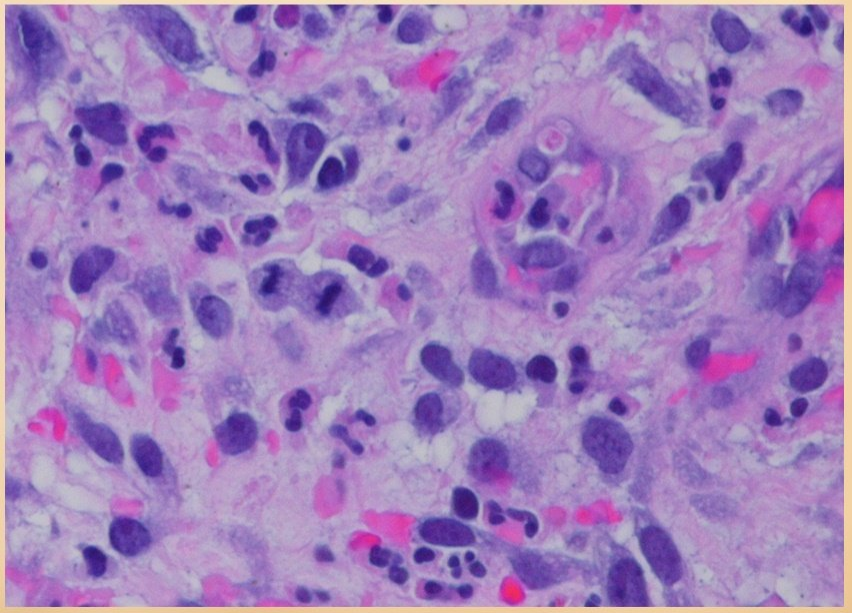
Collagen Vascular - Connective Tissue PATHOLOGY AND WOUND HEALING

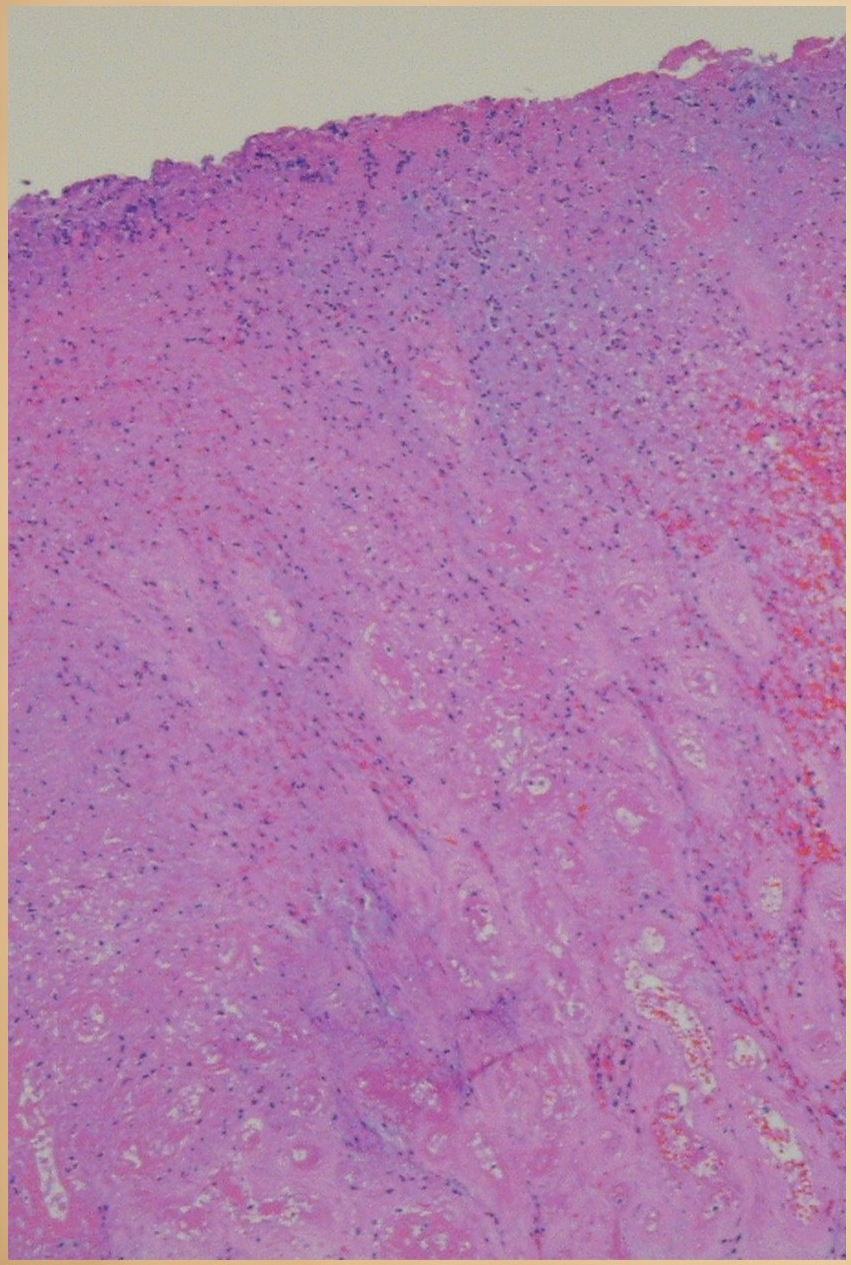


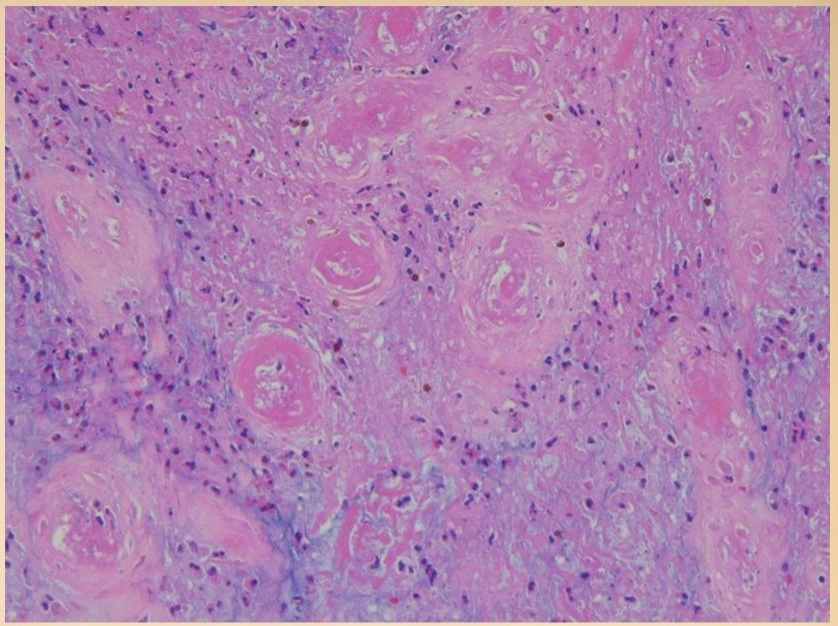










EFFECTS OF IMMUNE AND INFLAMMATORY STATES ON THE HEALING OF CHRONIC WOUNDS

Common Histologic Features

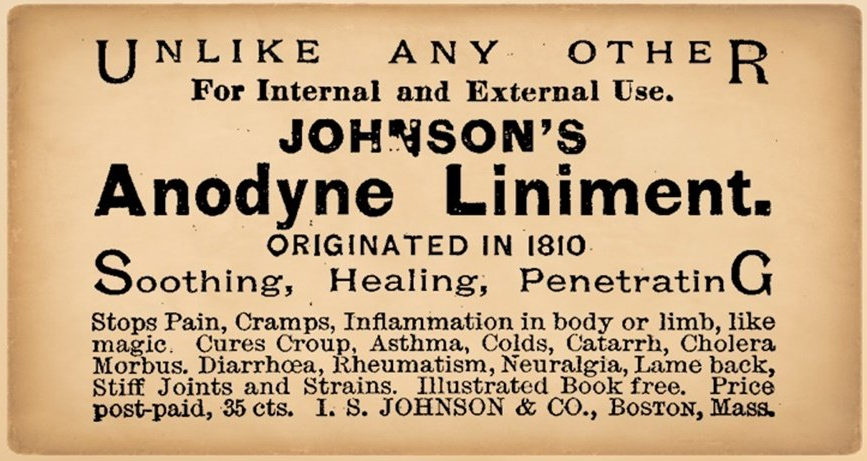
Acute inflammation
Chronic inflammation
Plasma cell infiltrates
Leukocytoclastic vasculitis
Chronic vasculitis
Peri-vasculitis
Vascular necrosis
Vascular hyalinization
Vascular disorganization
Fibrous disorganization
Epithelial arrest
Variations in anatomical depth of wound
Variations in physical depth of wound
Missing wound strata (proliferative zones)

