THE PHYSICS AND PATHOLOGY OF WOUNDS

2

AUTO-IMMUNOPATHY AND THE INTRINSIC DISEASE OF WOUND HEALING

1

The Wound as a System and a Controlled Machine

3

Chronicity and the Physics of Wound Failure

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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

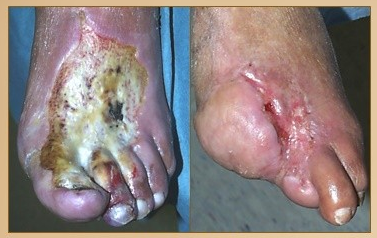
DISORDERS AND DISEASES OF THE WOUND HEALING PROCESS

CAP WOUNDS

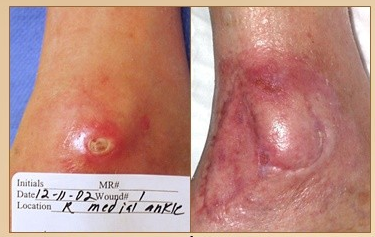
Chronic and Pathological

1 - Wounds caused by chronic illness or pathology.

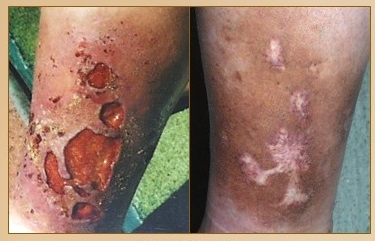
2 - Wounds that fail due to diseases of the healing process.



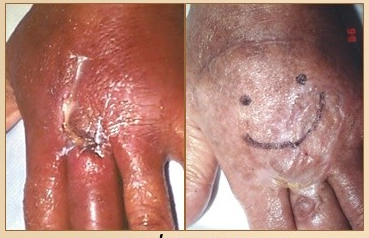
ARTERIAL



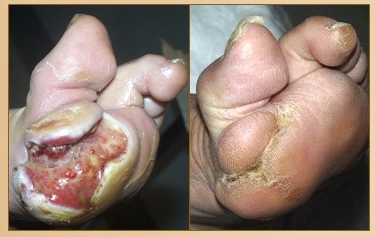
MECHANICAL / ANATOMICAL



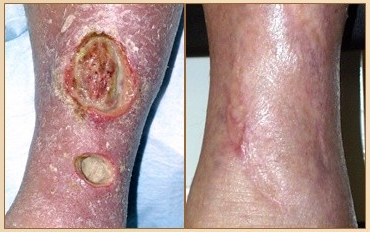
VENOUS



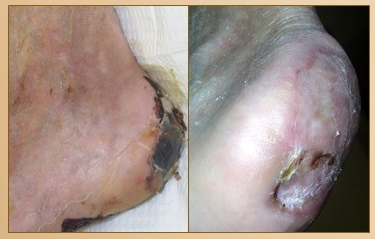
TOXIC / CHEMICAL



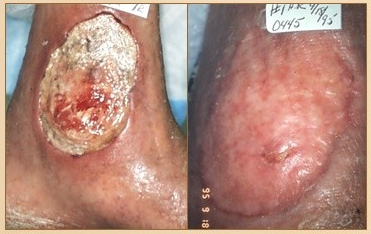
DIABETES



IATROGENIC / FACTITIOUS



PRESSURE



RADIATION

CAP WOUND DIAGNOSES

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?

THE PHYSICS AND PATHOLOGY OF WOUNDS

COMPARE WOUND STRUCTURE AND FUNCTION TO OTHER ORGANS

ORGAN	STRUCTURE & FUNCTION	FAILURE
HEART	*pump, valves, & pipes*	*chf = inadequate pump*
KIDNEY	*filter & resorption membrane*	*occluded filter*
LUNG	*bellows & diffusion membrane*	*faulty ventilation & respiration*
EYE	*light collector & detector*	*blindness*
EAR	*sound transducer & decoder*	*deafness*
BONE	*structural members & motion*	*impaired support & mobility*
NERVES	*electrical network & control*	*palsy & neurologic deficits*
WOUND	*cell set & self-re-organization*	*logistical disorganization*

What are the quintessential structures & functions of these organs ?

What is the quintessence of dysfunction for these organs ?

THE WOUND MODULE IS A SPECIAL AD HOC RESERVE ORGAN

What are the quintessential structures and functions of the wound ?

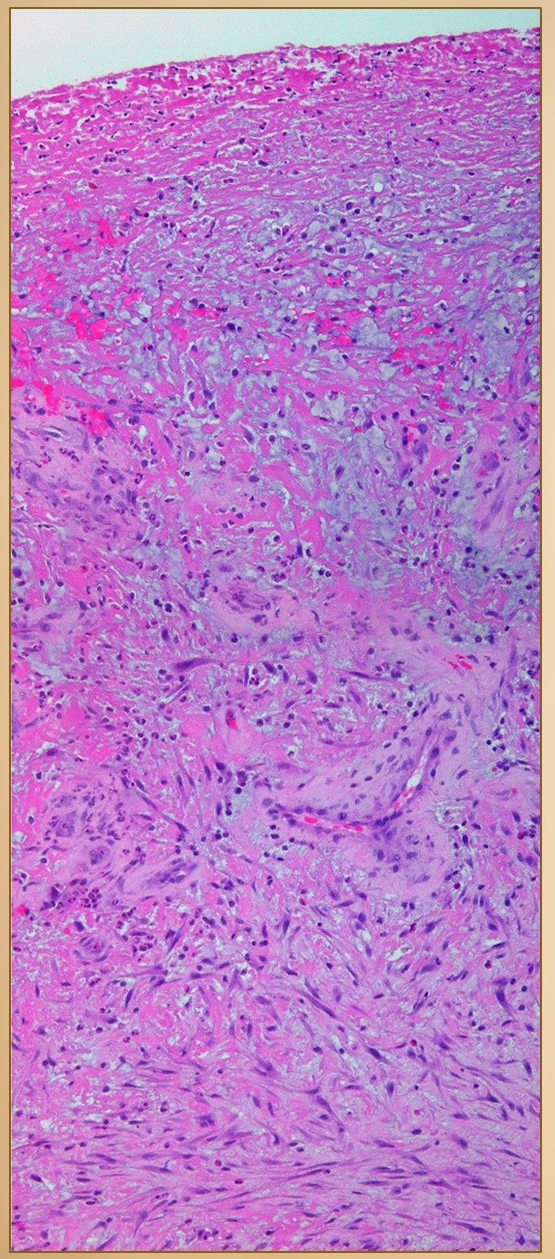
It is a set of mutually interactive cells that self-organizes to recreate generic stroma.

It has no function other than organizing itself into the generic stroma that is the foundation for other tissues and organs.

What is the quintessential derangement of intrinsic wound pathology and chronicity ?

It is a disorder of "logistical" self-re-organization, failing to restore the intended stroma.

When it fails, it simply fails to assemble into its intended final form, to complete its task to become something and then cease.



THE WOUND MODULE

OF PROLIFERATIVE REPAIR

and the

PHYSIOLOGIC EVENTS - CLINICAL SIGNS

0
injury
inflammation

1
inflammation
subsides

2
macrophages,
eschar separation,
cytokines

3
ground substance,
mucus

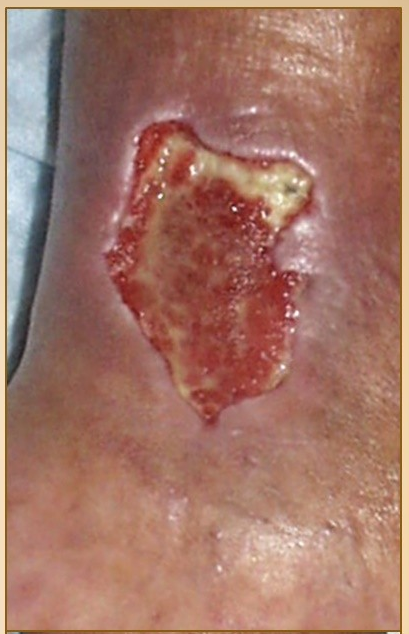
4
"granulation"
angiogenesis

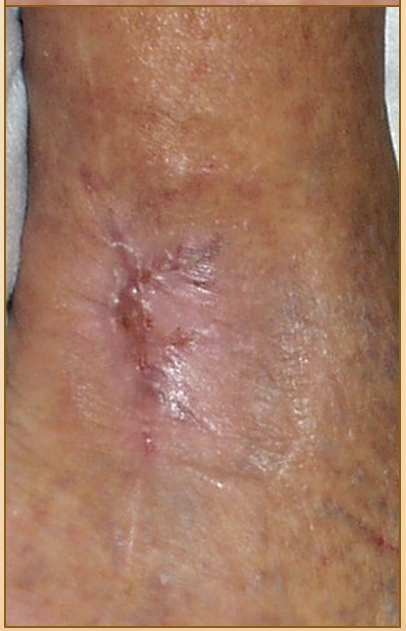
5
histioblasts, fibroblasts,
fibroplasia

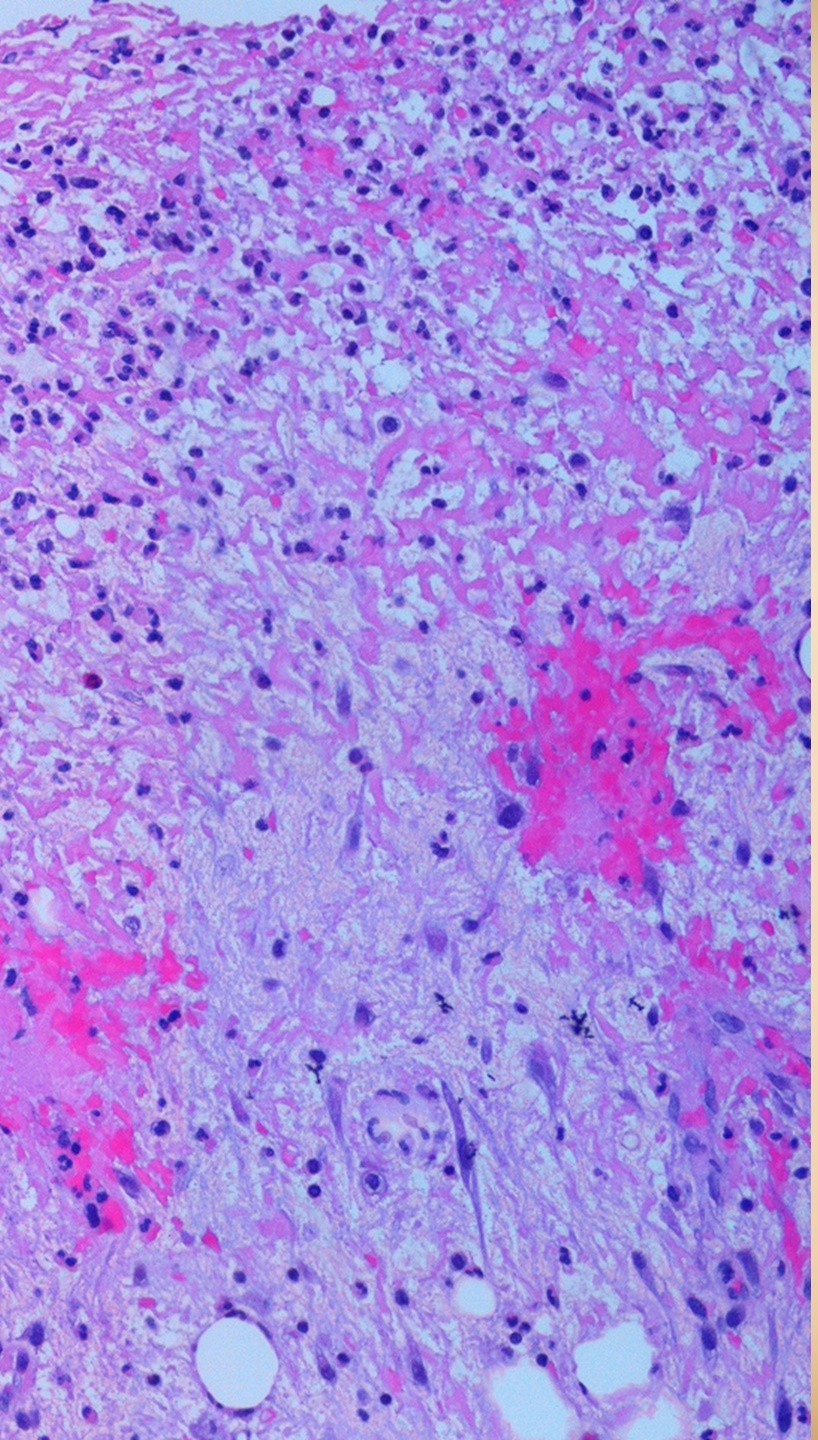
6
myofibroblasts
contraction

7
epithelialization

8
maturation







THE WOUND MODULE - NORMAL WOUND HEALING

MAIN EVENTS AND CELLS:

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

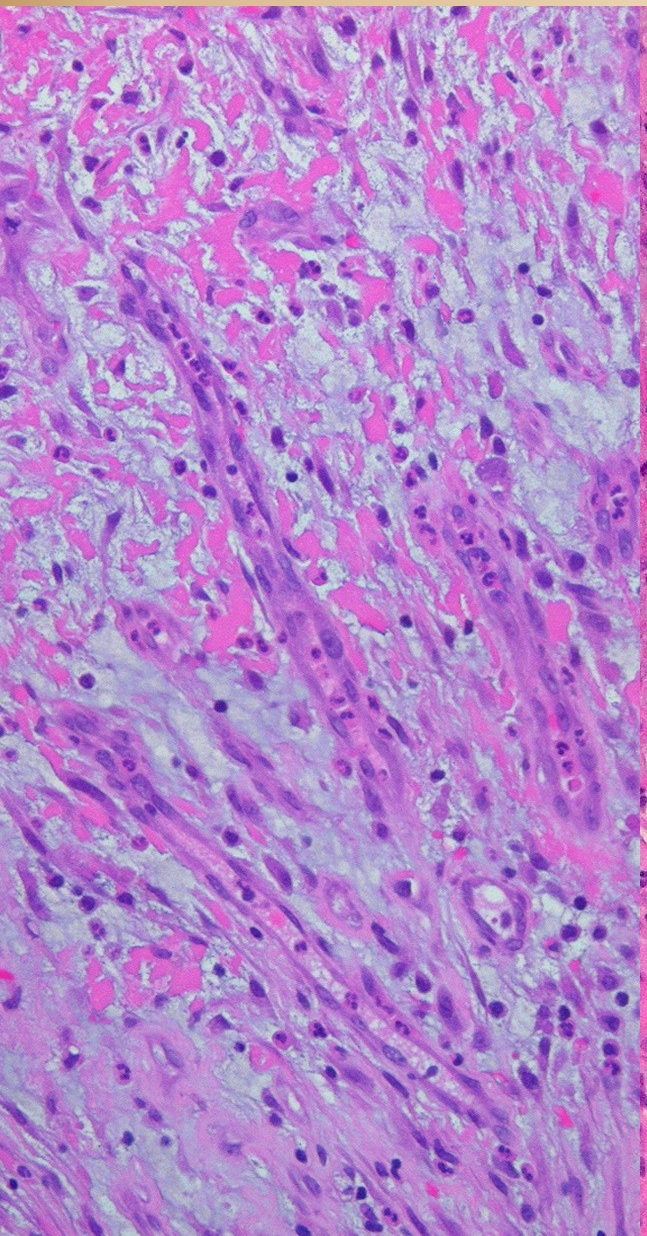
AFFERENT WOUND EVENTS
(TRANSFORMED CELLS)
Macrophages

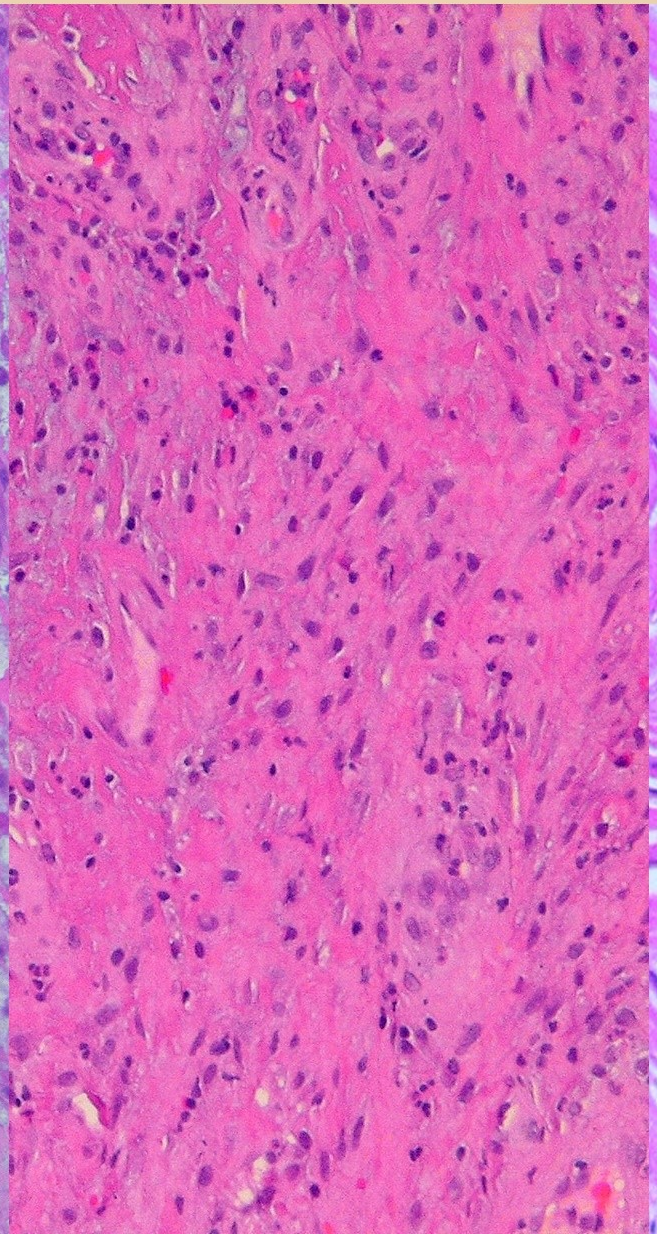
MESENCHYMAL REPAIR
(LOCAL CELLS)
2 cells:
Angiocytes & Fibroblasts

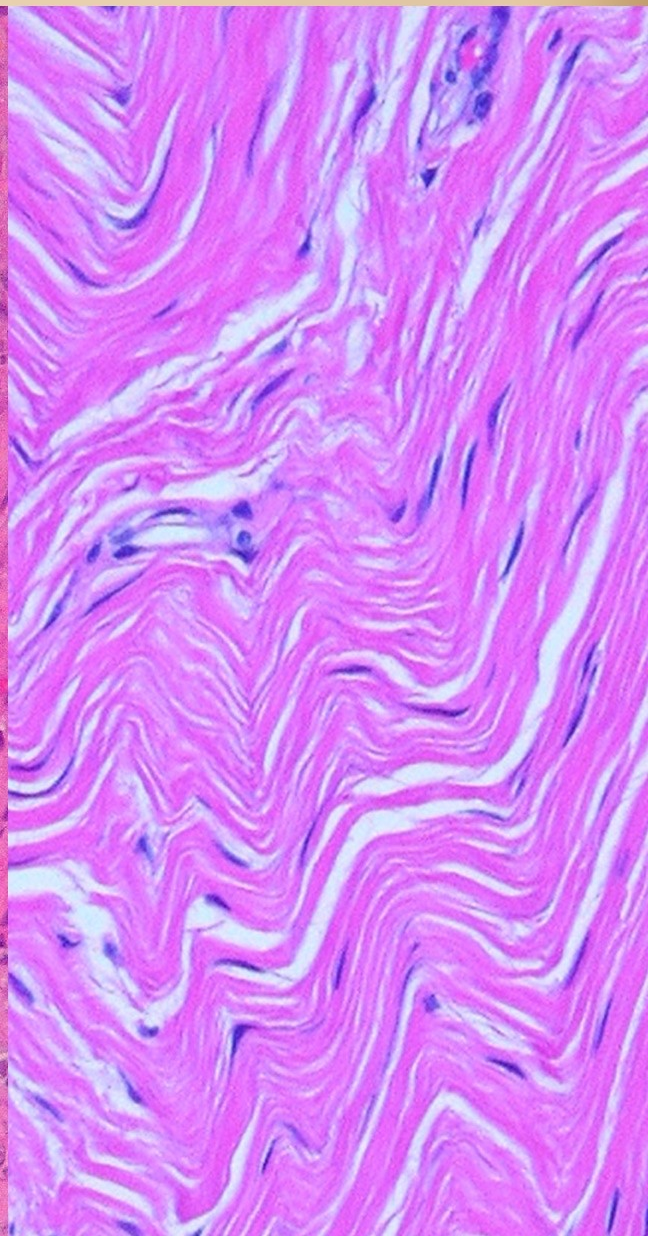
SEQUESTRATION
(LOCAL CELLS)
Epithelium

RESTORATION OF STROMA

REPAIR IS BASED ON 2 CELL TYPES - ANGIOCYTES & FIBROBLASTS







AUTOIMMUNOPATHY, CHRONIC INFLAMMATION, & CONNECTIVE TISSUE DISORDERS

THE TRUE INTRINSIC DISEASES OF WOUND HEALING

Stromal angiocytes and fibroblasts (wound cells) have remarkably few inherent metabolic or genetic faults.

Dysfunction of the aggregate population is almost always the result of deprivation or predation.

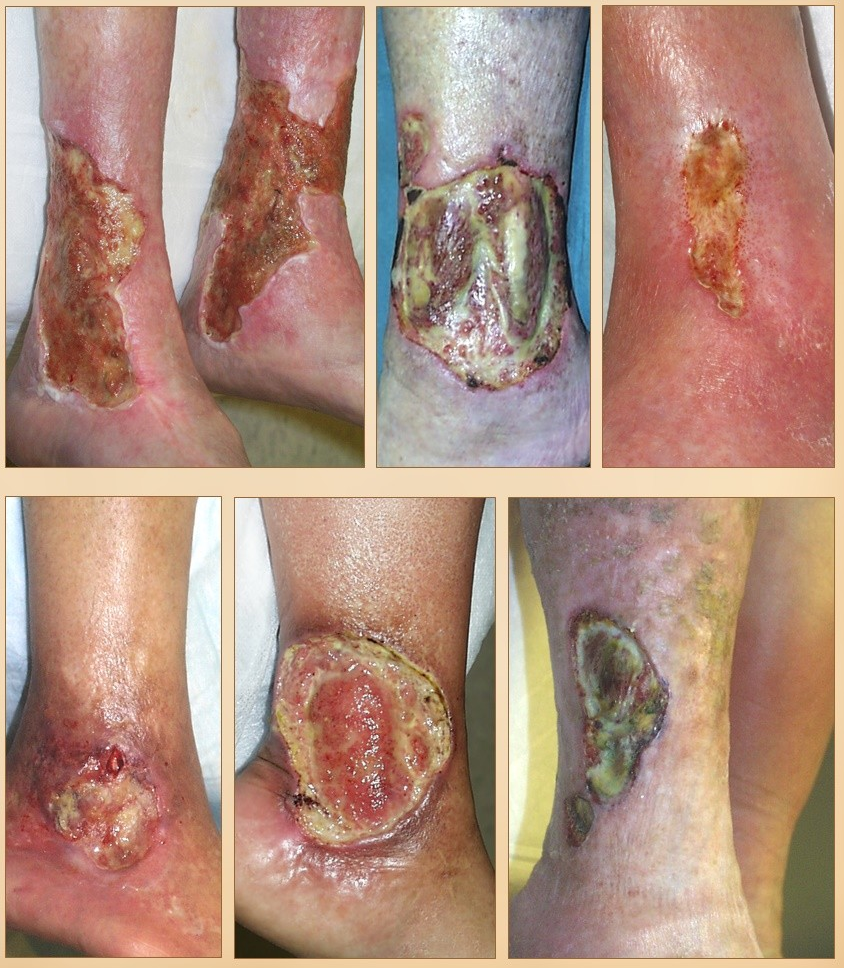
Such adverse states are caused by
(1) non-targeted exogenous conditions
e.g. arterial ischemia or repetitive trauma
(2) targeted damage directed against
these cells and their structures.

Targeted predation against the wound module is due to a state of auto-immunopathy in which lymphoid cells are sensitized to wound components.

This occurs with classic connective tissue disorders and other recognized auto-immunopathies.

It also happens when a wound becomes intrinsically chronic and pathological.

Hypercoagulability and other conditions of persistent thrombosis and acute inflammation are the underlying states that induce the auto-immunization.



NECROSIS & ULCERATION - TWO GENERAL PATHOLOGIES & PATTERNS

THROMBO-INFARCTIVE

Macro-occlusive

Micro-occlusive

Micro-angiopathies

Hemopathologies

Hypercoagulable / Coagulopathic

INFLAMMATORY-LYTIC

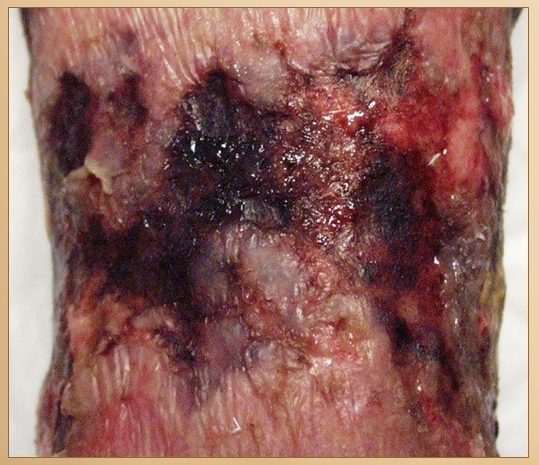
Inflammatory

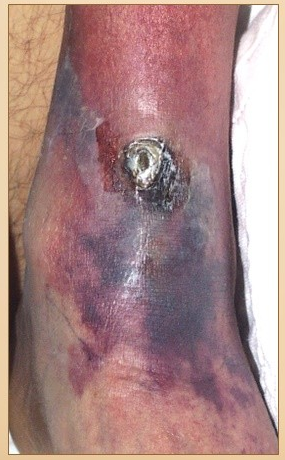
Autoimmune

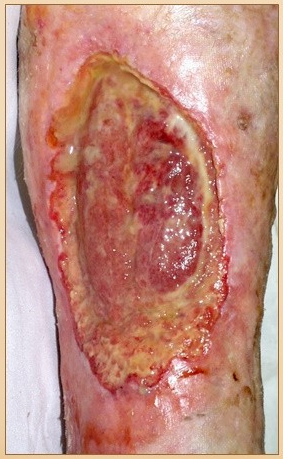
Atopic, Suppurative

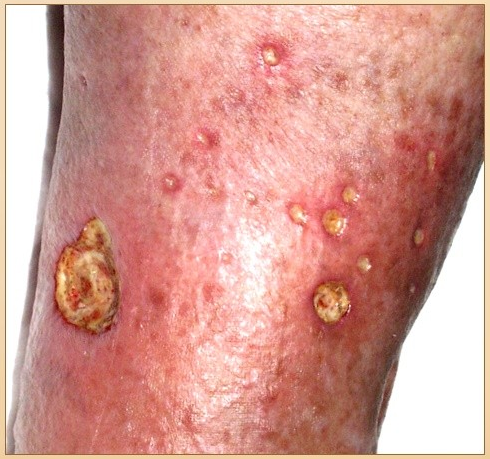
Connective Tissue Disorders

Lymphoreticular / Reticuloendothelial









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

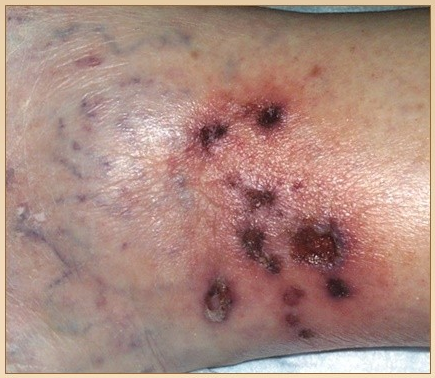
DYNAMICAL BEHAVIOR

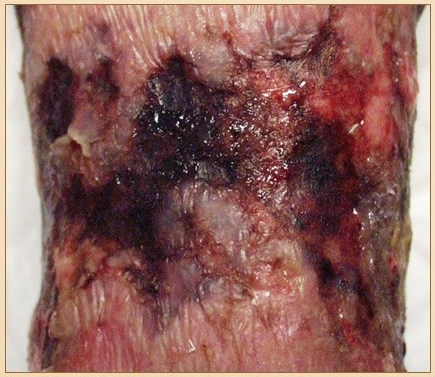
impaired wound
behavior characteristic
of severe ischemia

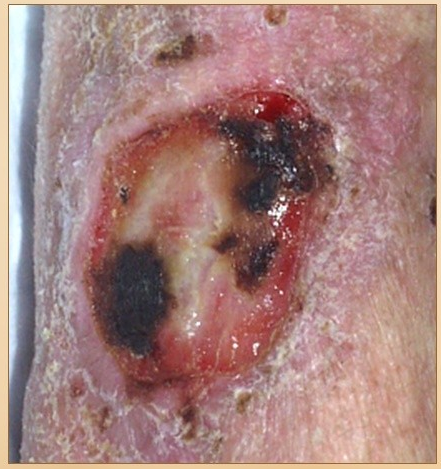
recalcitrant
continuously pathological
persistent active:
necrosis
pathergy
active ulceration

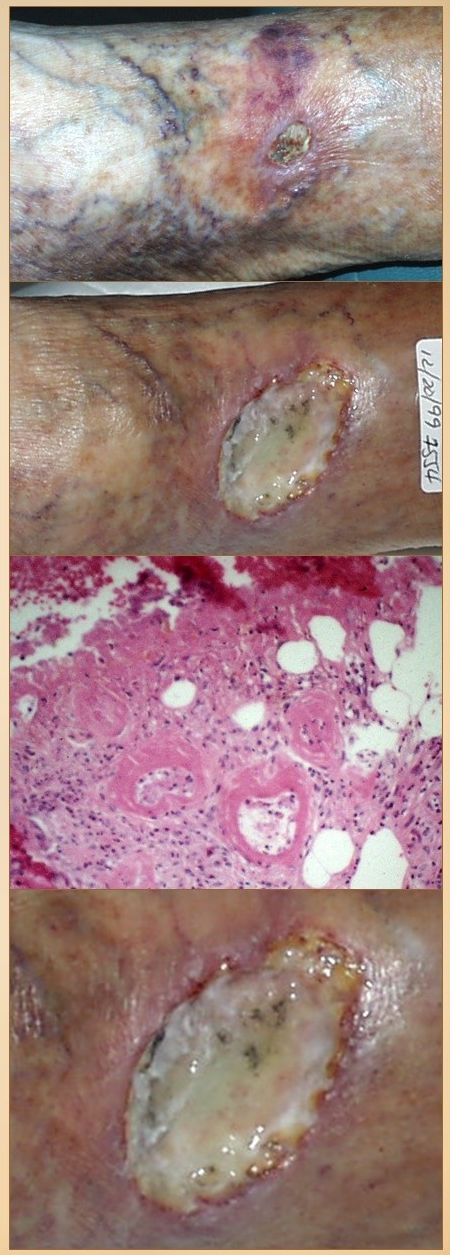
misbehavior over time

rapid evolution
slow resolution









HYPERCOAGULABLE STUDIES

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

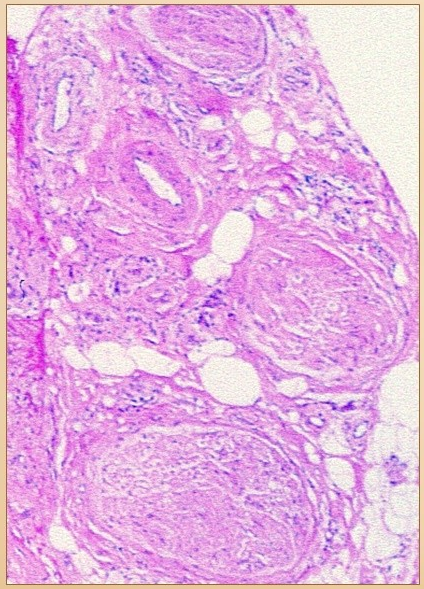
SCREEN FOR CONNECTIVE TISSUE DISORDERS

sedimentation rate
CRP
ANA
anti-DNA
rheumatoid factor

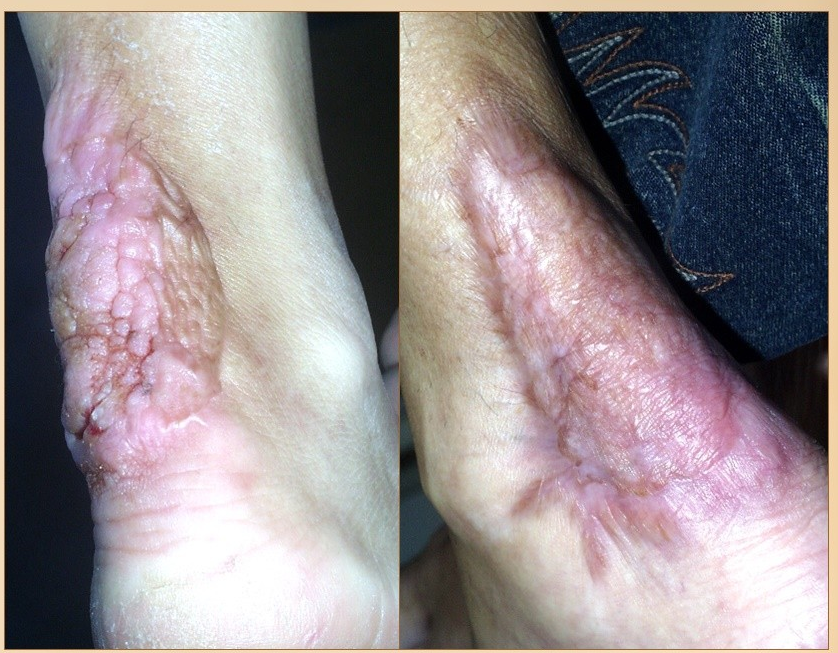
OTHER STUDIES

TcPO2
laser doppler

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



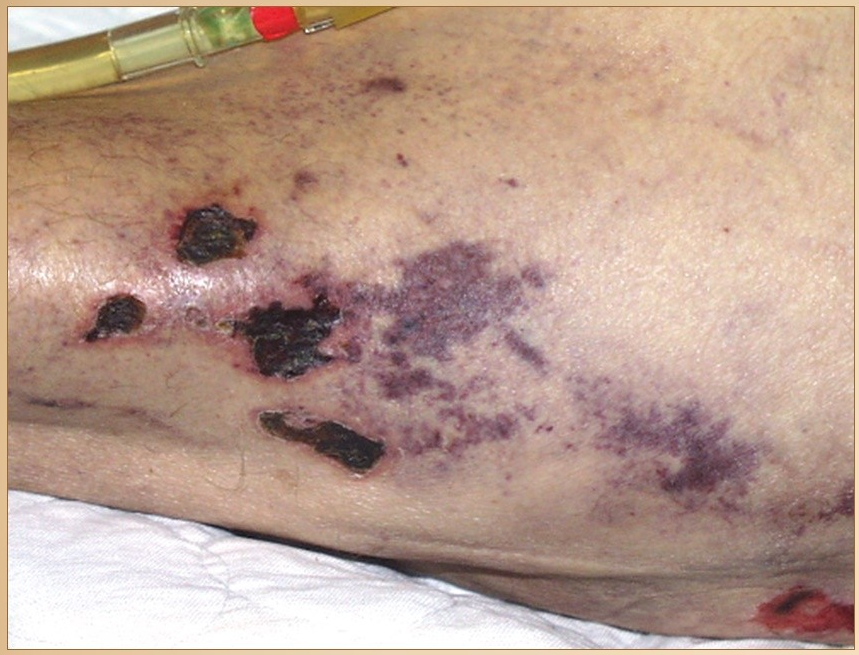
RECOGNITION & DIAGNOSIS - LABORATORY -

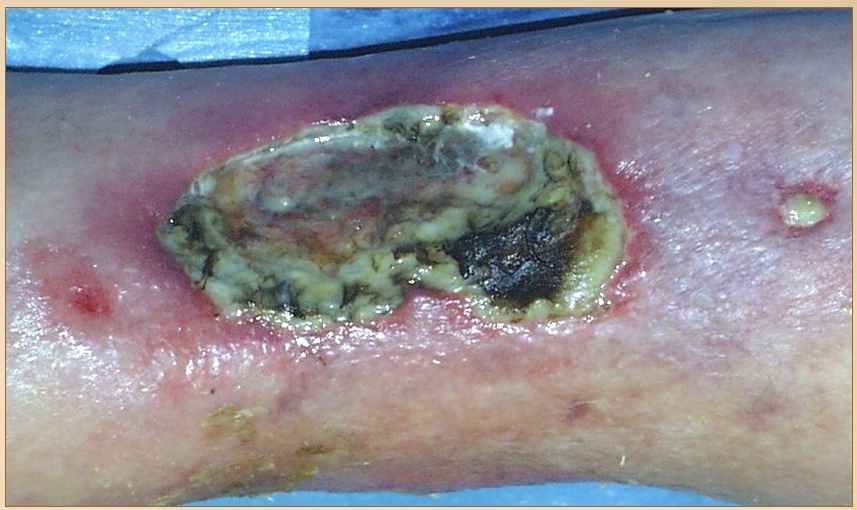


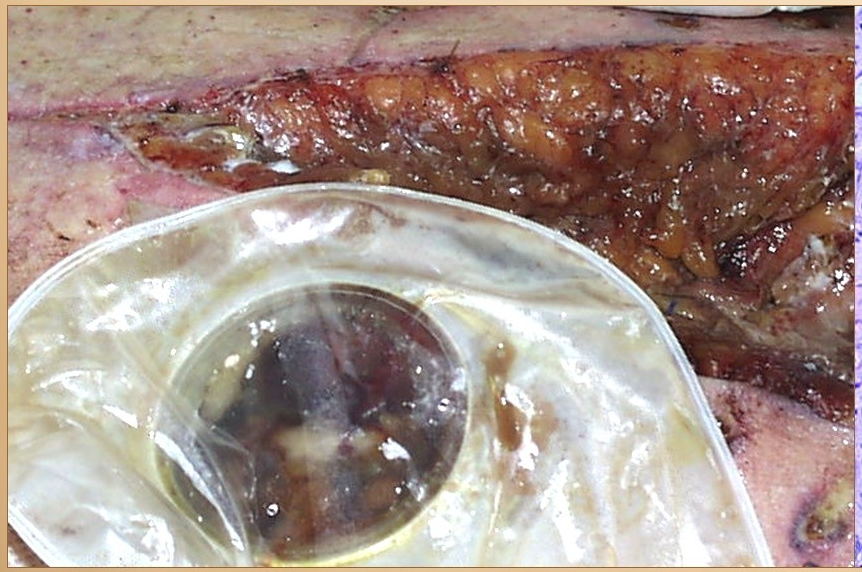
Hypercoagulable ulcers are NOT diagnoses of exclusion.

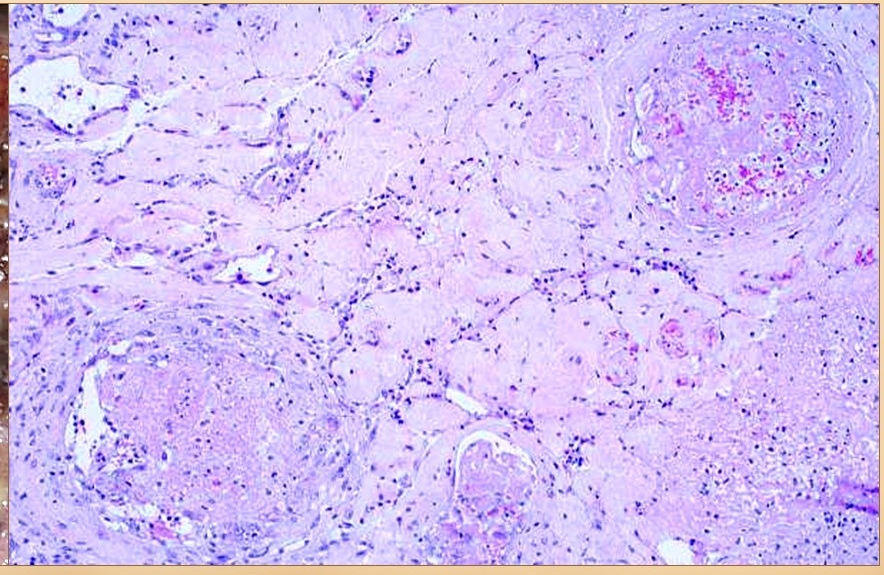
These diagnoses can be made on specific criteria.