Immunos

SUMMARY 3-A

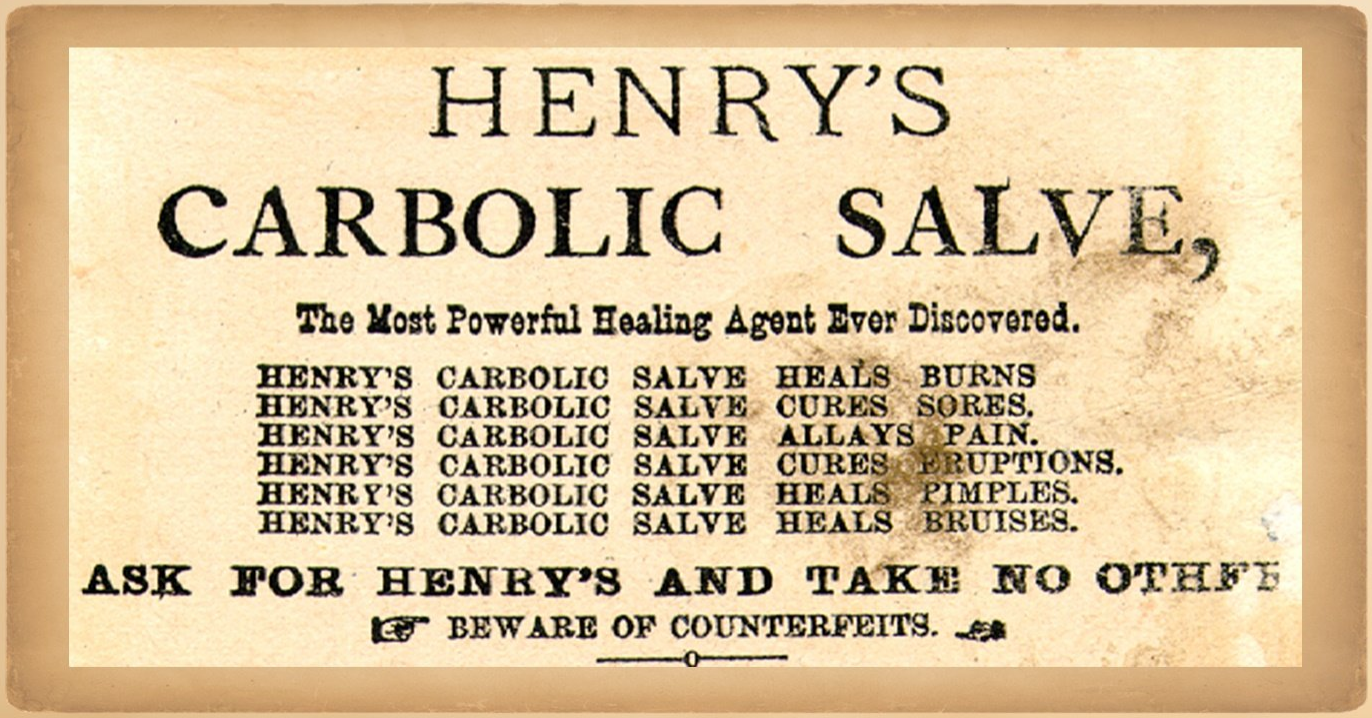
Wound healing is impaired in patients with immunopathic ulcers.

Histologic examination reveals variances from normal wound healing in which chronic and acute inflammation are associated with chronic vasculitis, fasciitis-fibrositis, and panniculitis, and with abnormal angiogenesis and fibroplasia.



3-3

The Intersection of Wound Biology and Collagen-Vascular Pathology



UNDERSTANDING HOW IMMUNOPATHIES AFFECT WOUND HEALING

All mesenchymal stroma is composed of 2 cell types:
fibroblasts, angiocytes

Wound healing, the mesenchymal wound module,
depends on 2 cell types:
fibroblasts, angiocytes

The targets of mesenchymal autoimmune attack
are the stromal soft tissues, i.e.
fibroblasts, angiocytes

Basic syllogism :

A

Diseases that affect collagen-vascular connective tissues
ipso facto affect the mesenchymal wound module.

B

The autoimmune / CVD-CTD diseases are diseases
that affect the collagen-vascular connective tissues.

Therefore, these are the diseases of wound healing.

Target Tissue Examples (Reprise)

Synovium (RA)
Scar (Lupus complications)
Panniculitis (Sjogren's, Weber-Christian)
Polyserositis (Lupus, Weber-Christian)
Muscle (Polymyositis, PMR,CREST)
Ligament & tendon (RA, MCTD)
Vessels (Vasculitis)

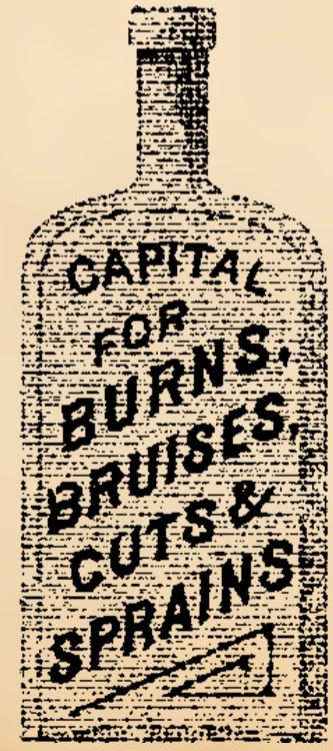
Dermis, sclerosis (Scleroderma)
Dermis, lysis (Ulcer)

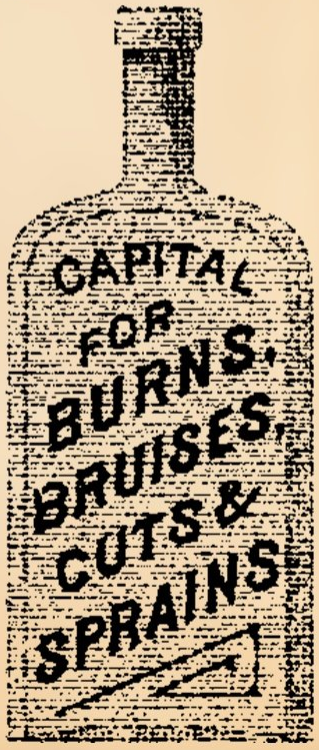
WOUNDS
Ulcers, Scars

AFFERENT EFFECTS
cause wounds

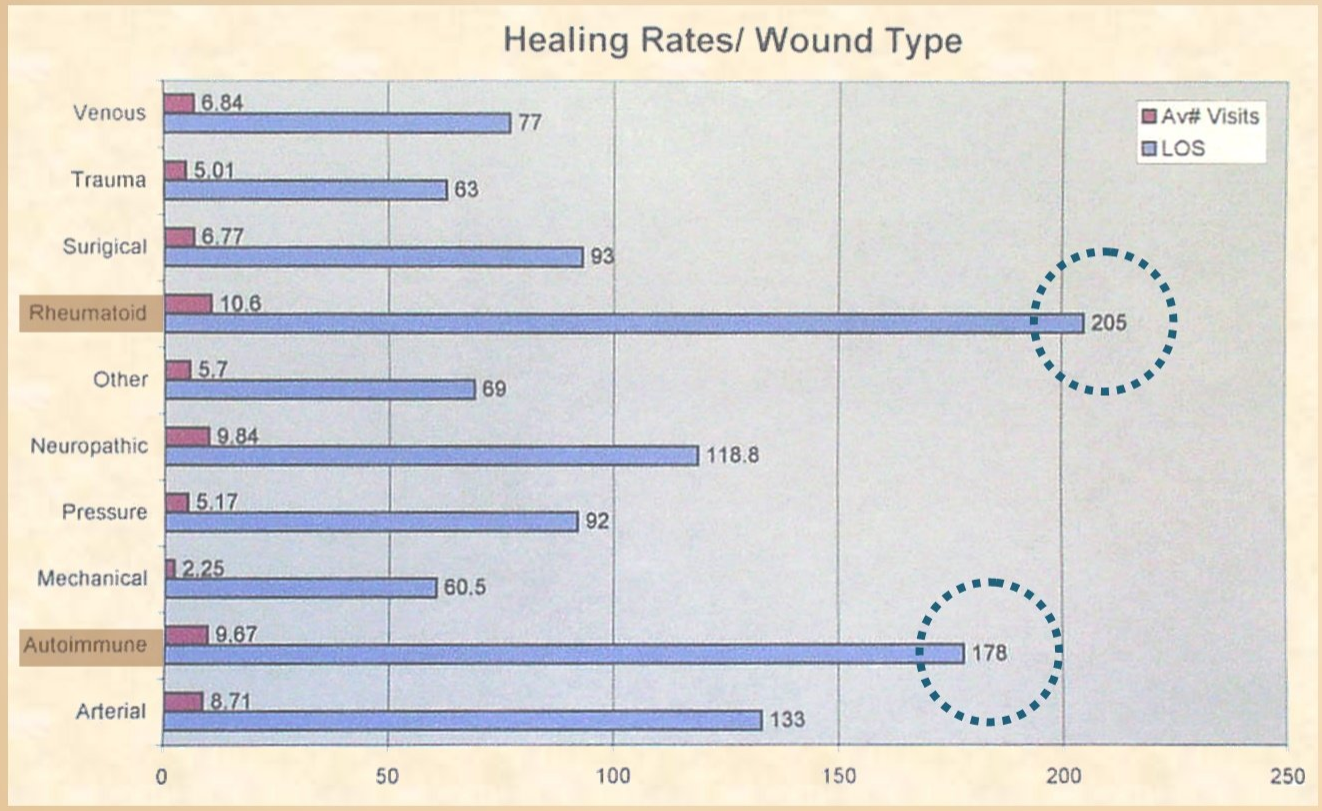
EFFERENT EFFECTS
keep wounds from healing

IMMUNOPATHY & AUTOIMMUNITY
" CVD-CTD " ARE THE
TRUE INTRINSIC DISEASES
OF WOUND HEALING





SIGNIFICANCE OF IMMUNOPATHIC ULCERATION AND IMPAIRED WOUND HEALING



Clinical research need: studies to match specific immunopathies, dermatoses, and wound profiles to the most effective anti-immune drugs for healing those wounds.

SUMMARY 3-B

A primary target of the immunopathic connective tissue disorders are the mesenchymal stromal cells, fibroblasts and angiocytes, which are also the principal agents of wound healing.

The CVD-CTD disorders are therefore also the intrinsic diseases of wound healing, and such ulcers are a major category of chronic wounds and wound pathology.

Inasmuch as these disorders affect the primary agents of wound healing, wound healing is more impaired than for other causes of chronic wounds which are extrinsic to the primary process.

4

Immunopathy Autoimmunity & Diseases of Wound Healing

- Epilogue -

WOUND CONTROL DYSDYNAMIA
THE OTHER INTRINSIC DISEASE OF WOUND HEALING

THE CENTURY OF THE SYSTEM

Bioengineering and Systems Biology

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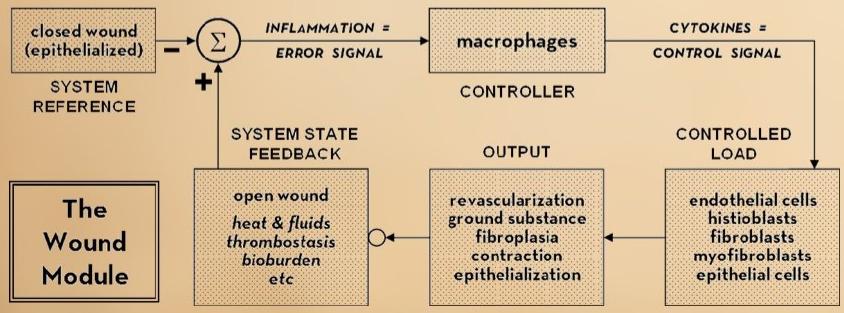
Annals of Biomedical Engineering, February, 2006

A field known as Systems Biology is emerging, from roots in the molecular biology and genomic biology revolutions—the succession of which has led biomedical scientists to recognize that living systems can be studied not only in terms of their mechanistic, molecular-level components but also in terms of many of them simultaneously. This computational algorithms for Mining the data to generate hypotheses concerning the potential interpretation of these data sets is necessary. In order to consequently develop new predictions for experimental test (or design), computational Modeling is required for similar reason: unaided human intuition likely cannot produce effective predictions concern-

- WOUND HEALING -
A CLOSED LOOP CONTROL SYSTEM



CVD - CTD

The diseases which affect the intrinsic elements and individual components of the wound healing system.

DYSDYNAMIA

The disorders which affect the inter-operations and collective function of the wound healing system.

SUMMARY

The autoimmune / immunopathic connective tissue & collagen vascular diseases are a major category of chronic wounds.

They cause wounds and they also impair wound healing. As diseases of fibroblasts and angiocytes, they impair the intrinsic ability of the wound module to function.

Immunopathic ulcers are a challenge to treat because wound healing is "broken", but comprehensive management of wound and underlying disease will prevail.

EDITORIAL ABOUT MODERN WOUND PRACTICE

ARIMEDICA

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Marc E. Gottlieb, MD, FACS
Phoenix, AZ

1

Chronic and pathological wounds (CAP wounds) represent a distinctive class of disease and clinical activity.

2

There is a non-expert misunderstanding of wounds that focuses only on trauma and the several classic wound types.

3

Legitimate practitioners of this specialty must have the professional knowledge required to master these diseases, starting with relevant pathologies and clinical skills.

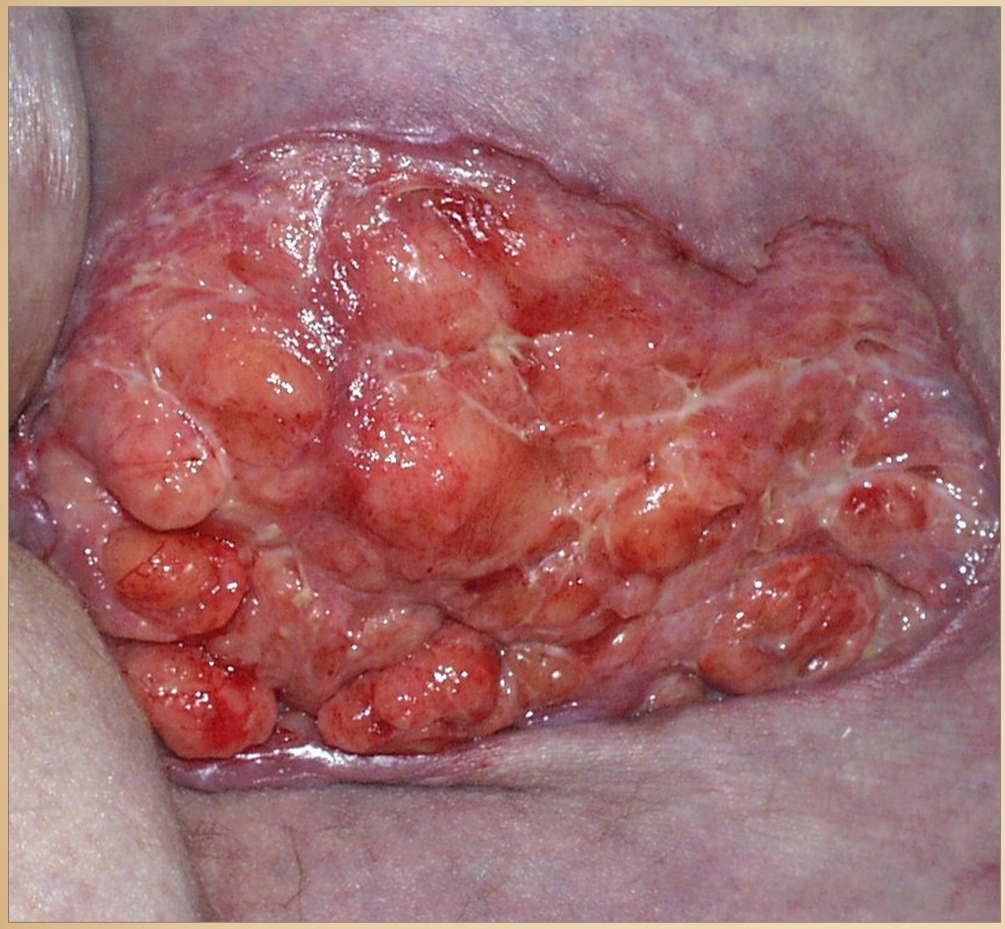
4

What are dismissed as "atypical wounds" are not atypical at all. They are the core of chronic and pathological wounds, far more abundant and significant than most perceive.

ADDENDUM

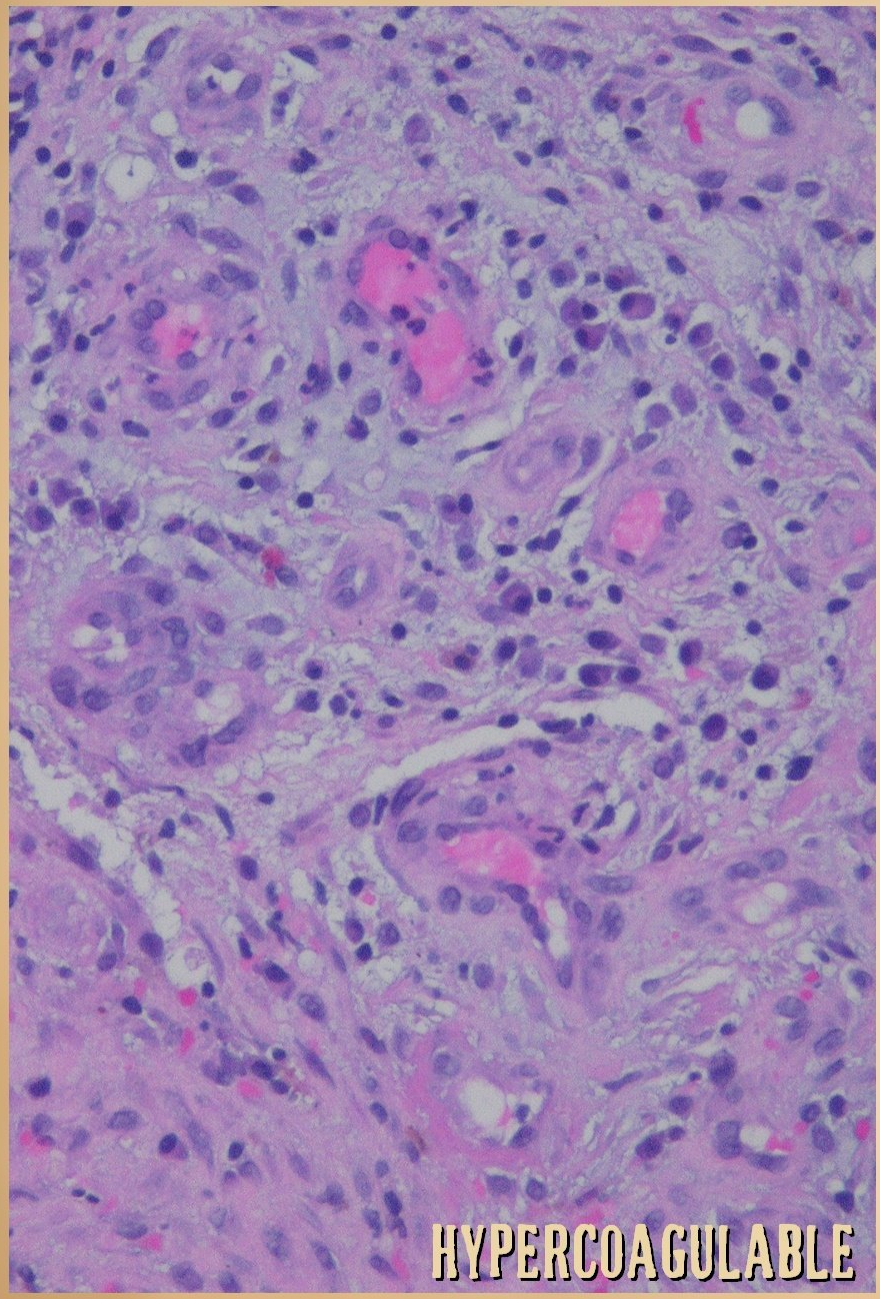
ARRESTED WOUND MODULE

ARRESTED WOUND MODULE



WOUNDS NOT HEALING: Rheumatoid, injury 6 months prior (buttock)