HYPERCOAGULOPATHY
- BAD OUTCOMES -





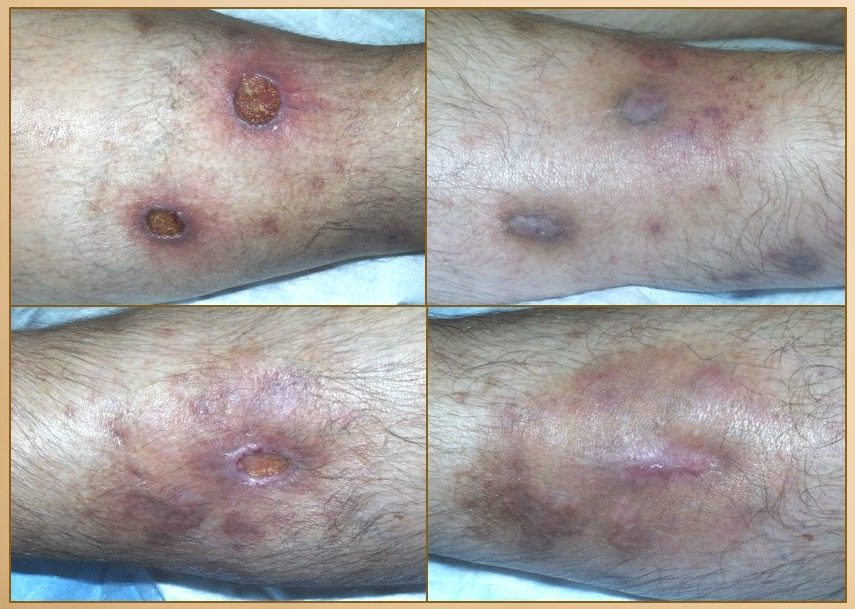


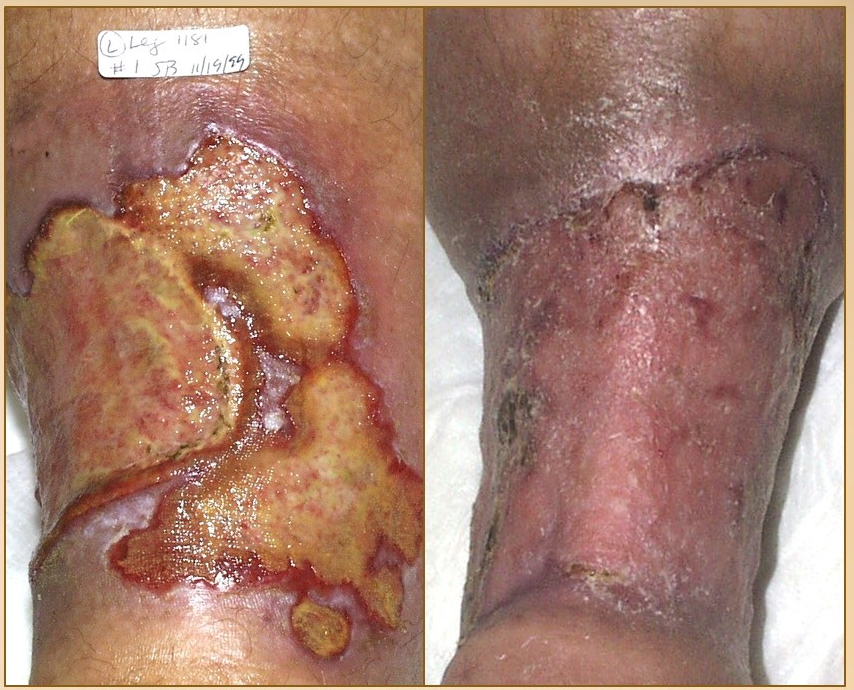


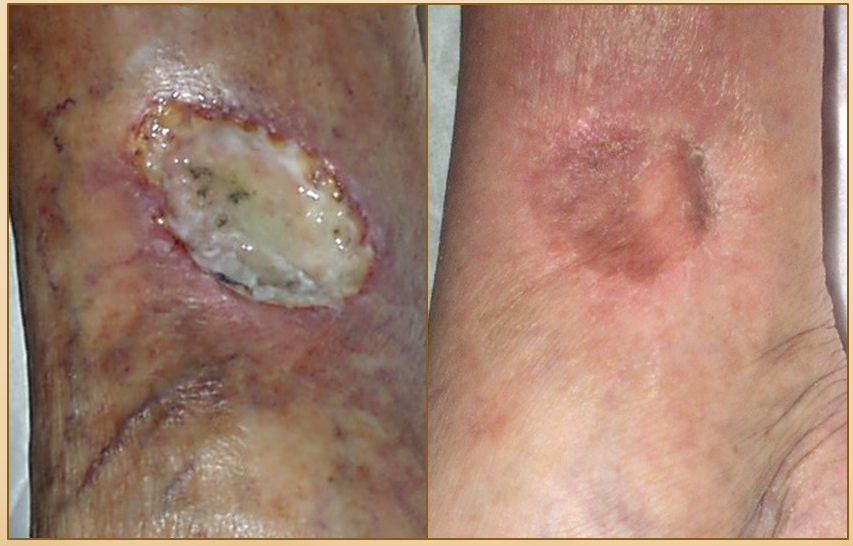
HYPERCOAGULOPATHY
- GOOD OUTCOMES -

KEY SYNDROMIC FEATURES

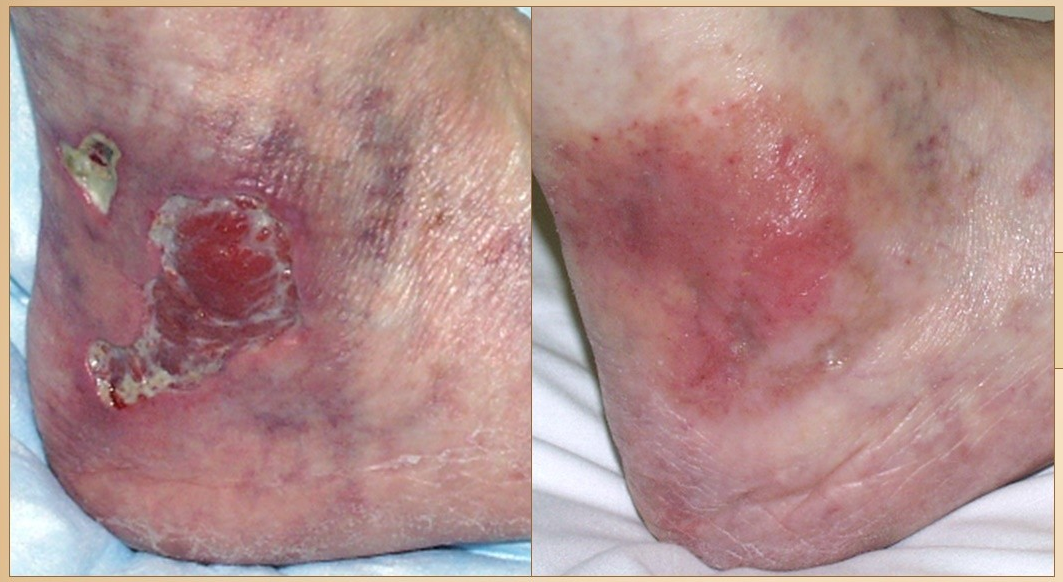
thrombotic - embolic events
miscarriages
wound pathergy
connective tissue disorder
family history