WOUNDS NOT HEALING: Polymyositis, injury 4 months prior (leg)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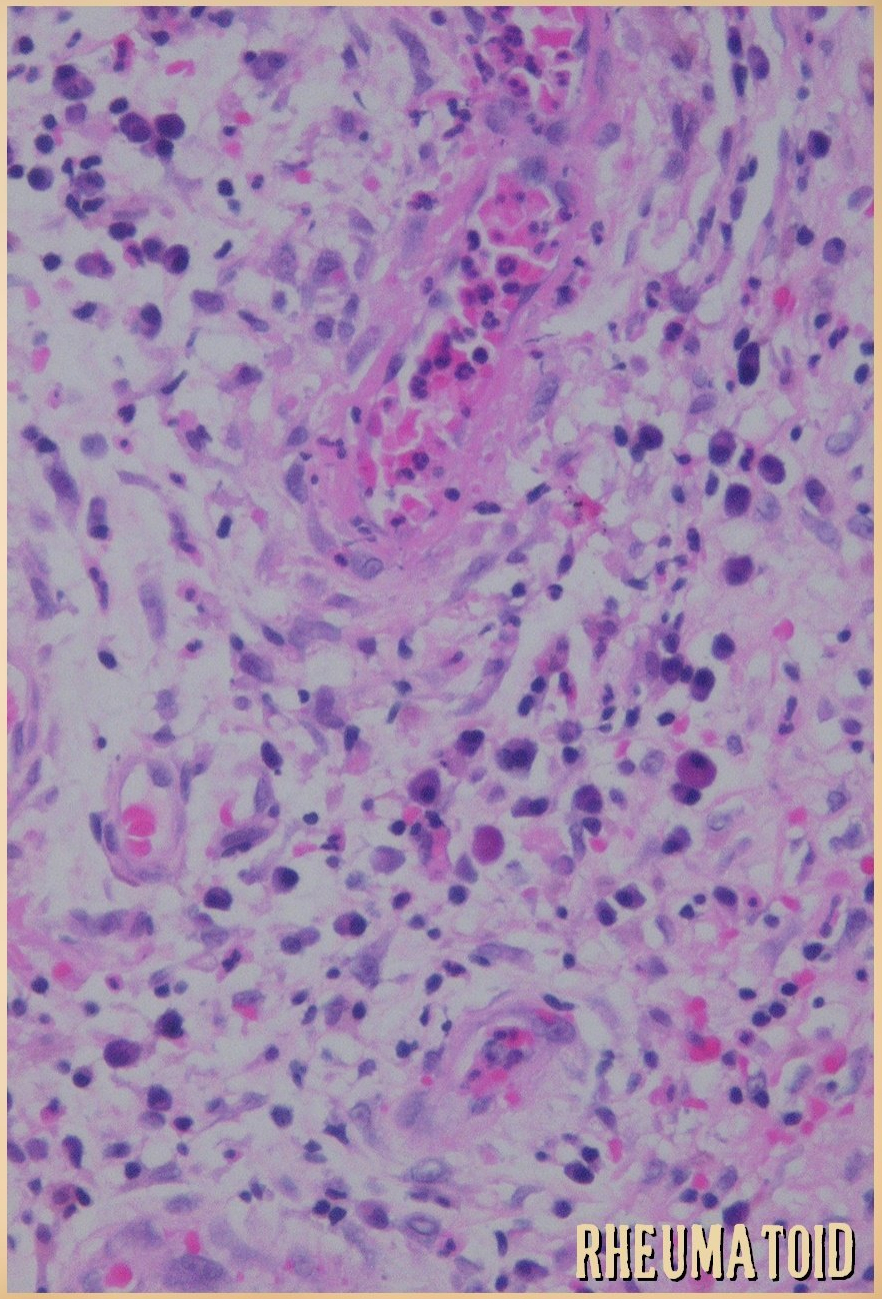
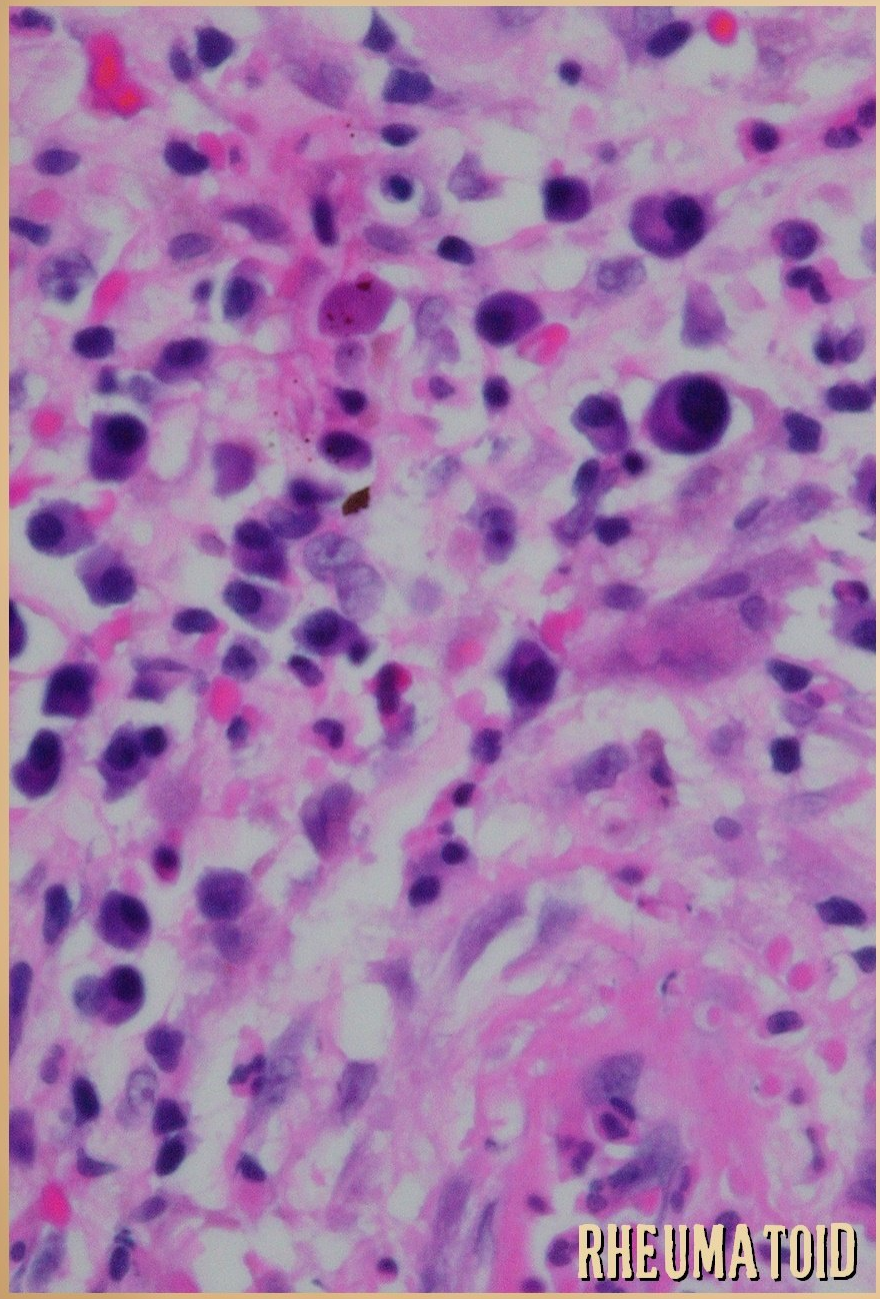

RHEUMATOID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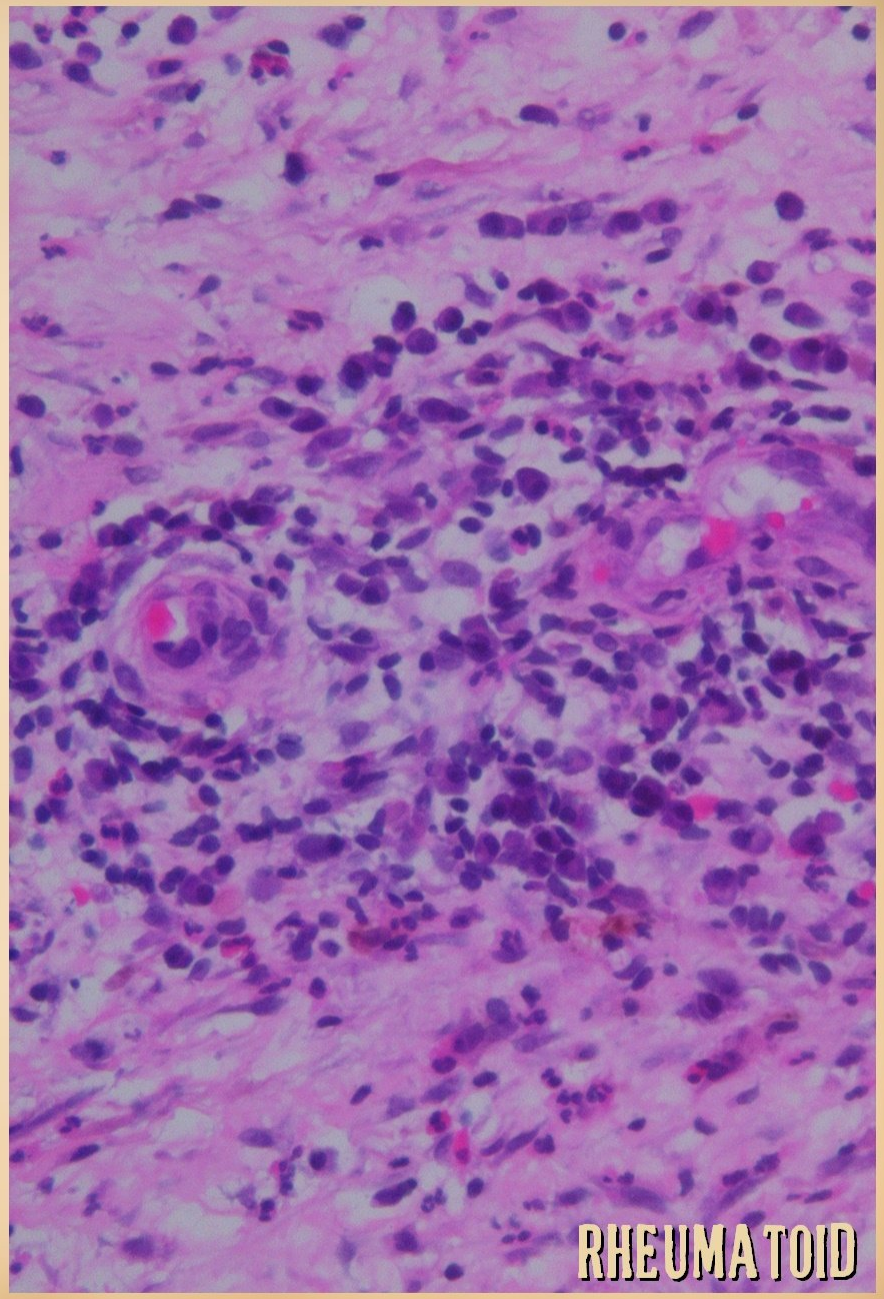
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