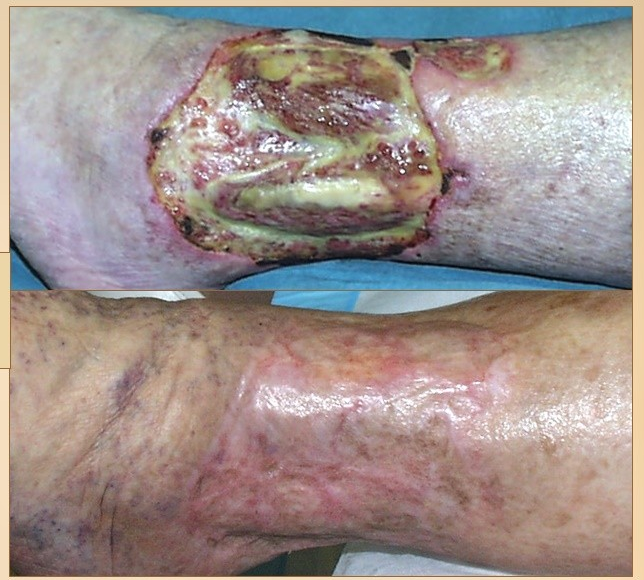


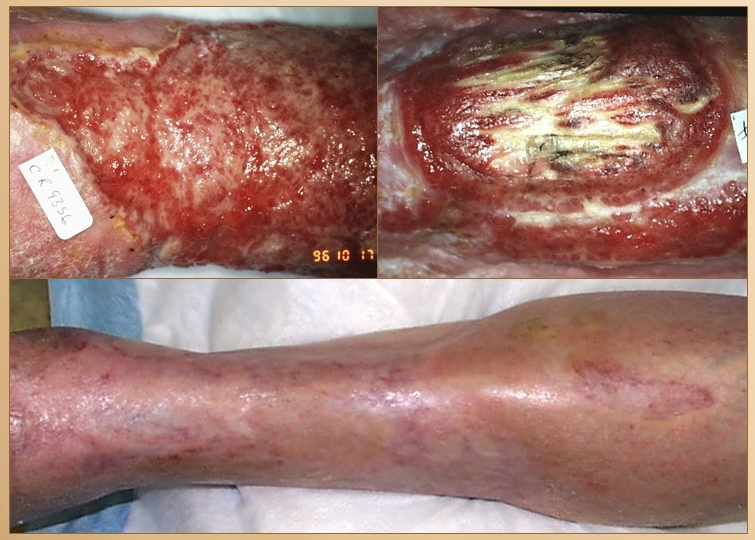


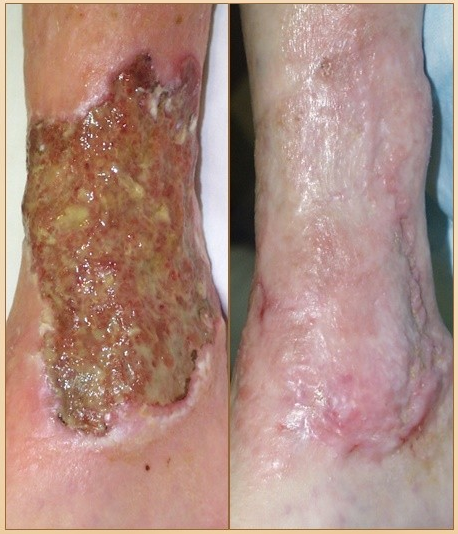


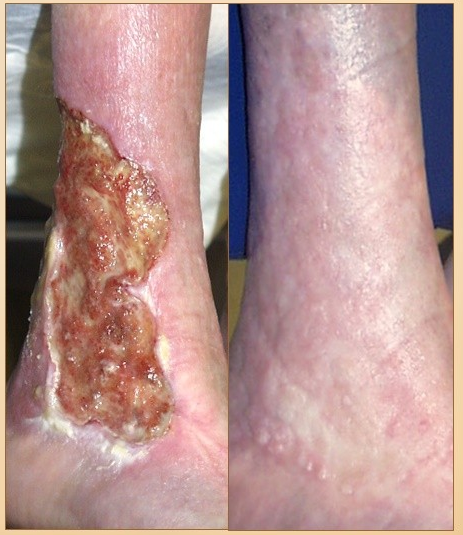
AUTO-IMMUNOPATHY

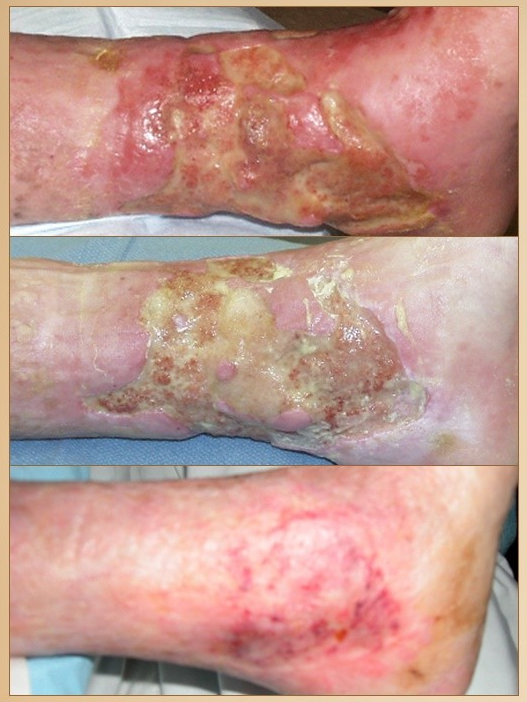


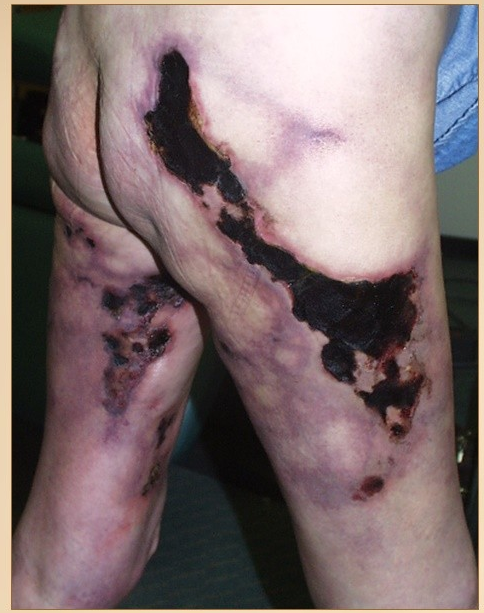


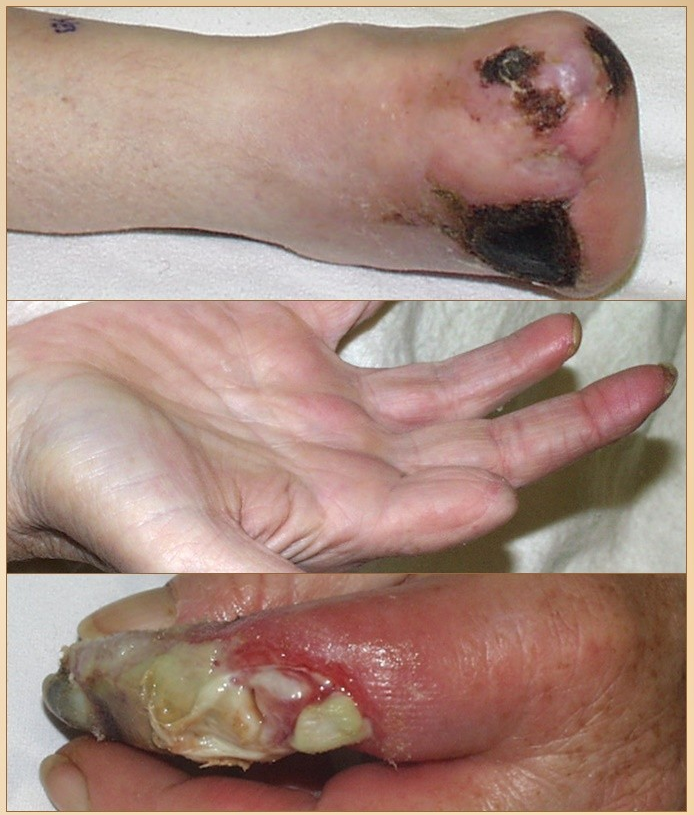


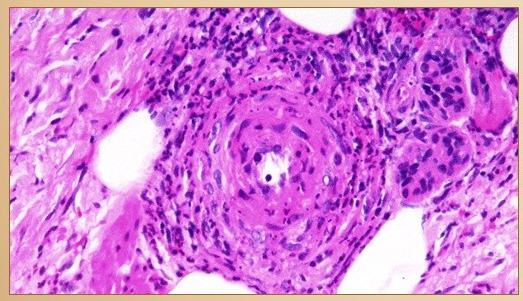


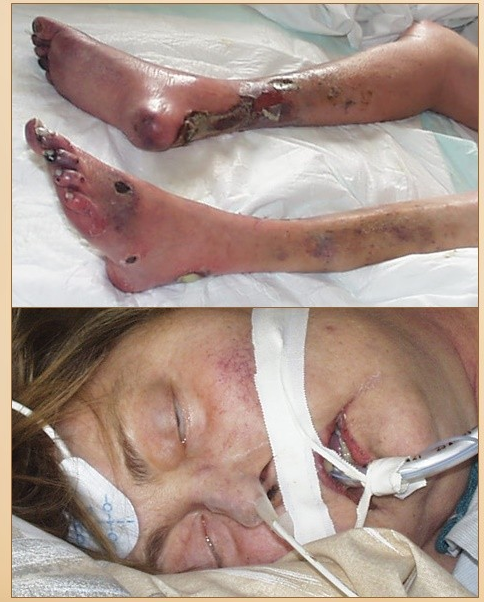


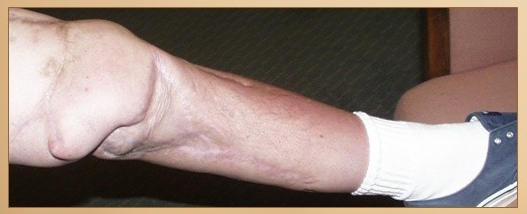


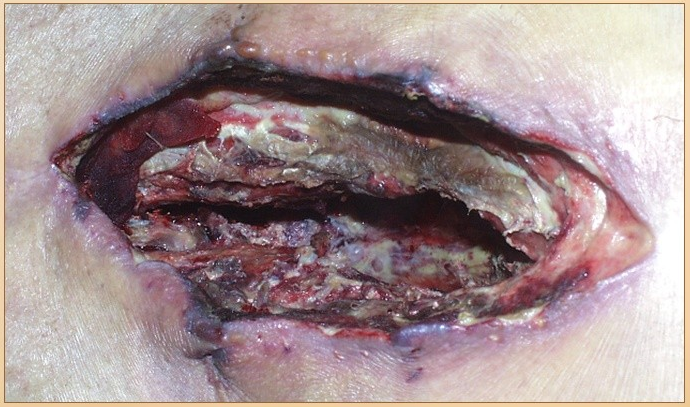








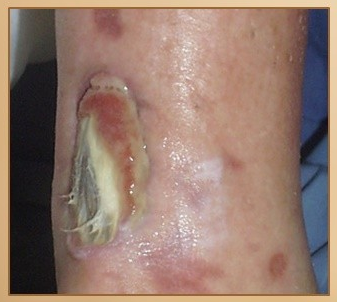




Immunopathies, Spectrum of Disease

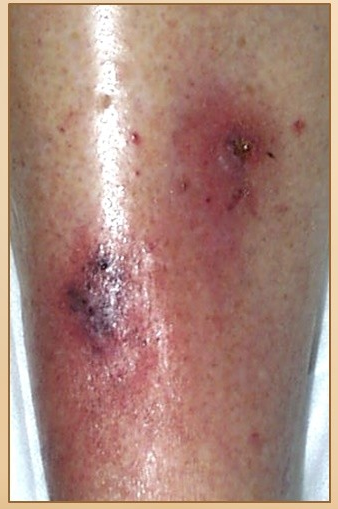
Connective Tissue Disorders

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



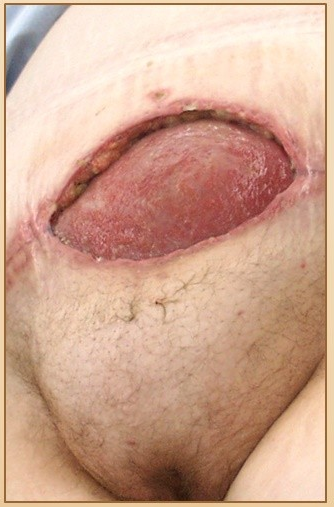
Vasculitides

polyarteritis nod.
autoimmune
giant cell
hypersensitivity
thromboangiitis



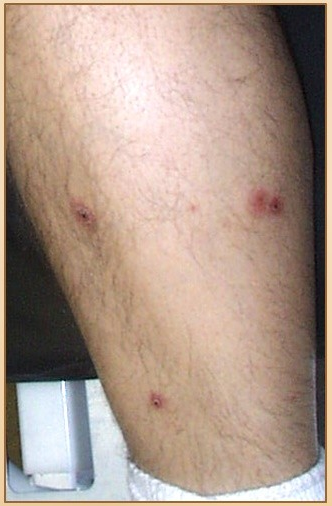
Fasciitis & Panniculitis

weber-christian
nodular fasciitis
erythema nodosum
necrobiosis
lipoidica



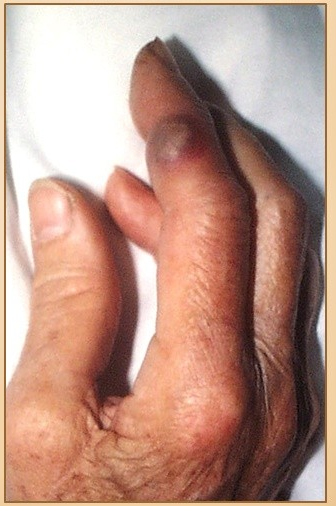
Miscellaneous

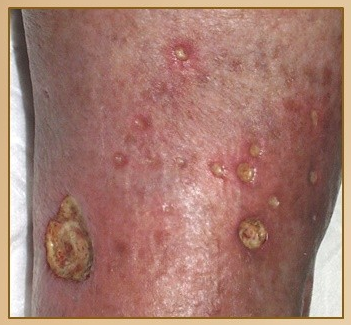
crohn's
ulcerative colitis
others

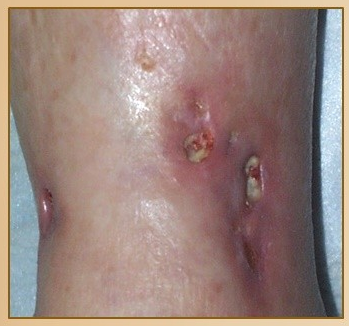


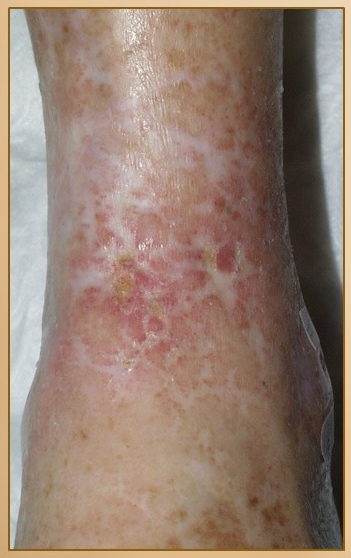
Inflammatory Dermatoses

eczema
pyoderma
gangrenosum
erythema nodosum
pemphigus / -goid



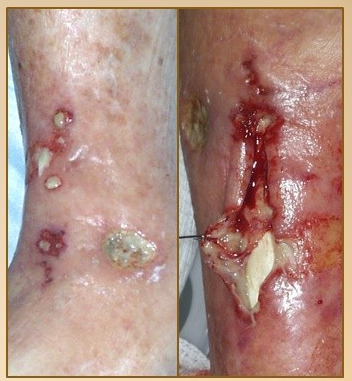


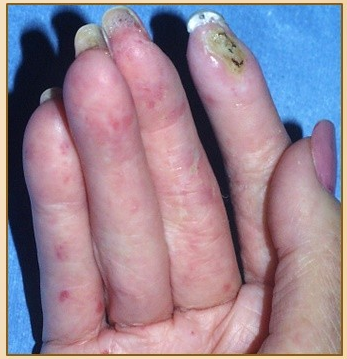


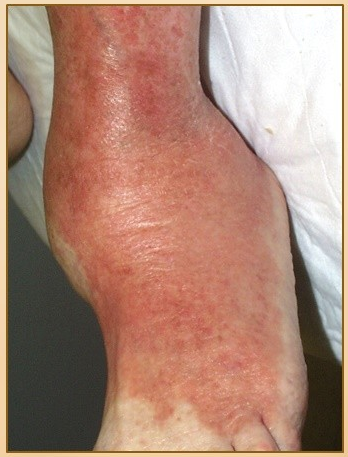


Immunopathies, Features and Findings

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

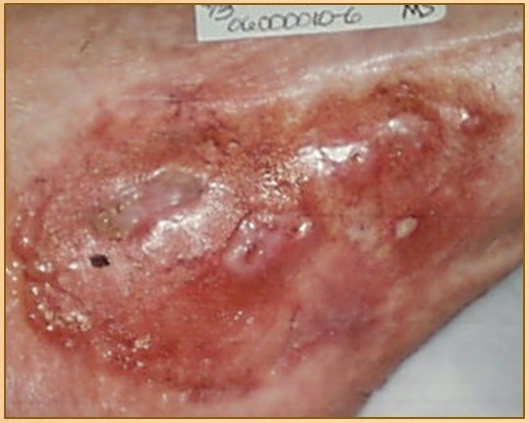


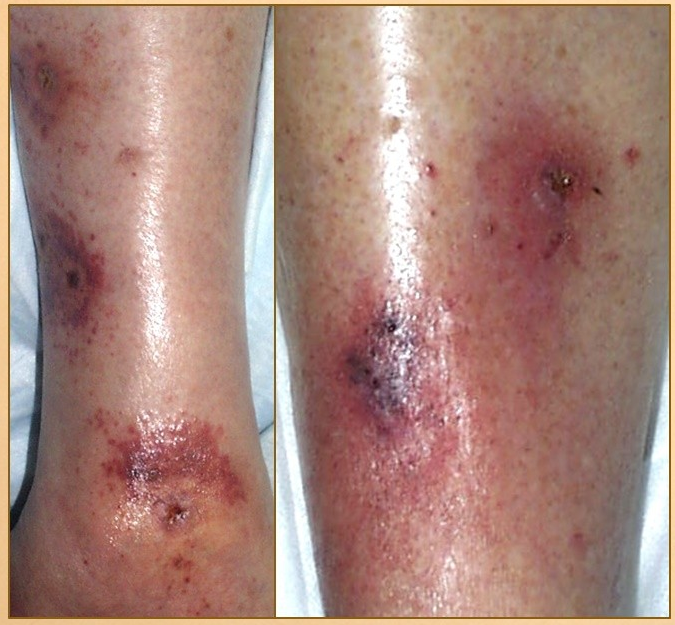




Immunopathic Ulceration . . . Physical Findings

Pre-Ulcerative



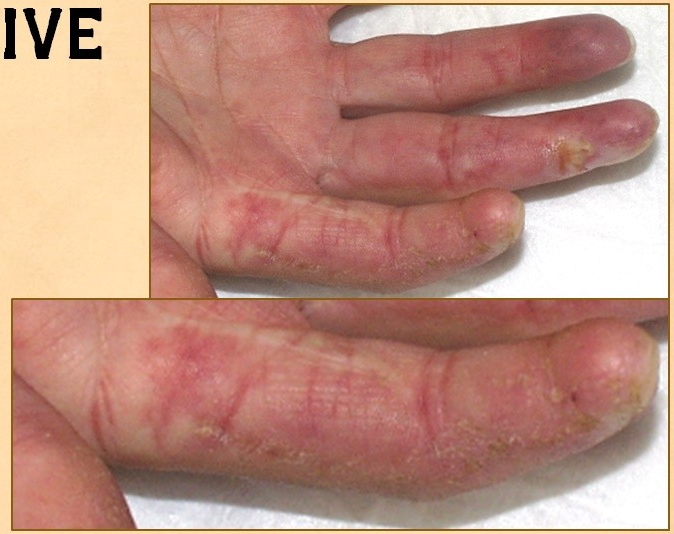


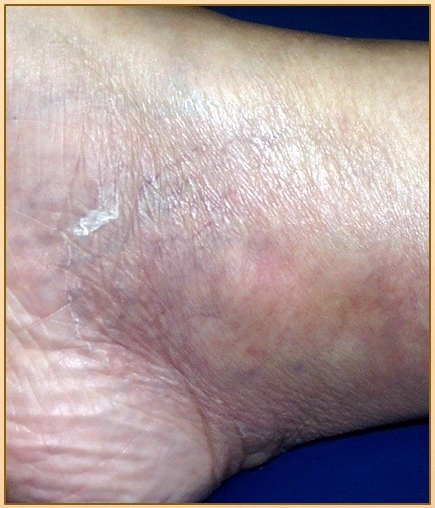
inflammation
edema
dermatitis
panniculitis

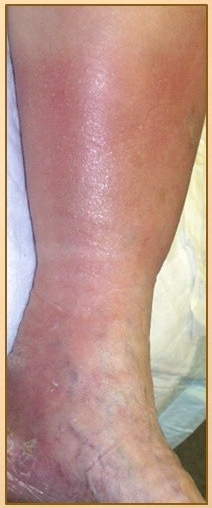
vascular stasis
congestion
infarction

systemic sx
malaise
athralgias, etc.
pain

distribution
focal
multifocal







Immunopathic Ulceration . . . Physical Findings

Acute & Early Ulcers

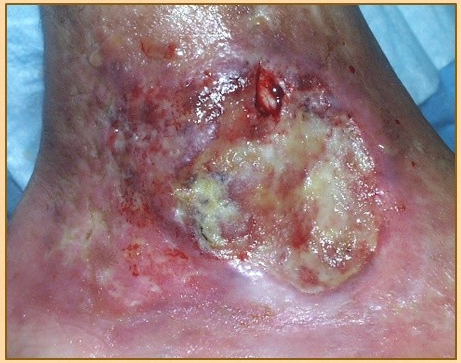
necrosis & ulceration

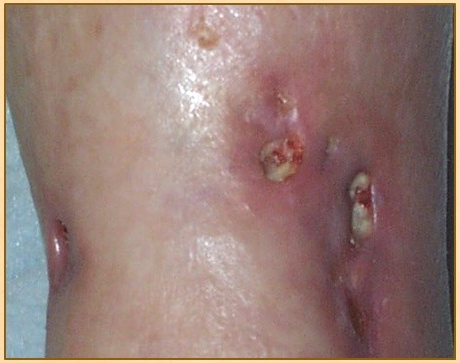
focal vs. multifocal

immune lysis vs. microthrombotic infarction

inflammed vs. bland

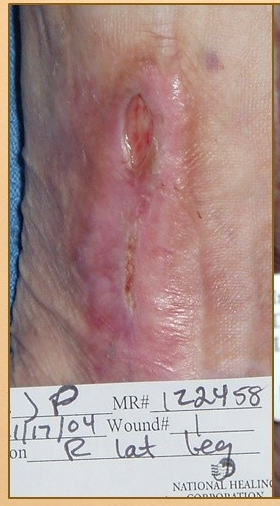
vasculitis & synovitis

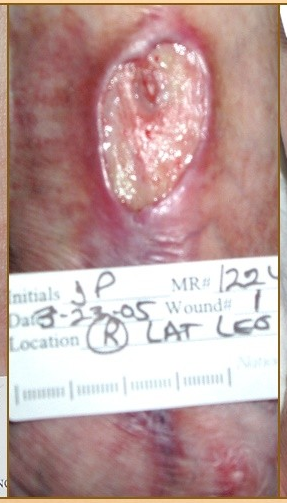


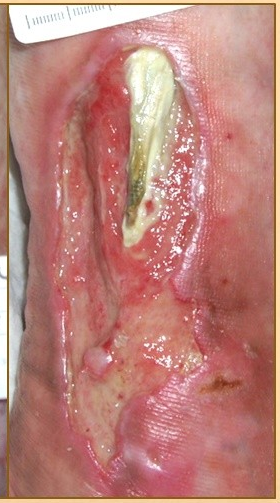


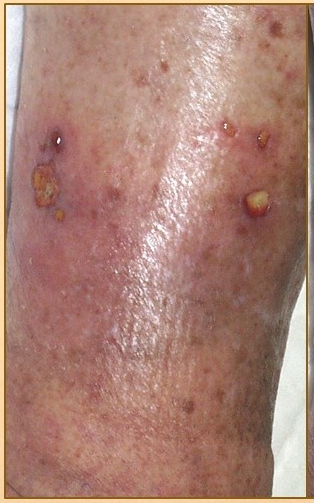
general

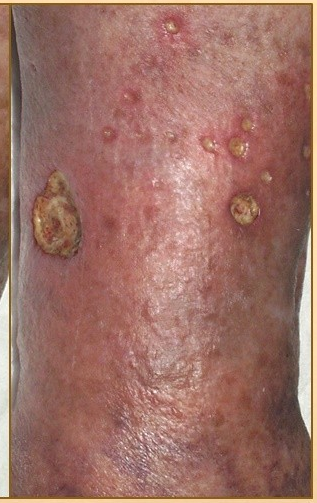
inflammation
dermatitis
panniculitis
vascular stasis
systemic sx
pain

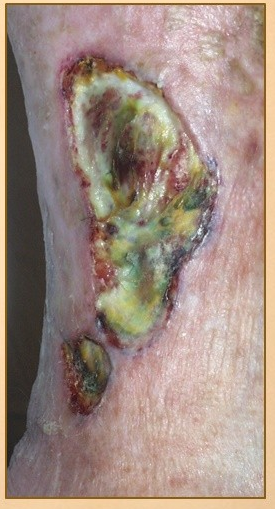






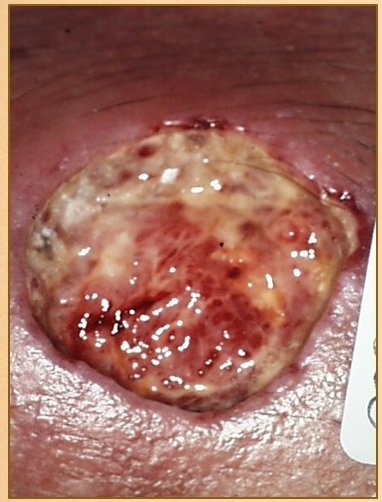


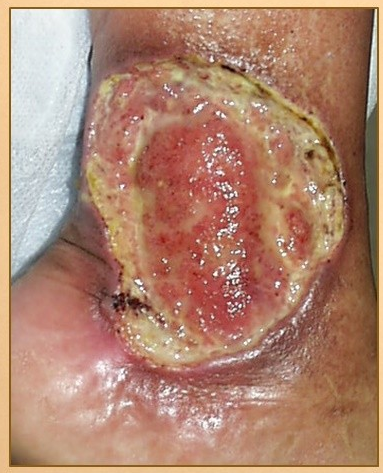


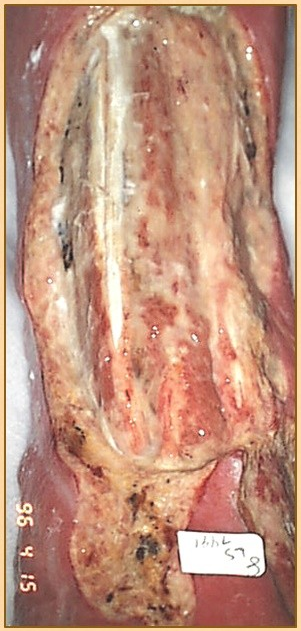


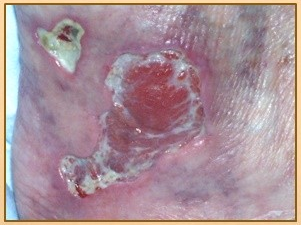
Immunopathic Ulceration . . . Physical Findings

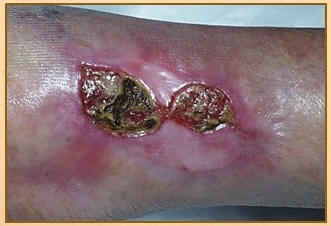
Late & Chronic Ulcers











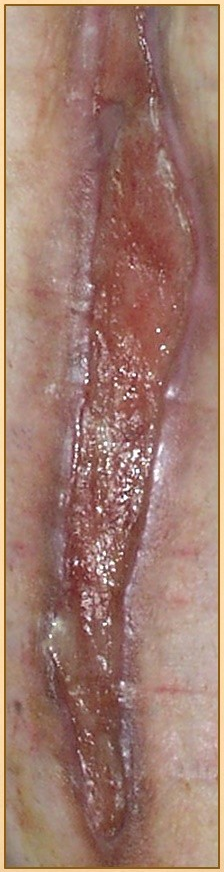
persistent inflammation

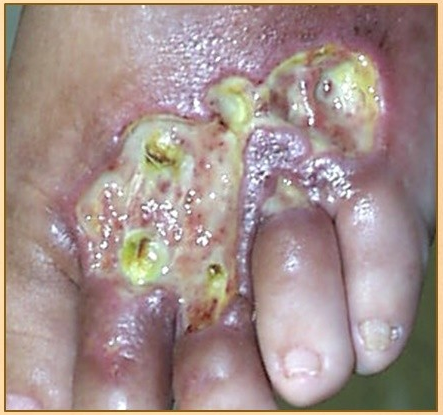
progressive ulceration

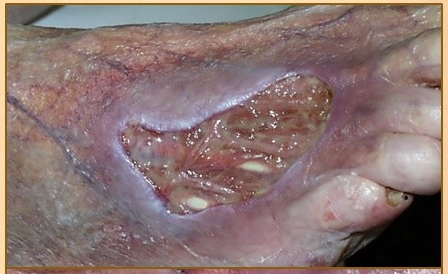
retarded wound module

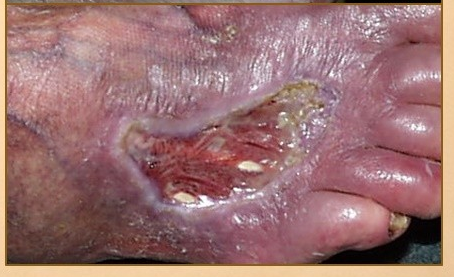
chaotic behavior

pain & symptoms

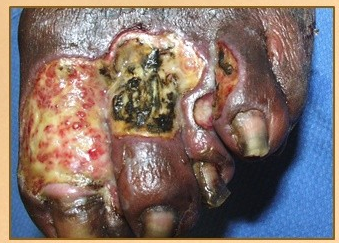




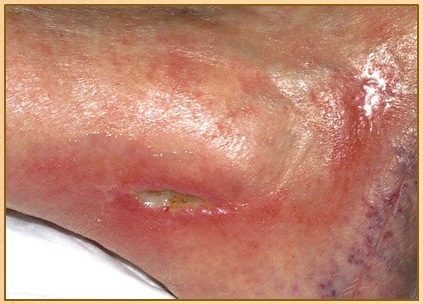


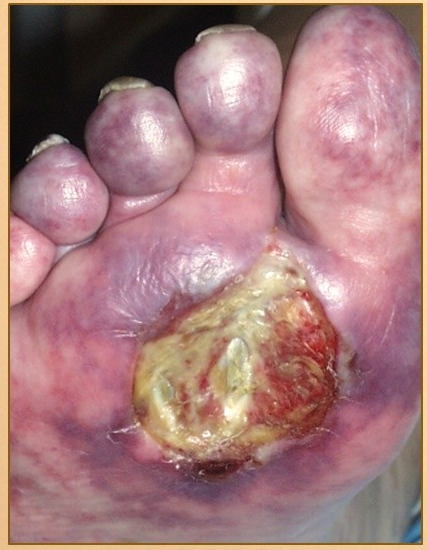


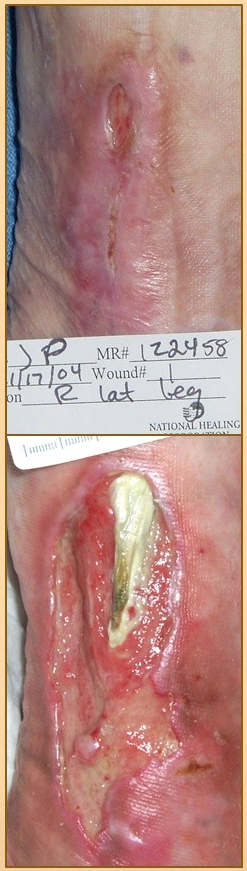
Immunopathic Ulceration . . . Physical Findings



Other Distinctive Findings







ulceration
along tendons

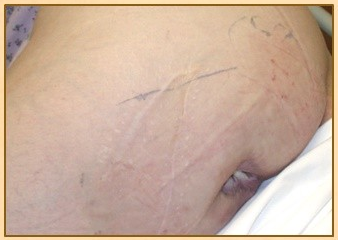
unstable scars
lysis & ulceration

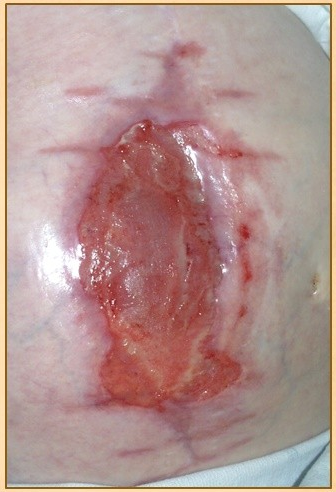
not just gaiter
not just leg

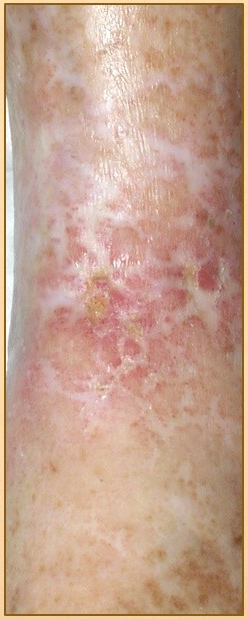
skin atrophy
skin sclerosis

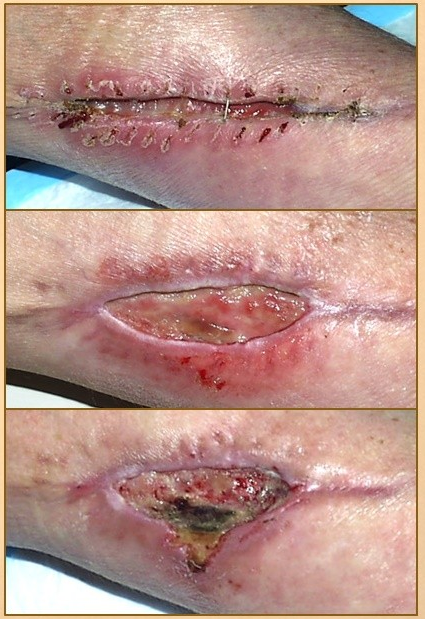
post-op & -injury
pathergy

features of
each disease



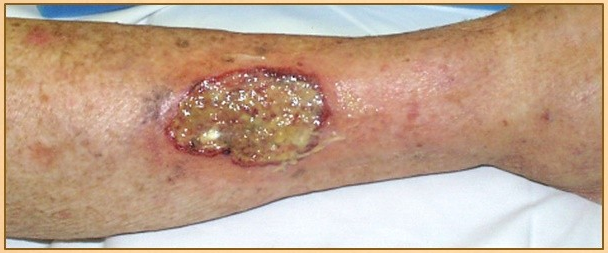


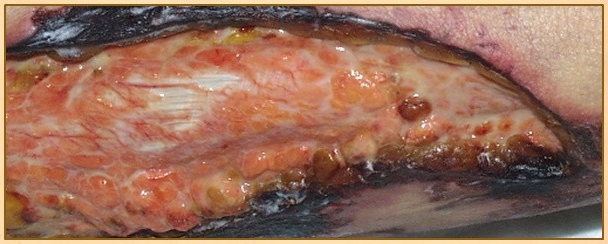


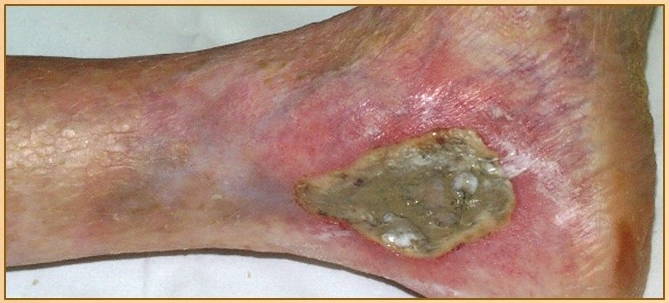


Immunopathic Ulceration . . . Physical Findings

What is NOT There







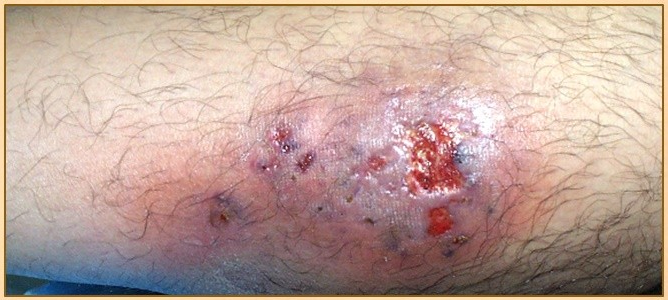
no venous

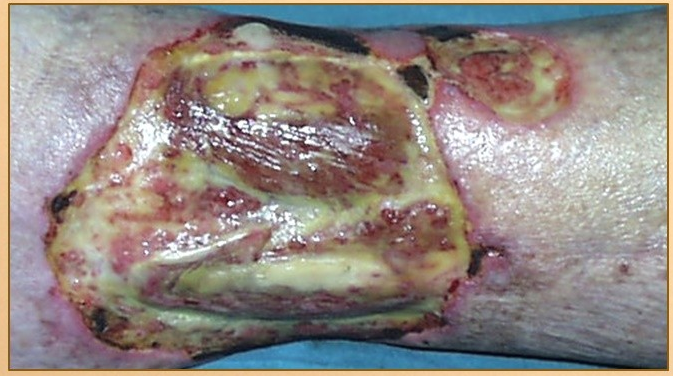
no arterial

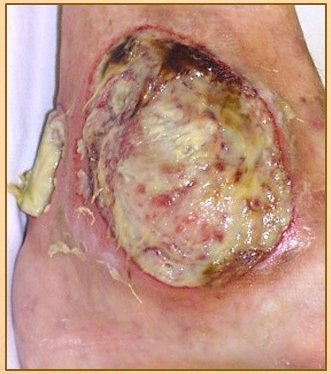
no eschar

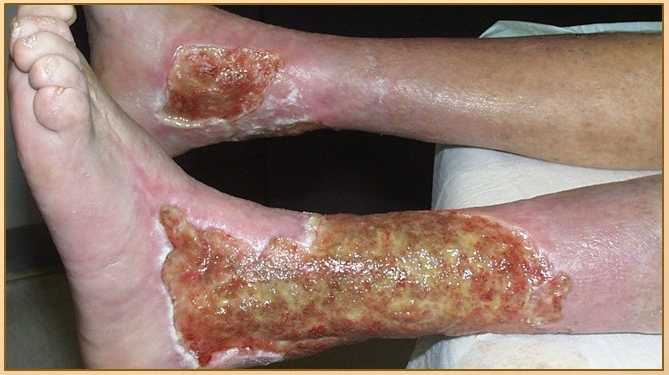
no wound module

age & risks

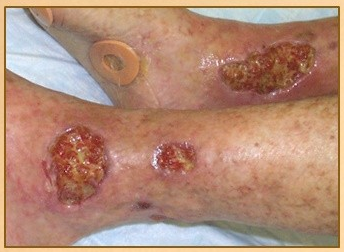




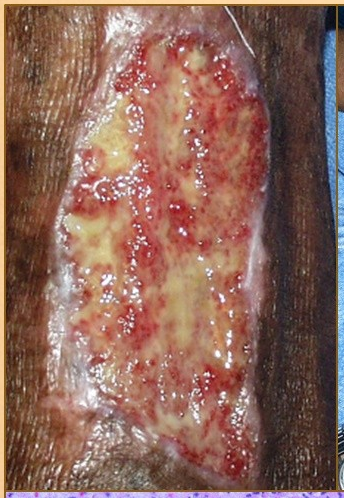


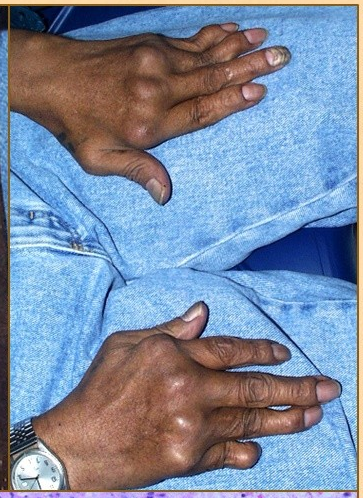


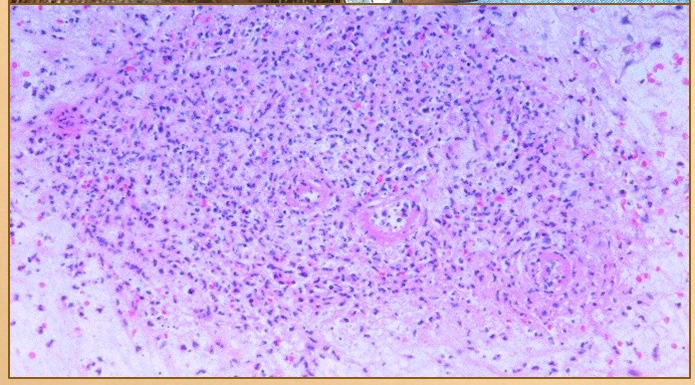
Immunopathic Ulceration . . . Physical Findings



General Exam & History







general physical exam

common signs of immunopathy

inflammatory state

arthropathies

neurolepsy & neurological

malaise & systemic

laboratory histology

history & system review

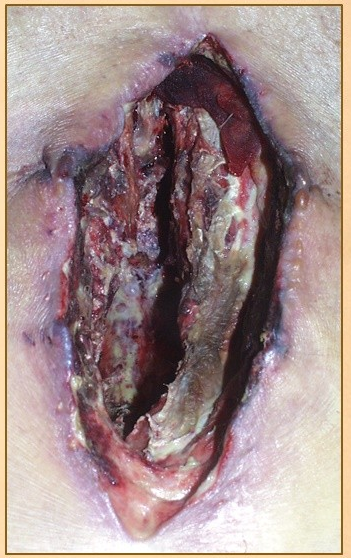
disease history
family hx
Rx history

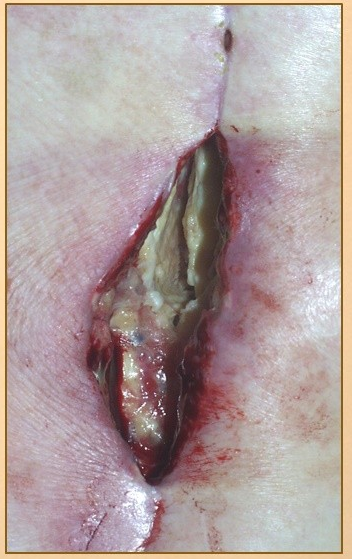
steroids lowered

complications of trauma or surgery

disease associations

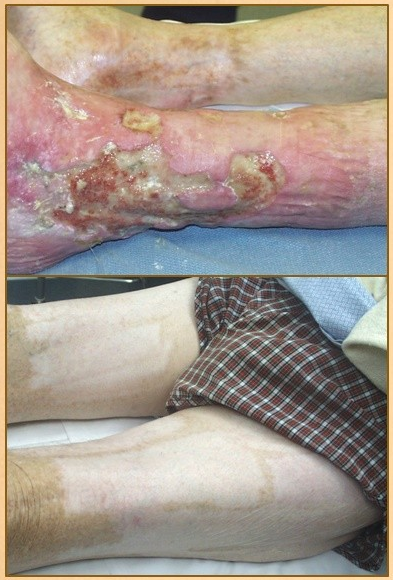
vasculopathies
hypercoagulopathy
neurological
renal
pulmonary

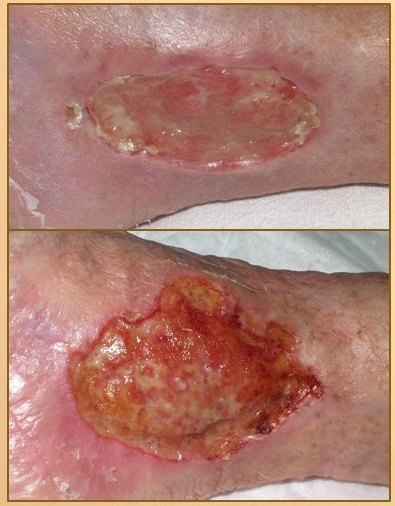


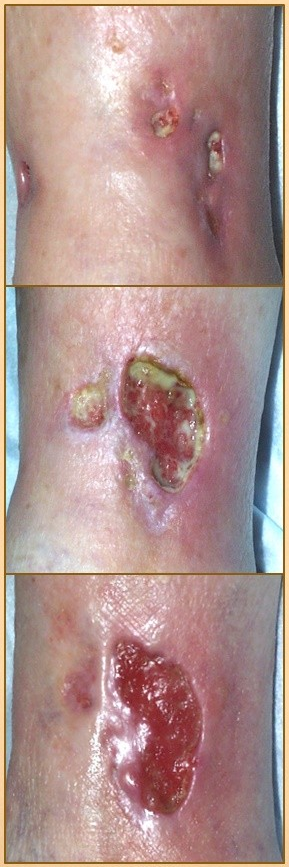


Immunopathic Ulceration . . . Physical Findings

Treatment History





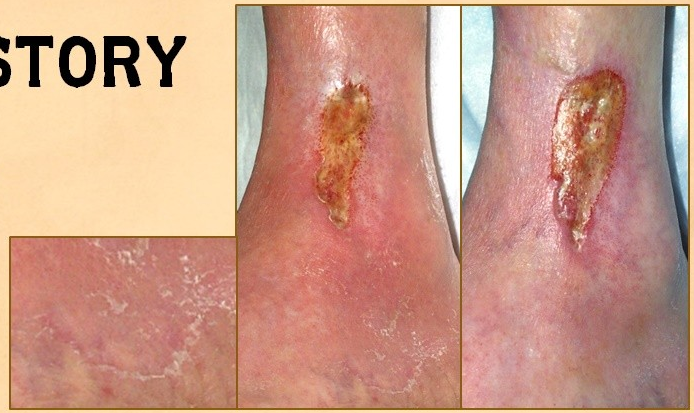


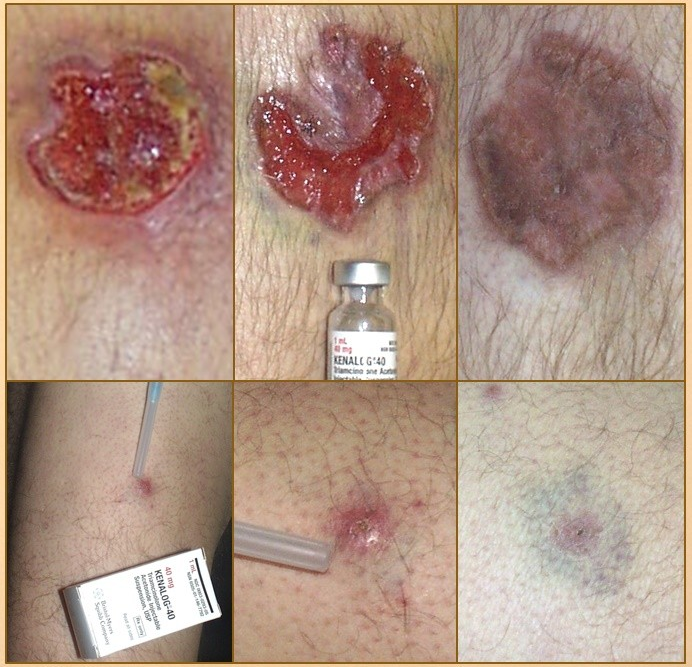
no response
failed Rx
multiple failed Rx
surgery failures

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

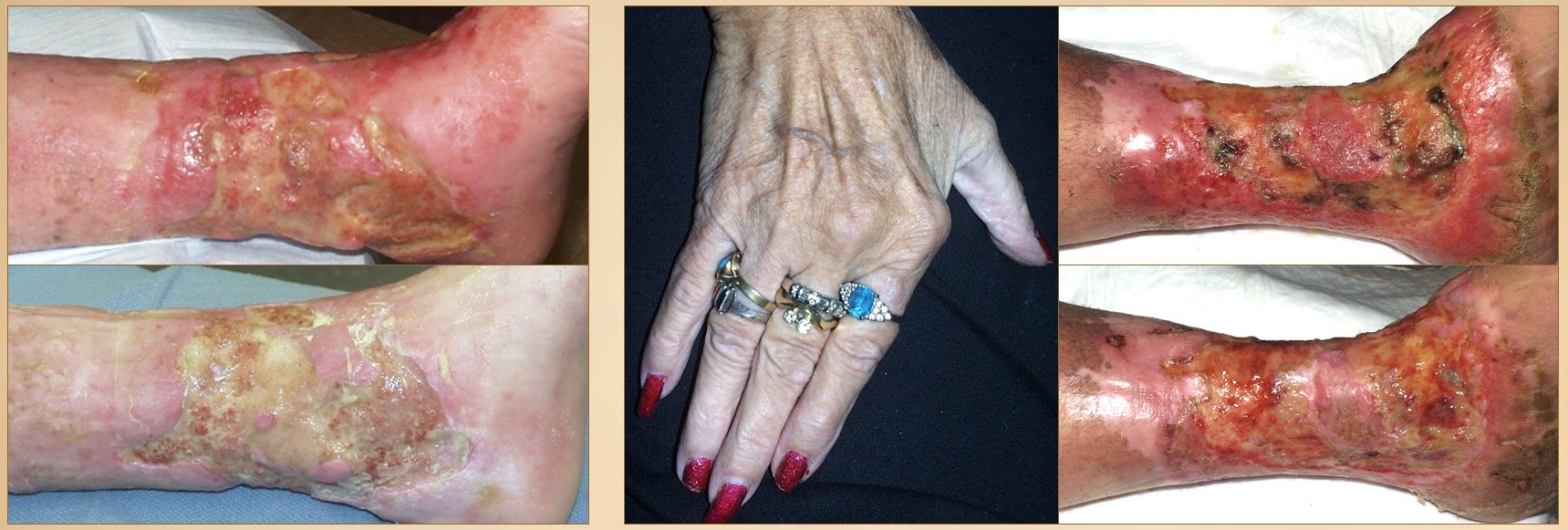
correct response
steroids
anti-immune
anti-inflammatory

contrary response
cytokines

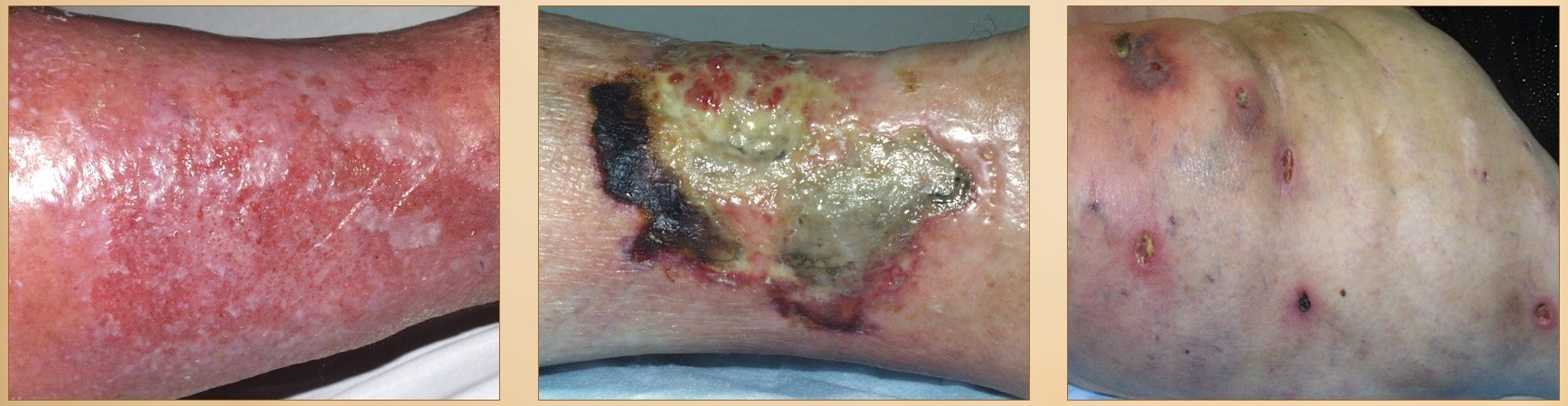




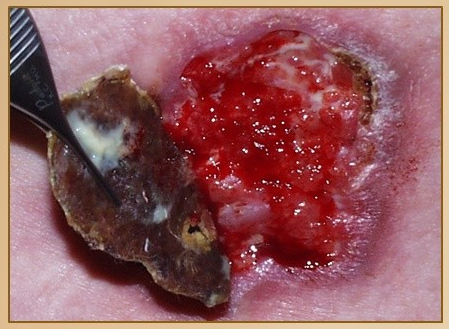
THE COMMONALITY of the CONNECTIVE TISSUE DISORDERS