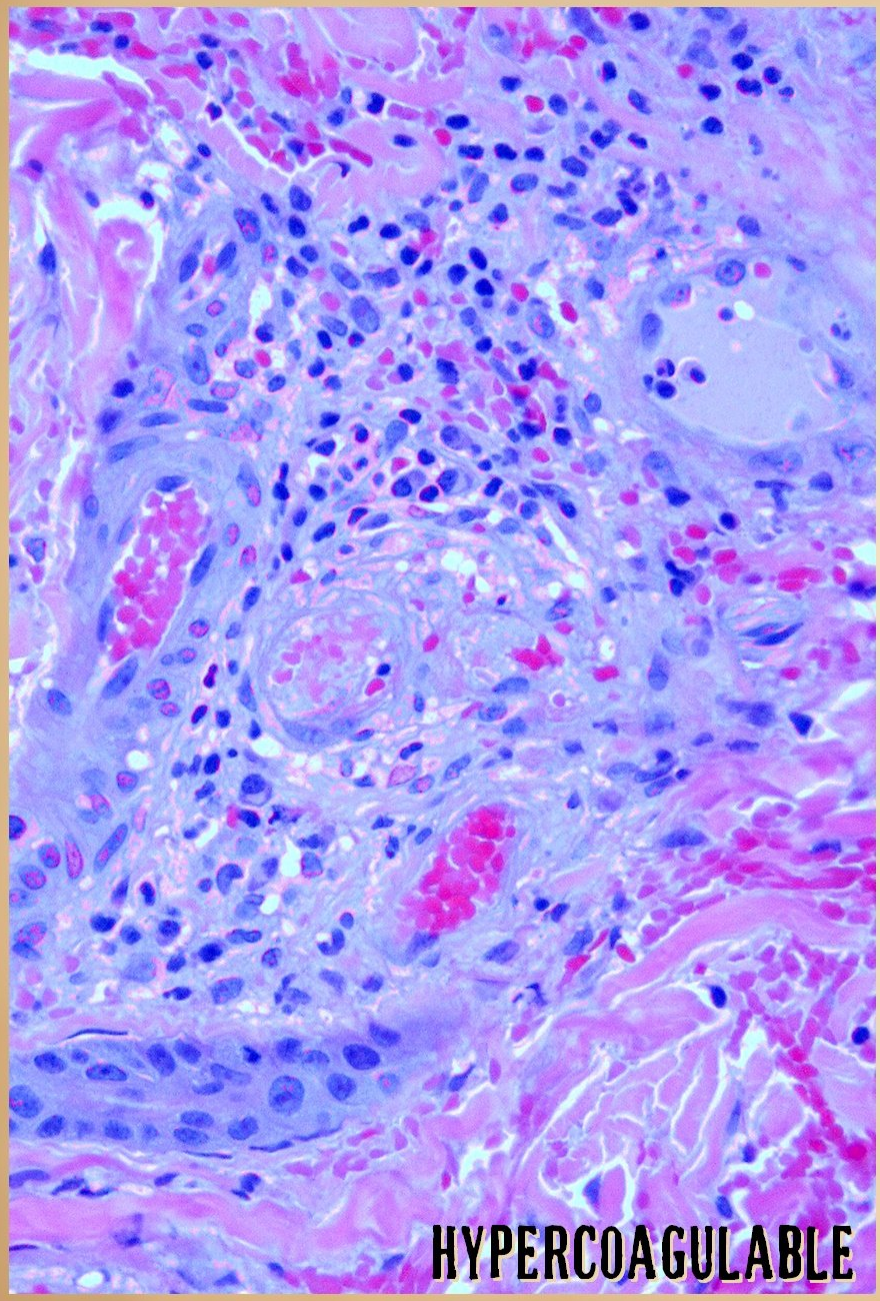
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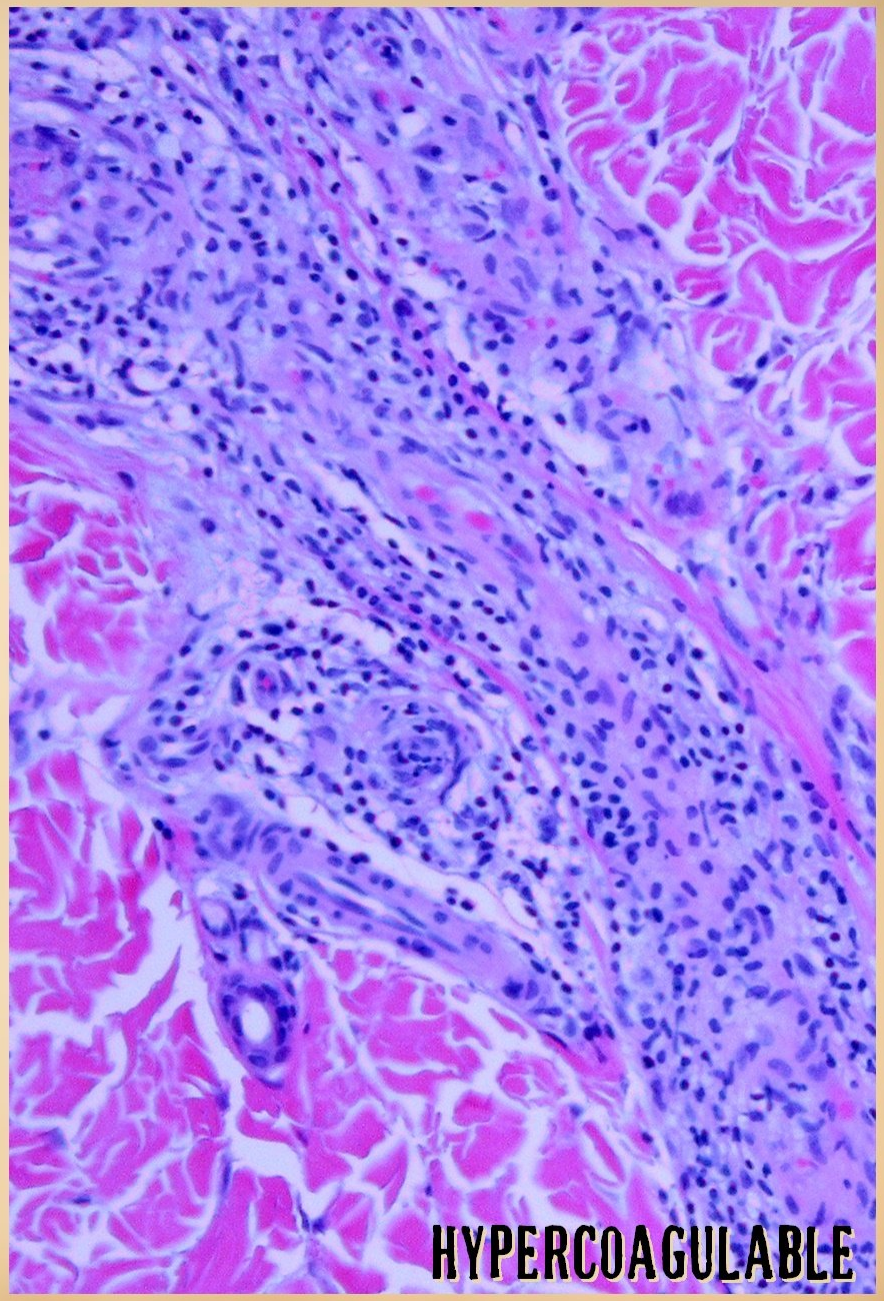
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