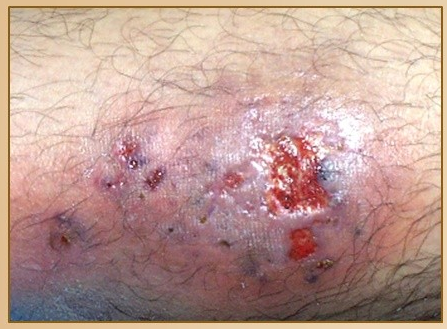


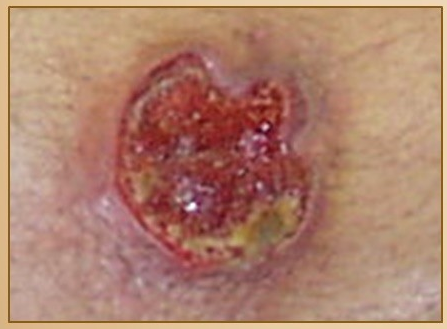
AUTO-IMMUNOPATHY & THE CONNECTIVE TISSUE DISORDERS :: RHEUMATOID WOUNDS

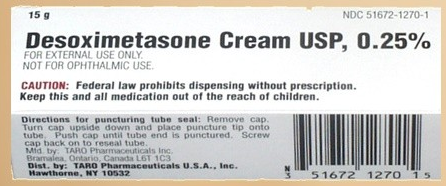


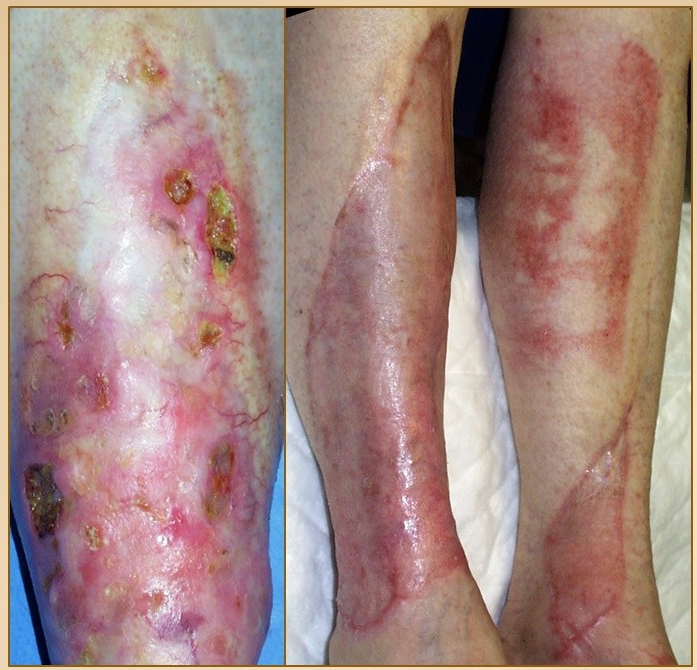
AUTO-IMMUNOPATHY & NON-RHEUMATOLOGY DISORDERS :: DERMATOSES & PANNICULOPATHIES

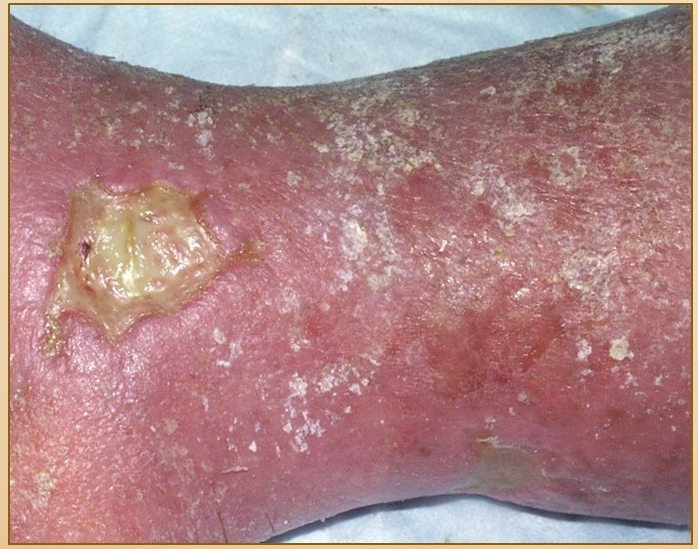


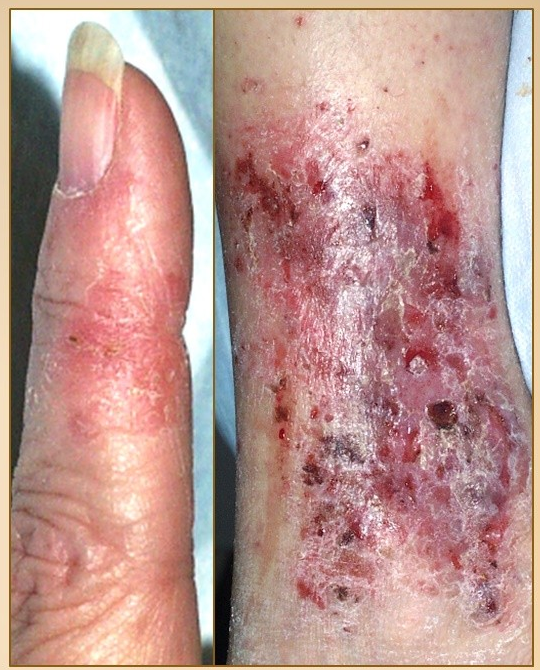


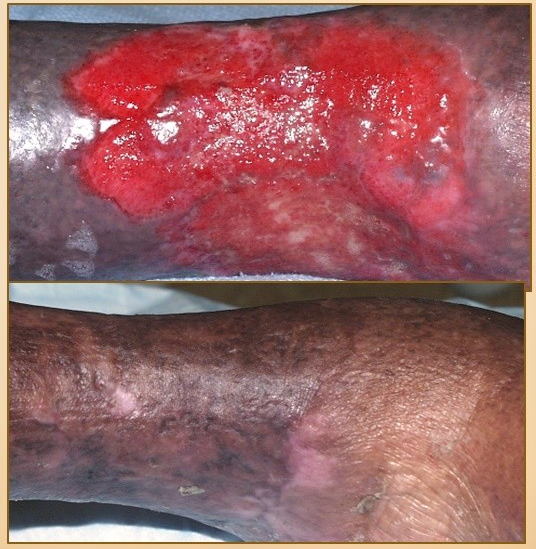



15 g
NDC 51672-1270-1
Desoximetasone Cream USP, 0.25%
FOR EXTERNAL USE ONLY.
NOT FOR OPHTHALMIC USE.
CAUTION: Federal law prohibits dispensing without prescription.
Keep this and all medication out of the reach of children.
Directions for puncturing tube seal: Remove cap. Turn cap upside down and place puncture tip onto tube. Push cap until tube end is punctured. Screw cap back on to reseal tube.
Mfd. by: TARO Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C3
Dist. by: TARO Pharmaceuticals U.S.A., Inc.
Hawthorne, NY 10532
51672 1270 1 5









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
Autoimmune pneumonitis
Polyserositis
MCTD – UCTD - NCTD

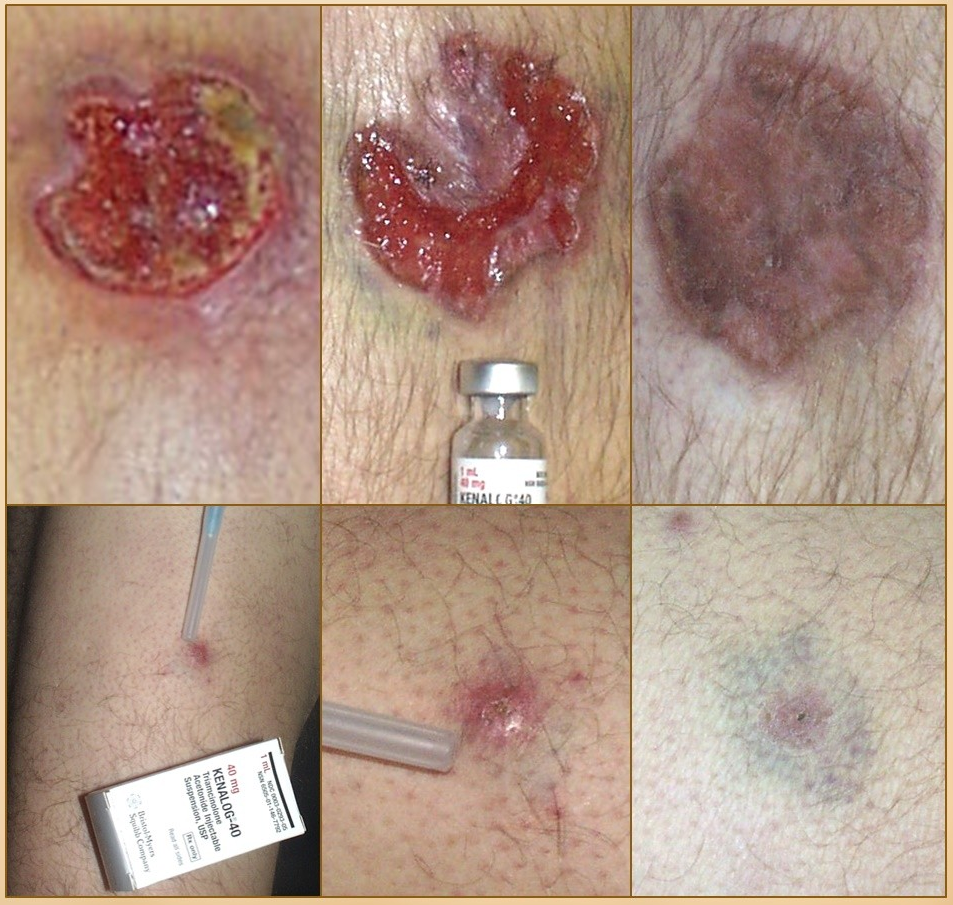
**Rheumatology, Dermatology,
Allergy & Immunology, Hematology
Gastroenterology, Neurology, Nephrology,
Endocrinology, Cardiology, Pulmonary**

Concept of a common autoimmune disease

MCTD
Mixed connective tissue disorder

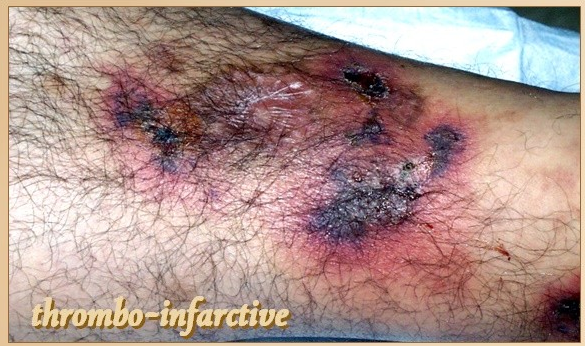
UCTD
Undifferentiated connective tissue disorder

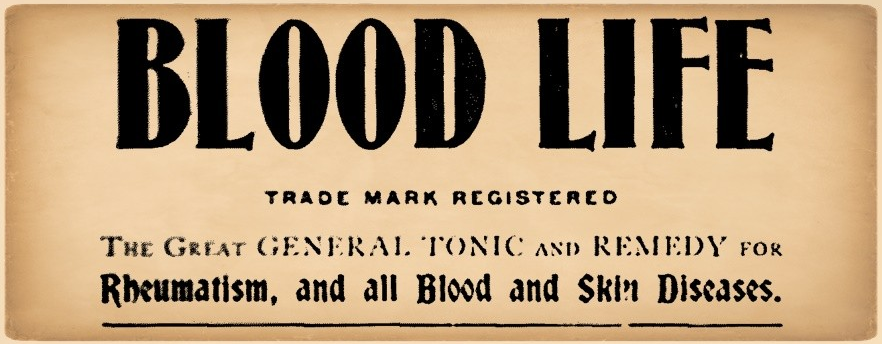
NCTD
Non-specific connective tissue disorder



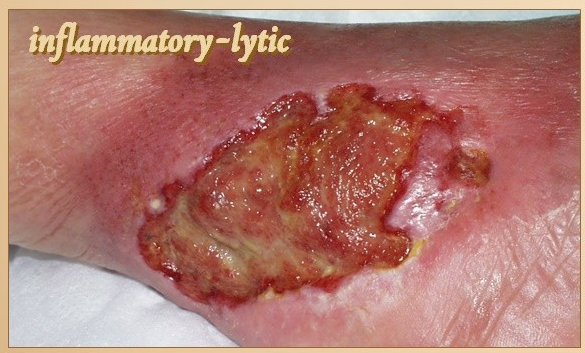
SUMMARY - HYPERCOAGULOPATHY & AUTO-IMMUNOPATHY

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





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



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 - UCTD - NCTD.

AUTOIMMUNITY - COLLAGEN-VASCULAR & CONNECTIVE-TISSUE PATHOLOGY

WHY ARE THESE CALLED

"COLLAGEN-VASCULAR DISEASES"
"CONNECTIVE TISSUE DISORDERS"

rheumatoid
lupus
sjögren's
scleroderma
polymyositis
dermatomyositis
ank. spondylitis
behçet's
wegener's
reiter's syndrome

sarcoidosis
fam. med. fever
polyarteritis nodosa
giant cell arteritis
takayasu's
thromboangiitis
weber-christian
nodular fasciitis
eosinophilic fasciitis
erythema nodosum

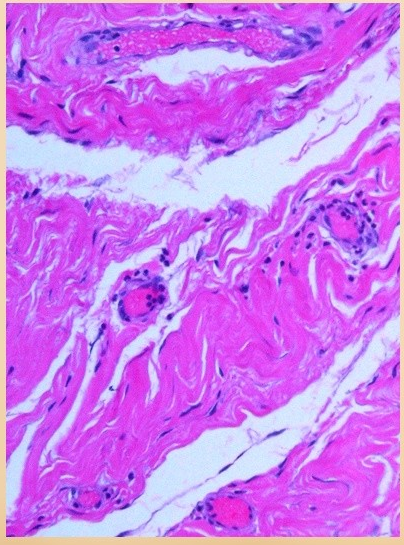
WHY ARE THESE TISSUES, CELLS, & STRUCTURES AFFECTED?

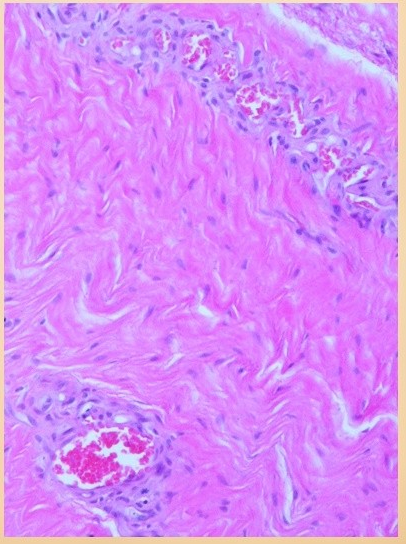
Mesoderm - Mesenchyme

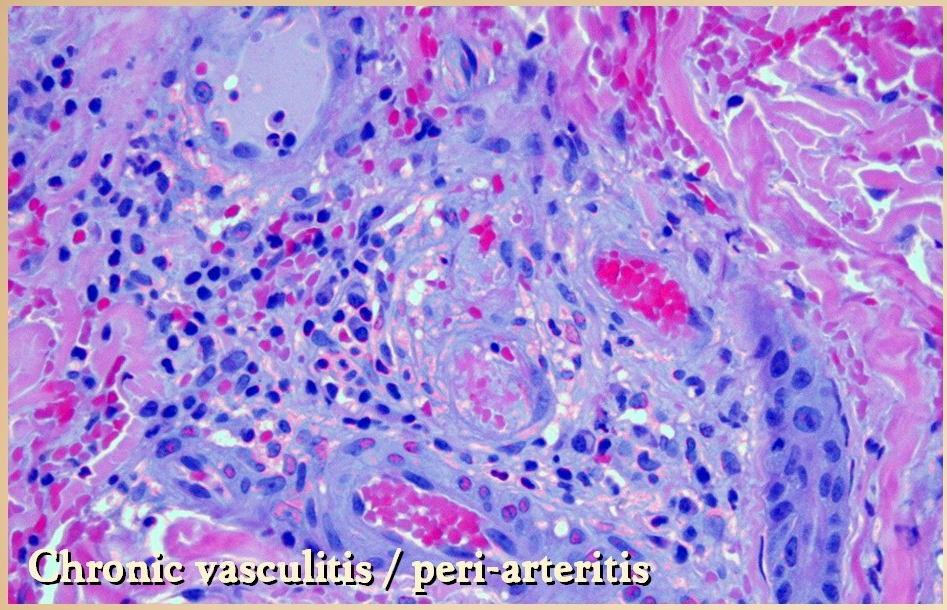
Soft Tissue - Stroma

Histioblasts - Fibroblasts - Angiocytes

Connective tissue - (collagen)
Blood vessels - (vascular)

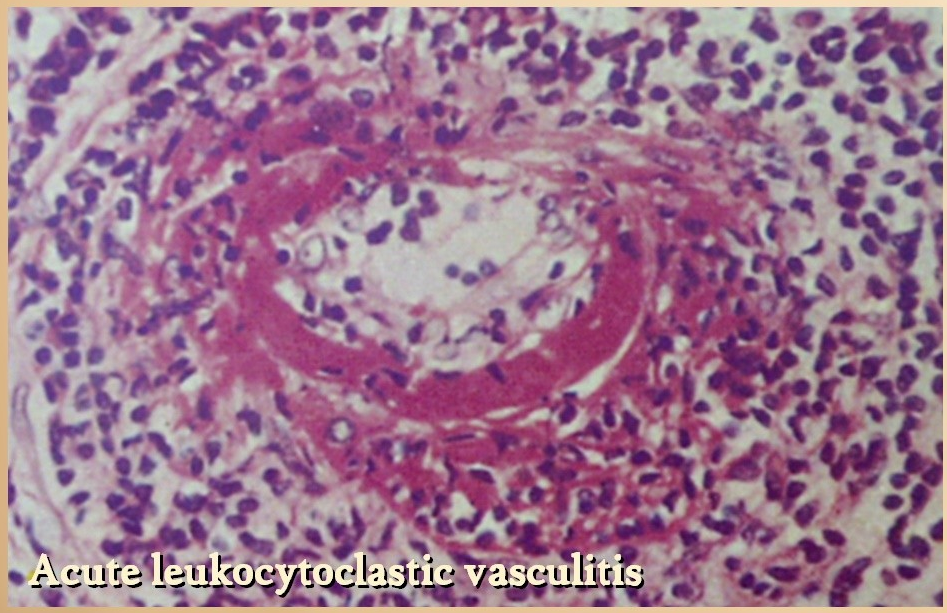


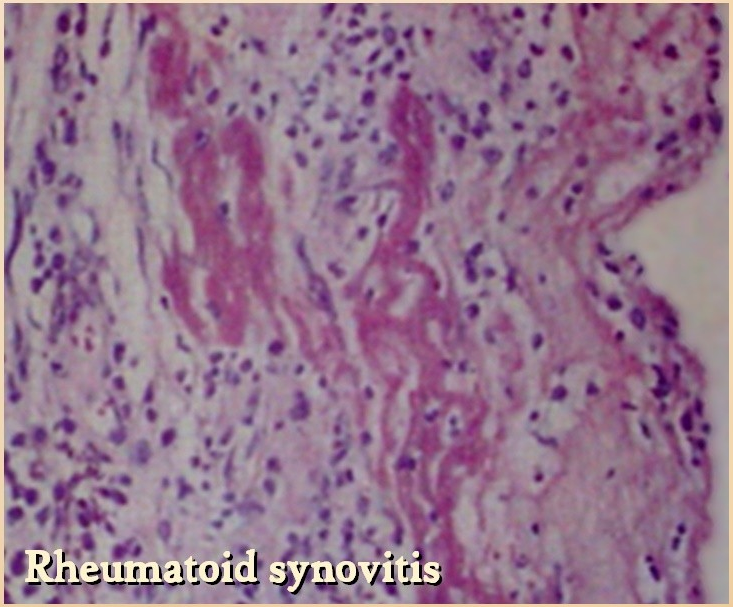


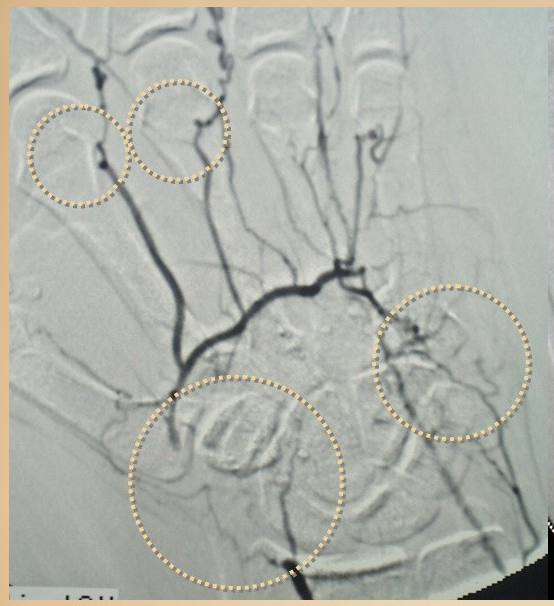
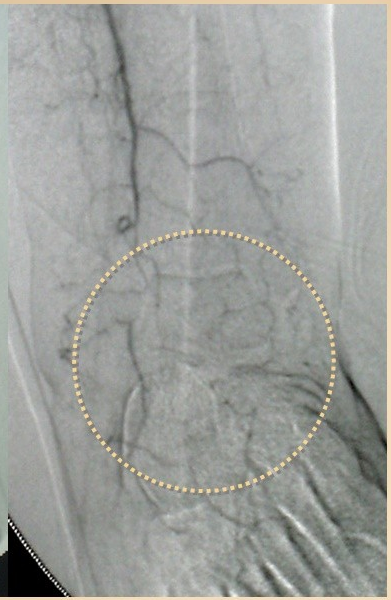
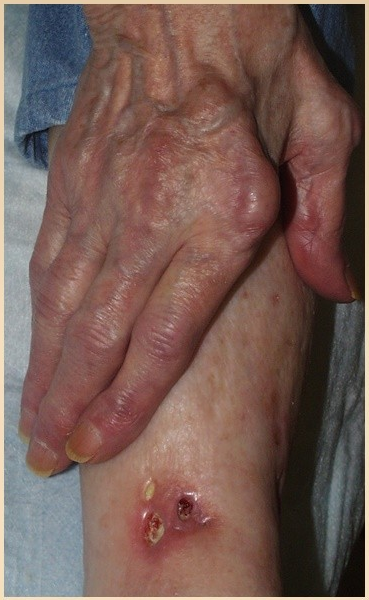
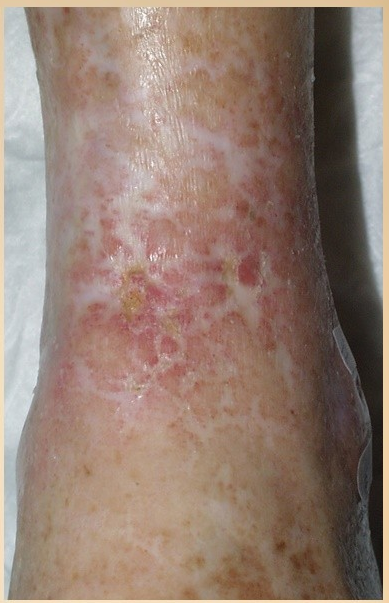

Chronic vasculitis / peri-arteritis

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.