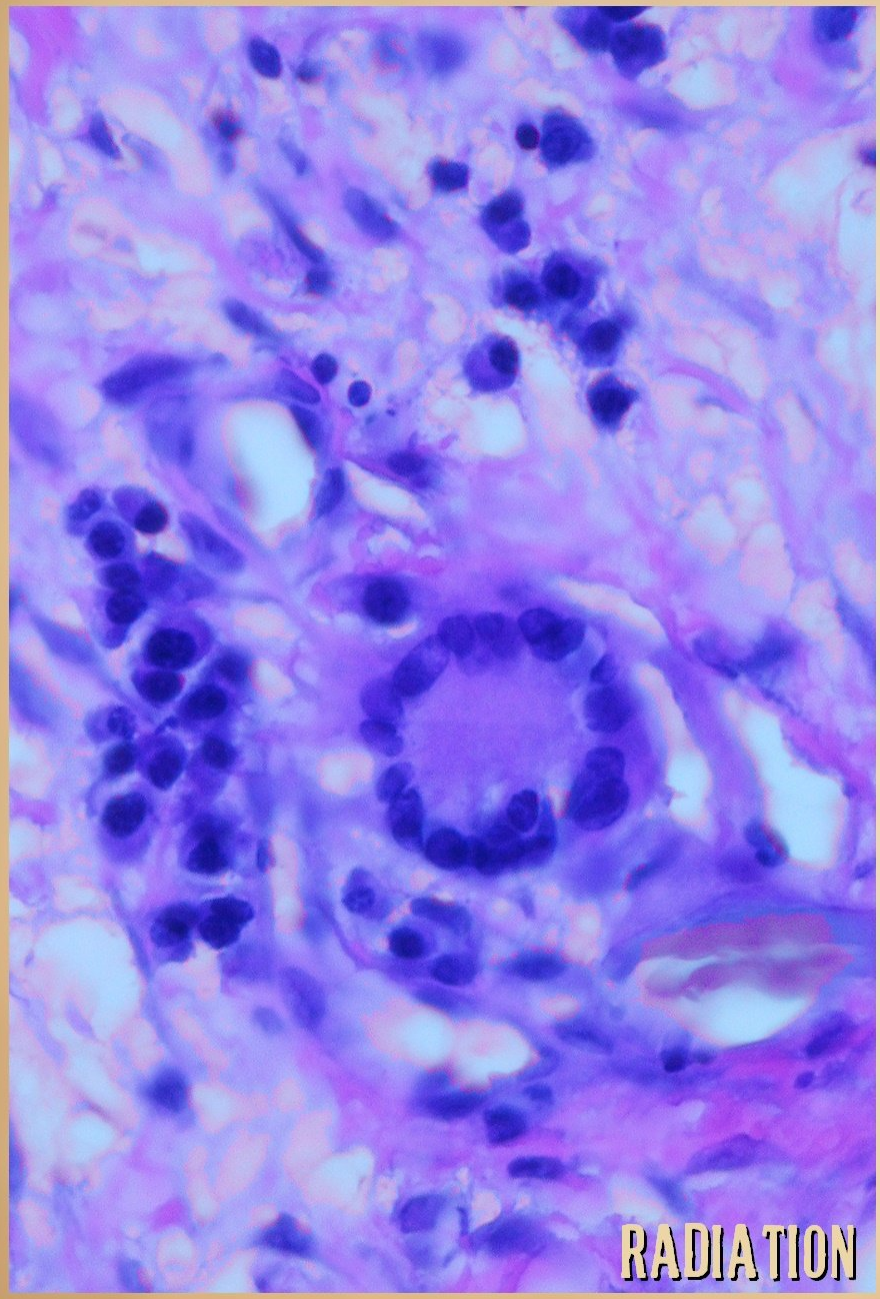
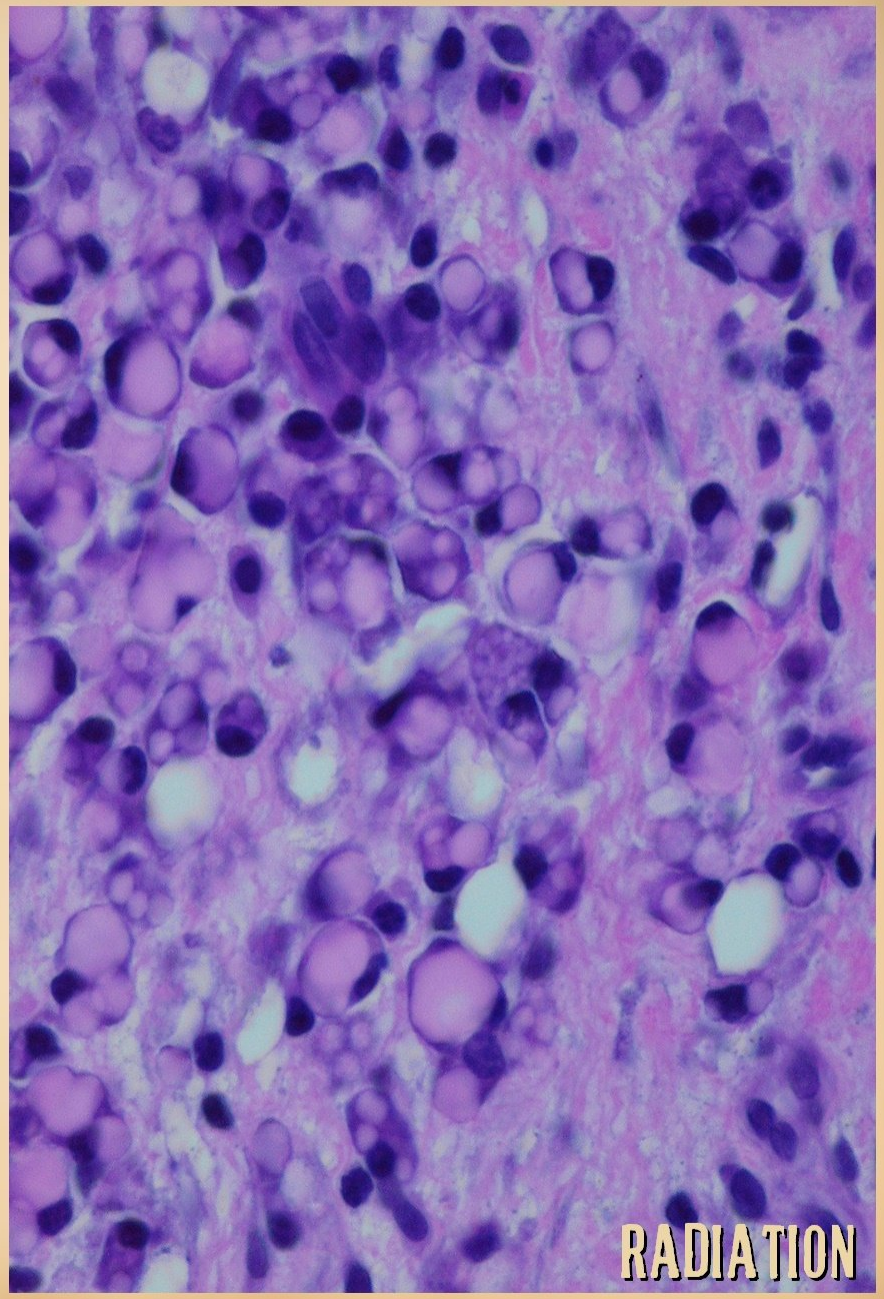
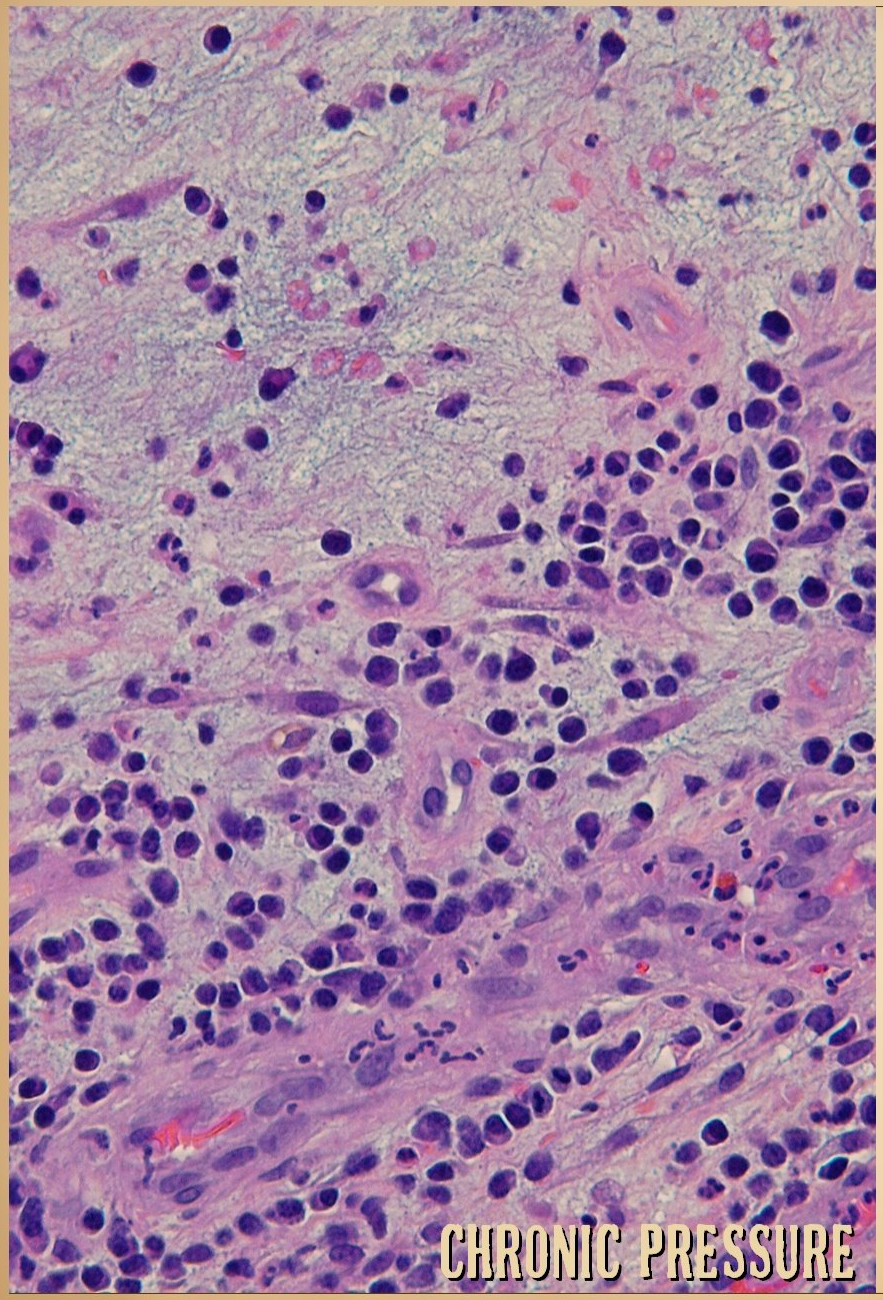
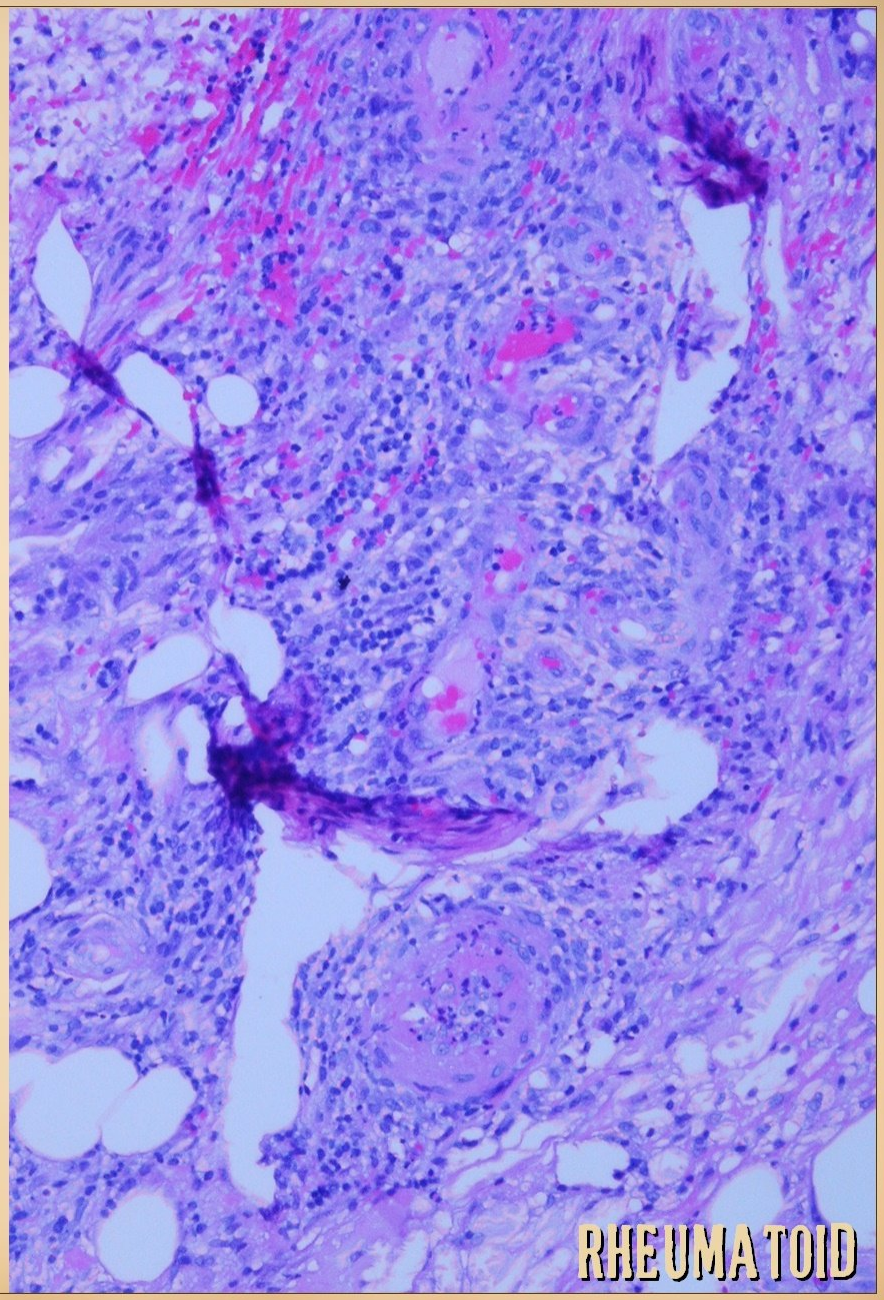