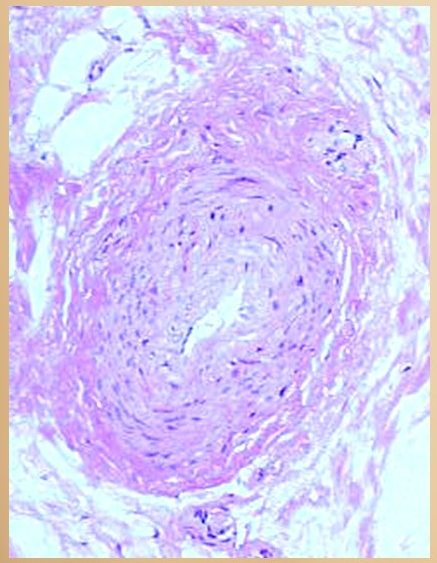
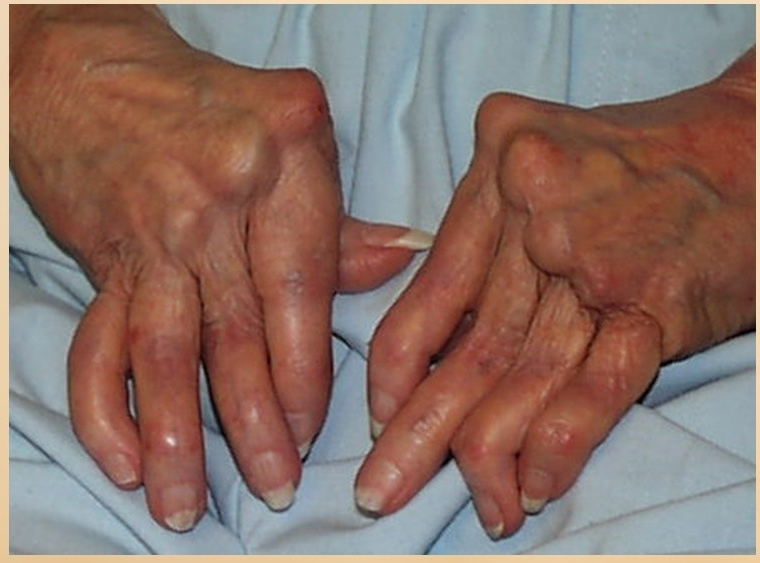
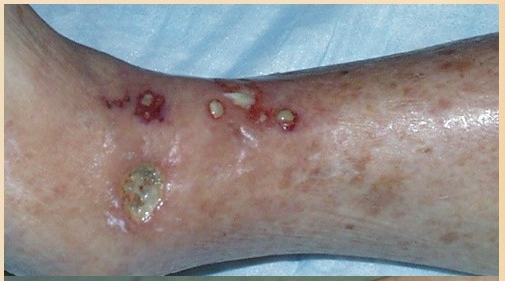
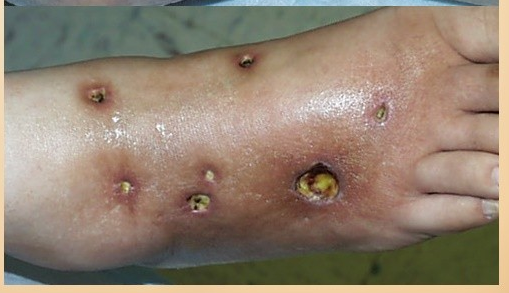
These cells, structures, and tissues are often the target of the autoimmune disorders and immunopathies.


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

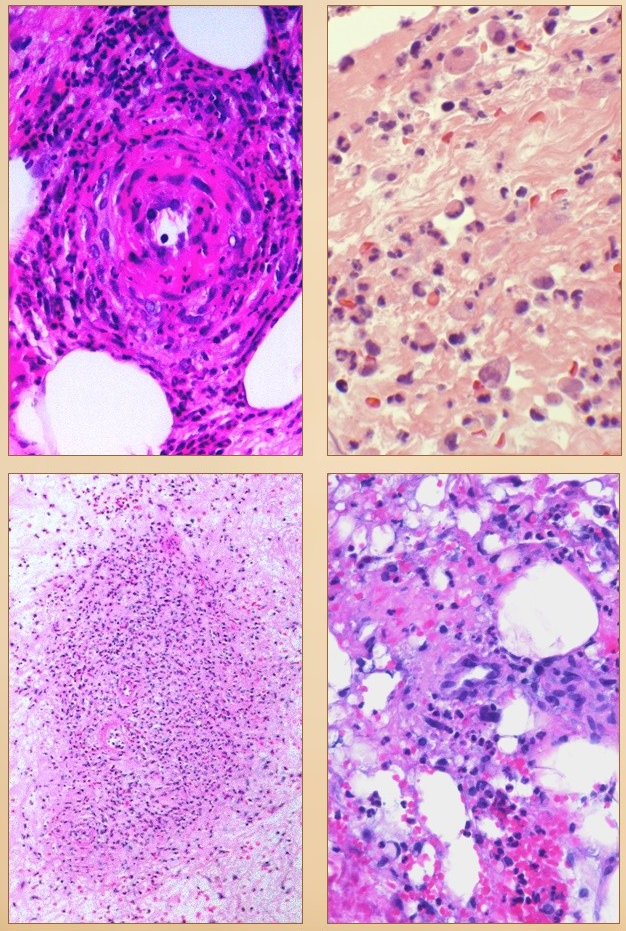
Mesoderm
Mesenchyme

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

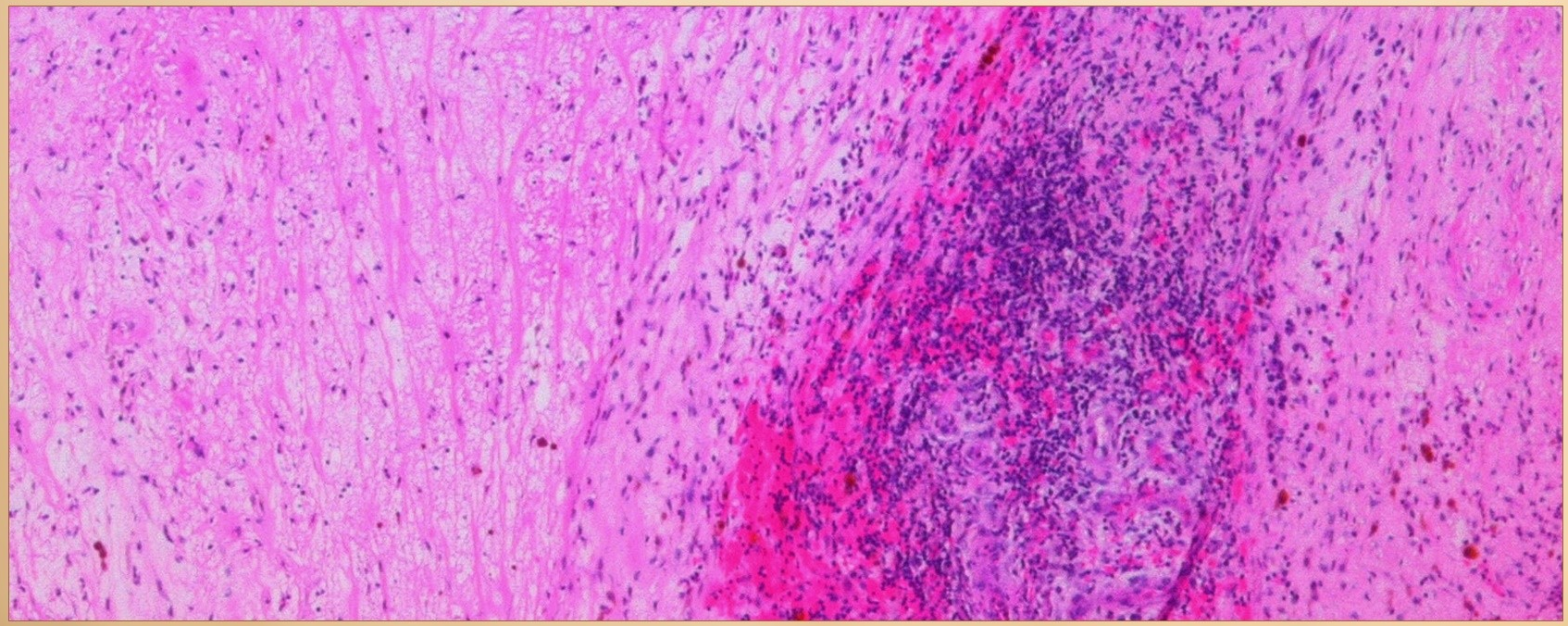
Targets Against Ento-Ectoderm

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

SUMMARY - COLLAGEN-VASCULAR & CONNECTIVE TISSUE PATHOLOGY

Why are these called "Collagen-Vascular Diseases" & "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.



Theories About the Origins of Autoimmunization & Autoimmune States

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	-	-	+

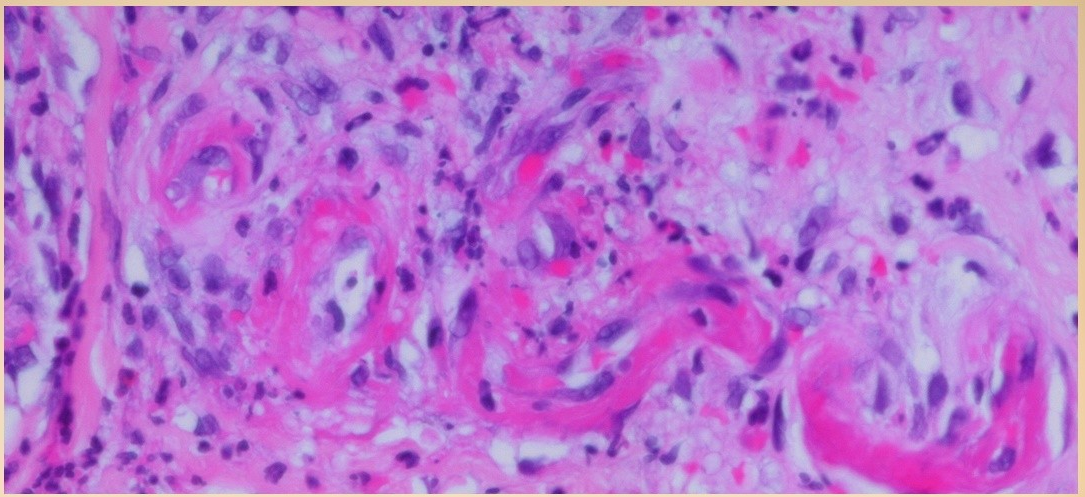
Table 3. CREST Syndrome and Neurologic SLE

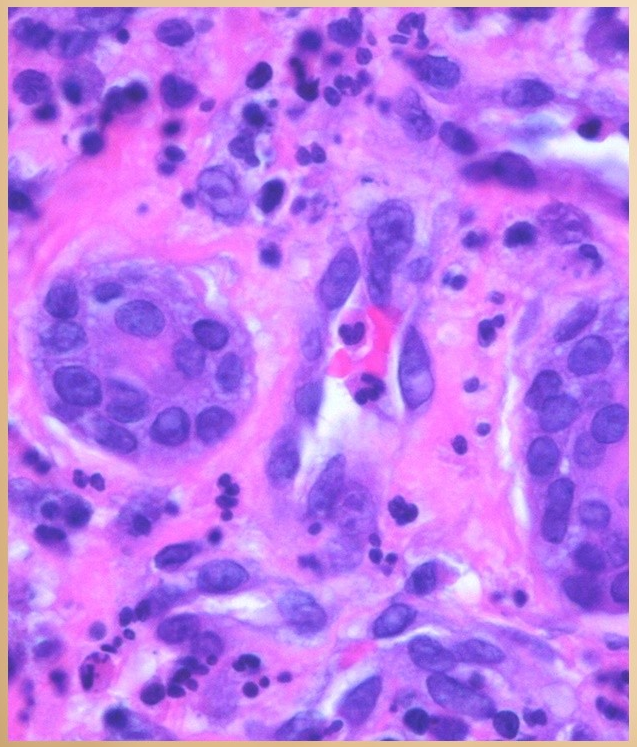
Test	CREST Syndrome	Neurologic SLE
Centromere antibody	+	-
Ribosomal P antibody	-	+

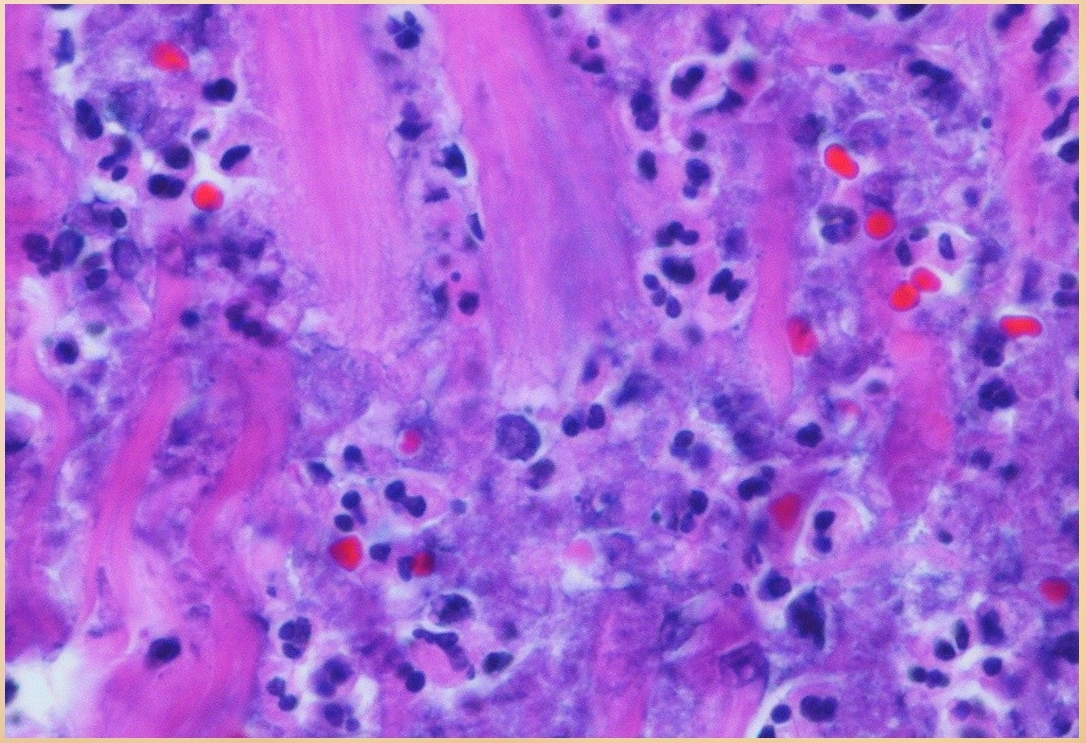
SLE, systemic lupus erythematosus.

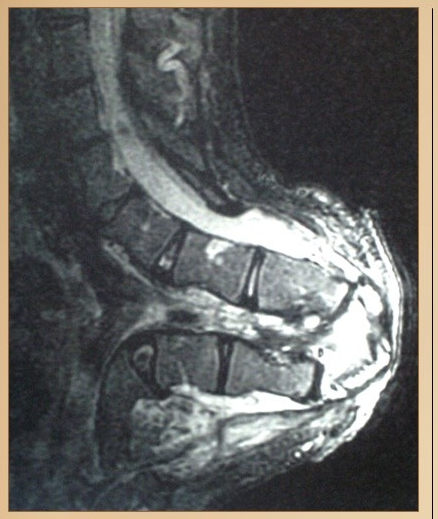
The origins of anti-cytoplasmic & anti-nuclear antibodies

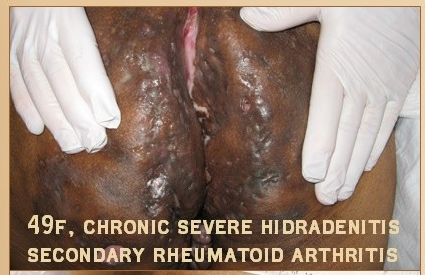
endocellular debris
nuclear debris
poly dust

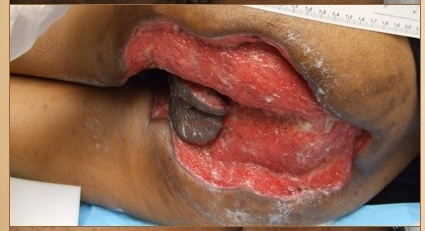












AUTO-IMMUNOPATHY

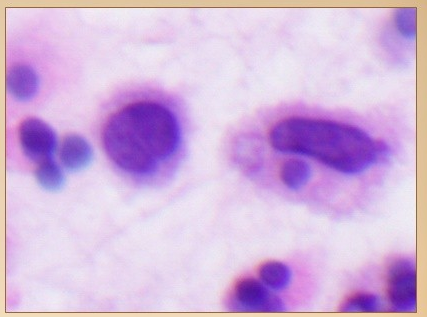
MECHANISMS OF AUTOIMMUNITY

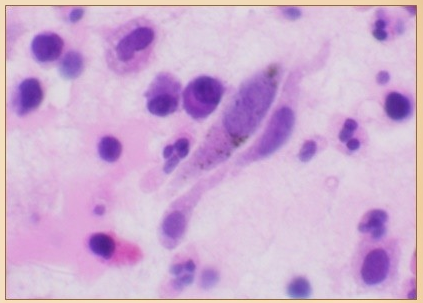
Auto-Sensitization
depends on recognition, processing,
& presentation of antigens to lymphocytes

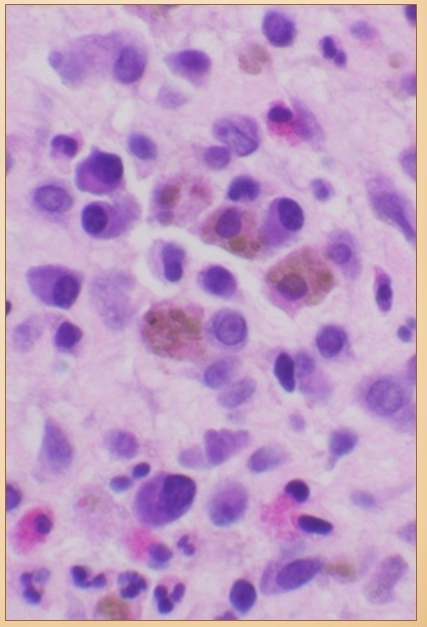
Exposure of Occult & Sequestered Antigens
endocellular debris (acute inflammation)
intra-cytoplasmic antibodies
endonuclear debris (acute inflammation)
anti-nuclear antibodies
cell and tissue specific debris
e.g. hidradenitis
e.g. uveitis
antigen cross-reactivity
e.g. latex & spima bifida