RADIATION


RADIATION


CHRONIC PRESSURE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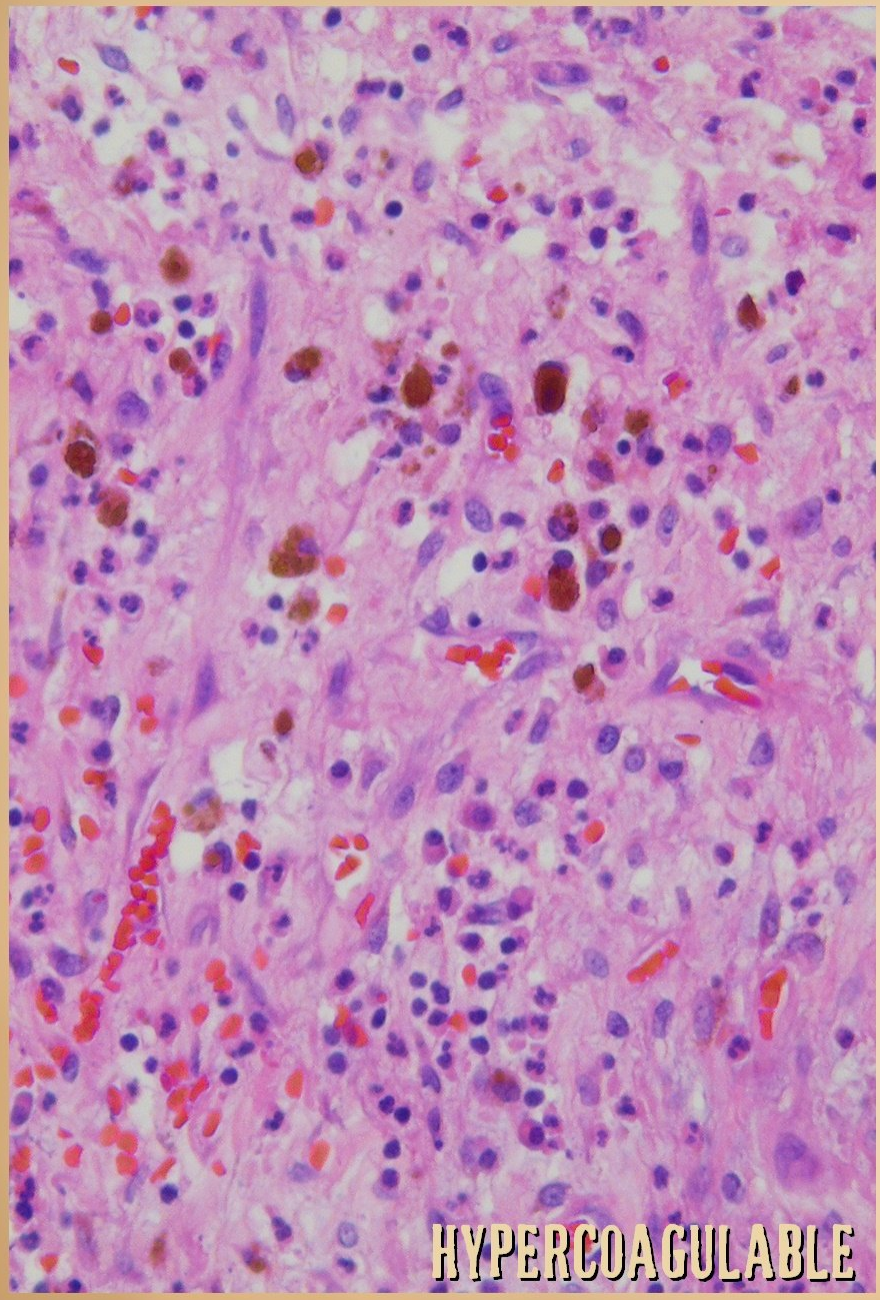
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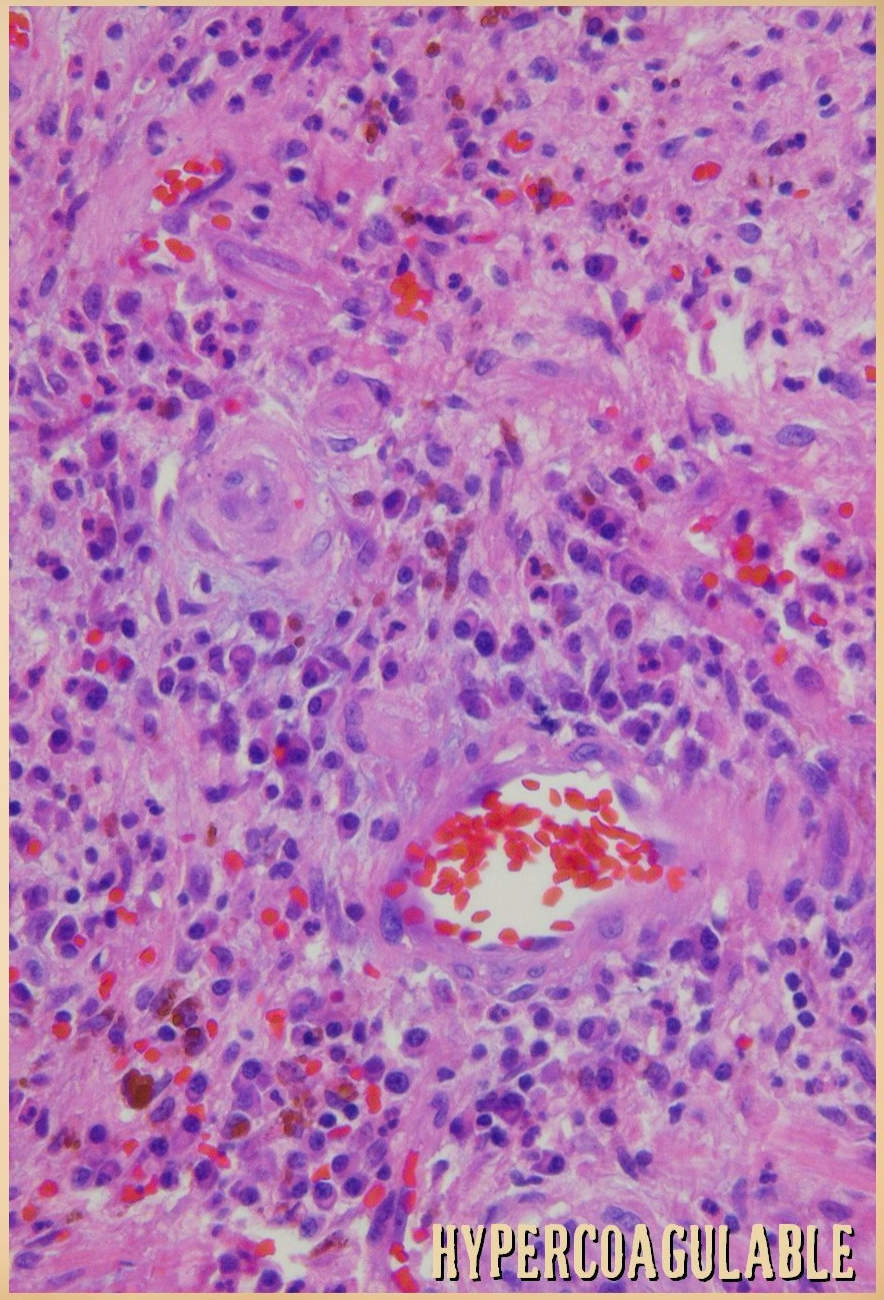
HYPERCOAGULABLE

RX WITH STEROIDS

RX WITH STEROIDS

10 days

21 days

RX WITH ANTI-IMMUNE

END

ABSTRACT: (NOT) ATYPICAL ULCERS

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This is a simple conspectus of the presentation that will be given. The final presentation will be posted at the website arimedica.com. You can view the presentation and annotations there. The main concepts presented are:

1 - Chronic and pathological wounds (CAP wounds) represent a distinctive class of disease and clinical activity.
2 - There is a non-expert legacy understanding-misunderstanding of wounds that focuses only on trauma and a few standard categories of CAP wounds - arterial, venous, pressure, diabetes.
3 - Legitimate purveyors, professors, practitioners, and professionals of the specialty of wounds must understand the professional level of knowledge that appertains to understanding these diseases. Like all specialties, that starts with an understanding of the full spectrum of relevant pathologies.
4 - What are often dismissed as "atypical wounds" are not atypical at all. In fact, they are the core of chronic and pathological wounds, and they are far more abundant and significant than non-experts perceive.
5 - The subject of CAP wounds is encyclopedic, both in scope and in established knowledge and experience, and a comprehensive summary will not be made.
6 - Relevant concepts will be briefly illustrated by two of the most common types of misunderstood, under-appreciated, and overlooked problem wounds: mechanical ulcers and coagulopathic ulcers.
7 - Relevant concepts will then be further illustrated by a more detailed review of immunopathic ulcers and diseases.
8 - The talk culminates in understanding one crucial concept - that the autoimmune connective tissue disorders are the true intrinsic diseases of wound healing.
9 - Emphasis will be drawn to the prevalence and significance of immunopathic ulceration, then to the caveats and all-too-common poor outcomes attributable to improper diagnosis and uninformed care of these all-too-typical ulcers.

Regarding items #6 & 7, concerning hematological and immunopathic ulcers, the following key points will be illustrated and explained:
- Wound and soft tissue pathology is vitally contingent on several core, highly interconnected, non-linear auto-amplifying combinations of events and responses:
  coagulopathy - immunopathy - angiopathy - panniculopathy
  injury - inflammation - thrombosis
  pathergy - necrosis - ulceration
- Understanding these chains is crucial to understanding and anticipating the behavior of the causative diseases and the resulting wounds, and then to applying effective care.
- Patients presenting with pathological wounds not only have some aberration of these chains, but they almost invariably have multiple such abnormalities, e.g. markers of auto-immunopathy almost invariably accompany the hypercoagulable disorders.

Regarding item #8, that the autoimmune connective tissue disorders are the true intrinsic diseases of wound healing, the following key points will be illustrated and explained:
- The mesenchymal component of wound healing has just two intrinsic proliferative cells, angiocytes and fibroblasts, which are likewise the only two cells which constitute the generalized stroma of the body.
- The connective tissue disorders, aka collagen vascular diseases affect these cells. Thus the collagen vascular diseases affect wound healing.
- While this syllogism might seen overly simple, it is not. It is the core paradigm of pathology that disrupts the functioning of these cells, preventing them from re-establishing a continuous stroma.
- Key to understanding this relationship is in understanding that the connective tissue disorders are auto-immunopathic.
- The origins of autoimmunopathy against apocryphal and sequestered antigens will be explained, as a function of chronic primary inflammation and micro-thrombosis.
- The subsequent effects of autoimmunopathy on the functioning of the proliferative wound module can then be understood.
- Immunopathic disorders are a two-edged sword: they both cause ulceration and then impair subsequent healing. As the true diseases of wound healing, clinical management is prone to frustrations, failures, and prolonged healing times.

In summary, what naives call "atypical wounds" are not. They are common and ordinary, and they constitute the core of chronic and pathological CAP wounds - they are typical. Among the several interconnected primary pathologies that cause them, the autoimmune connective tissue disorders are the important archetype, and they are in fact the true intrinsic diseases of wound healing.

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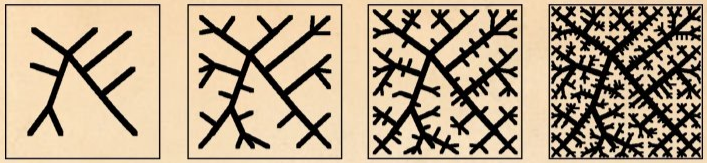

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AUTOIMMUNOPATHY AND CONNECTIVE TISSUE DISORDERS THE TRUE INTRINSIC DISEASES OF WOUND HEALING

Original presentation September, 2009, Miami, FL
at the 4th Annual Wound Symposium of
Baptist Health South Florida

The presentation and related materials can be viewed and used at:
arimedica.com