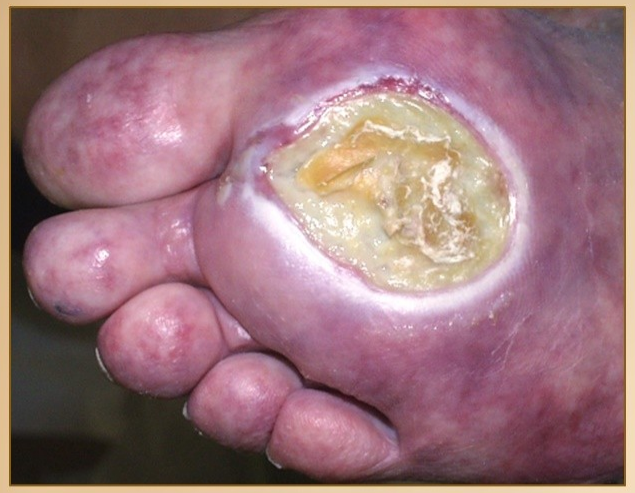
Opsonization - Haptenization of Open Antigens
opsonization / inverse haptenization
e.g. rheumatic carditis & parf
e.g. reiter's syndrome

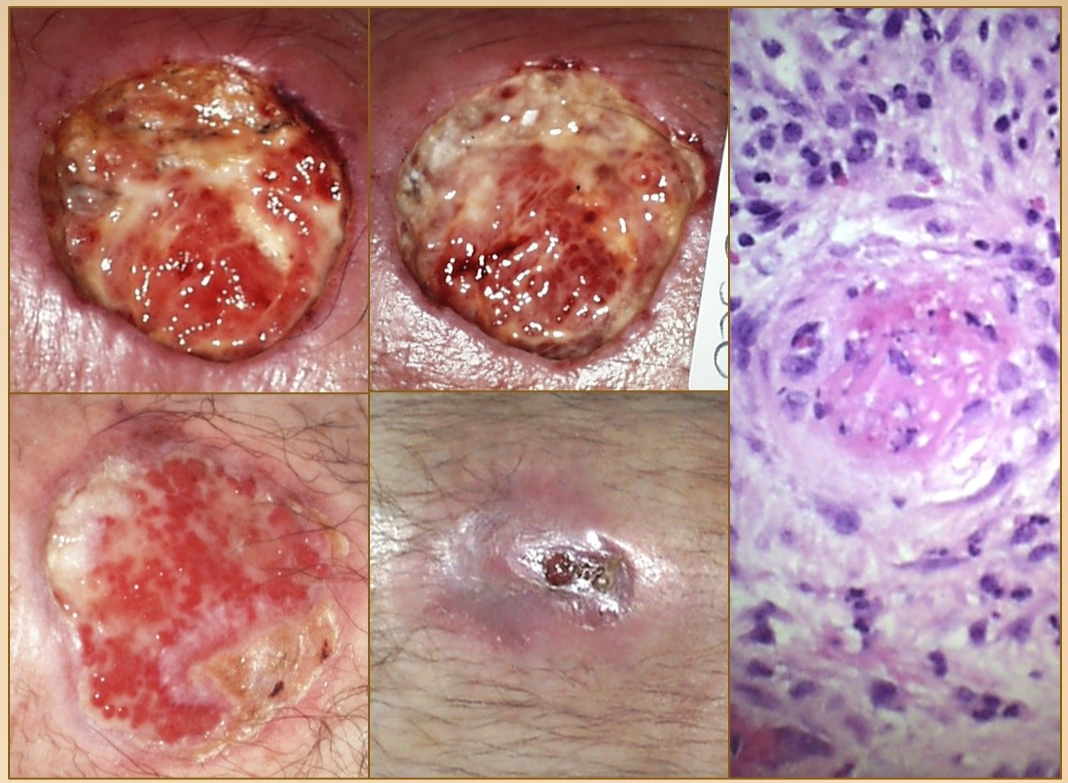
Antigen Processing & Presentation
neutrophil & acute inflammatory debris
local & specific cell debris
macrophages, histiocytes, & antigen
lymphocytes & plasma cells
sustained acute inflammation
chronic inflammation











TOMBSTONE CLINICAL LABORATORY

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

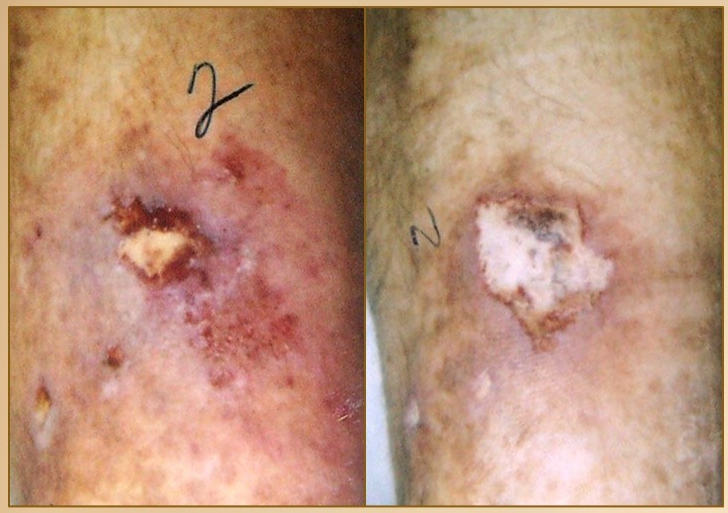
34M, lupus, trauma wounds

pathergy, multiple wound failure: hand, groin, leg

multiple failed operations, refractory to all care

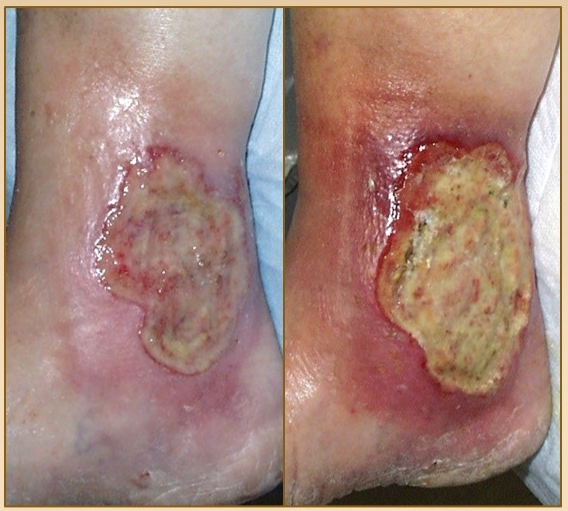
antiphospholipid antibodies

healed with warfarin



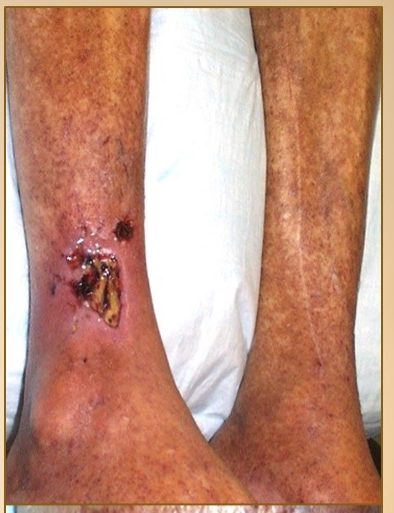
54M No prior diagnosis

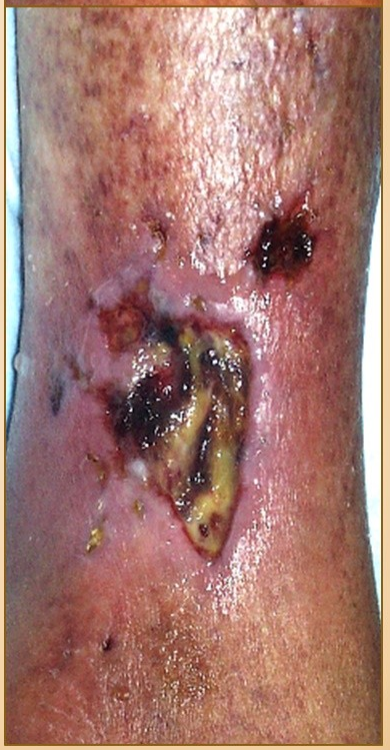
FactorV Leiden	heterozyg	+
ANA	1:80-sp	+
lupus anticoag	pos	+
cardiolipin IgA	15	+
cardiolipin IgG	>150	+++
cardiolipin IgM	20	+
protein C	60	-
protein S	56	-
homocysteine	14.6	+



72F Polycythemia Vera

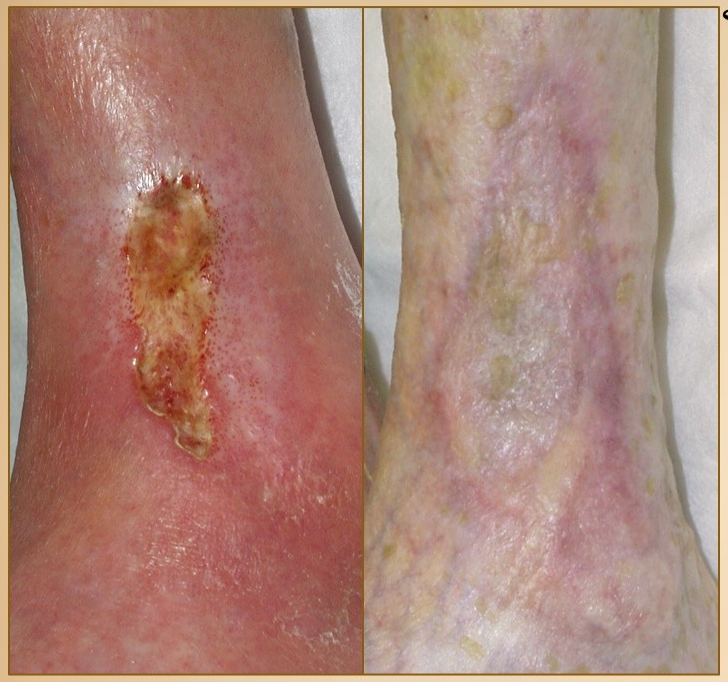
ANA	1:160	+
cardiolipin IgM	80	++
protein S	53	-

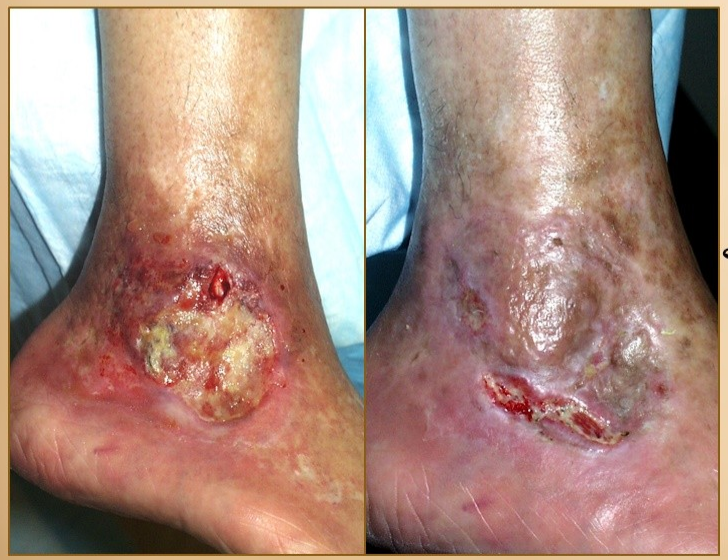




75M Anemia / Cythemia

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





69F **Rheumatoid Arthritis**

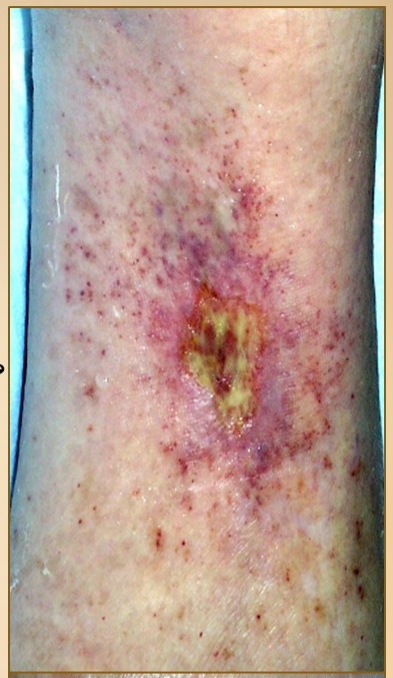
FactorV Leiden	heterozyg	+
protein C	51	-
protein S	52	-

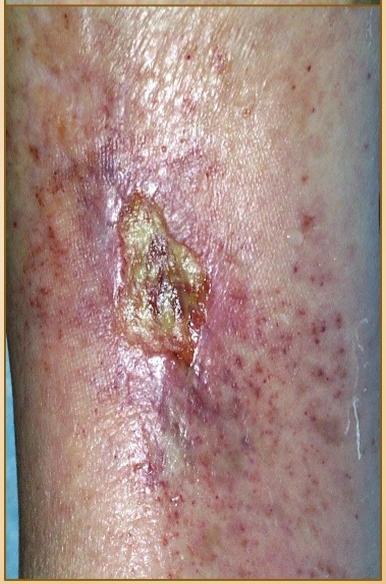
81F **Leg ulcer**

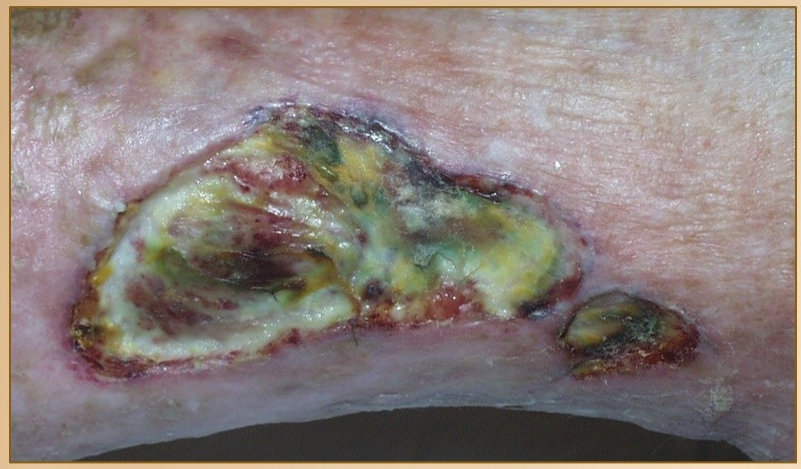
rheumatoid factor	27	+
ANA	1:1280-hm	++
lupus anticoag	pos	+
cardiolipin IgM	51	+
protein C	142	+
fibrinogen	429	+
homocysteine	19.3	+

66F **Scleroderma / MCTD**

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

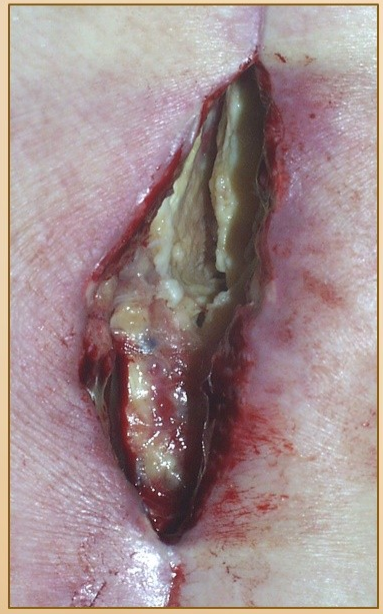






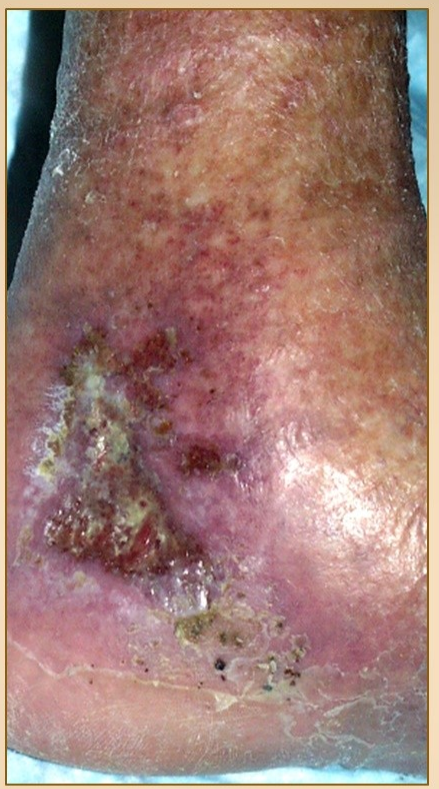
78F **Sjögren's**

protein C	60	-
fibrinogen	565	++



67F **Rheumatoid Arthritis**

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



67 & 176

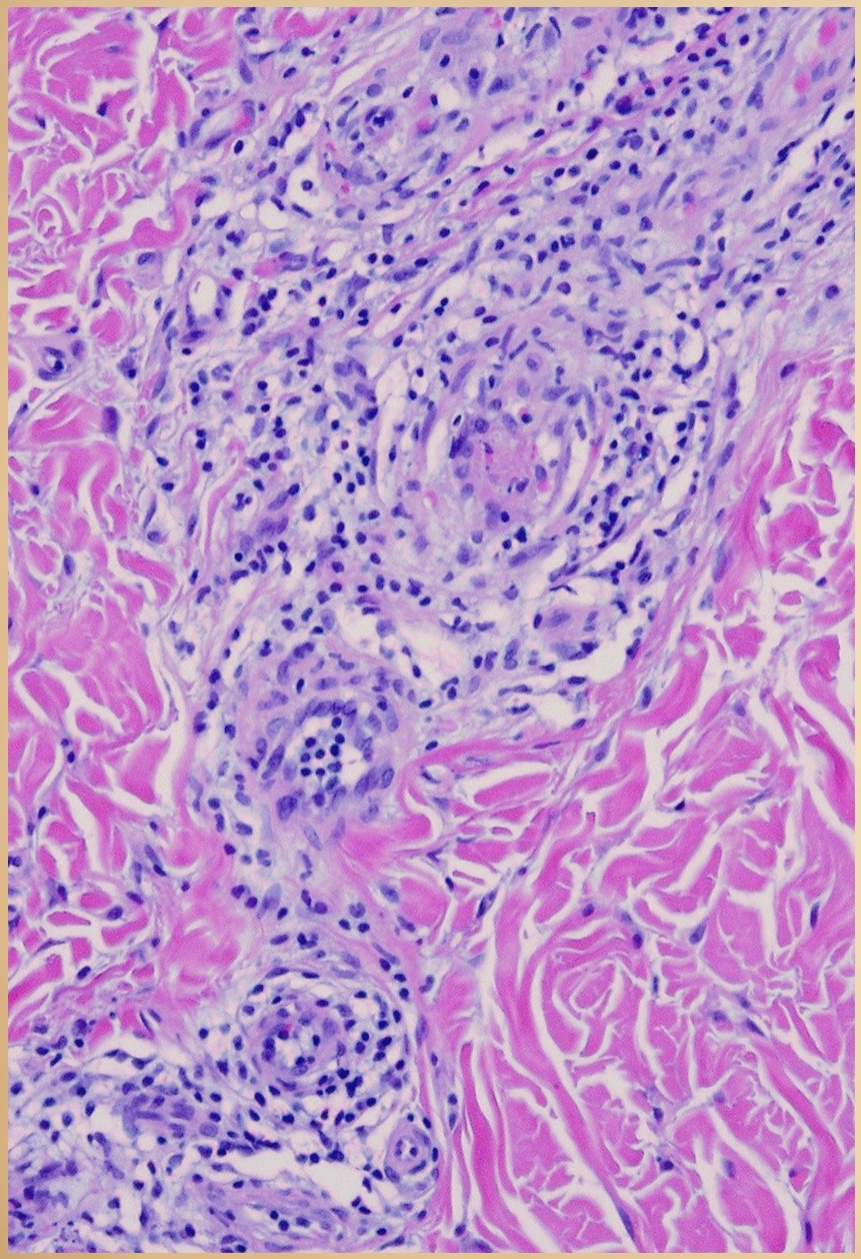
1 & 3

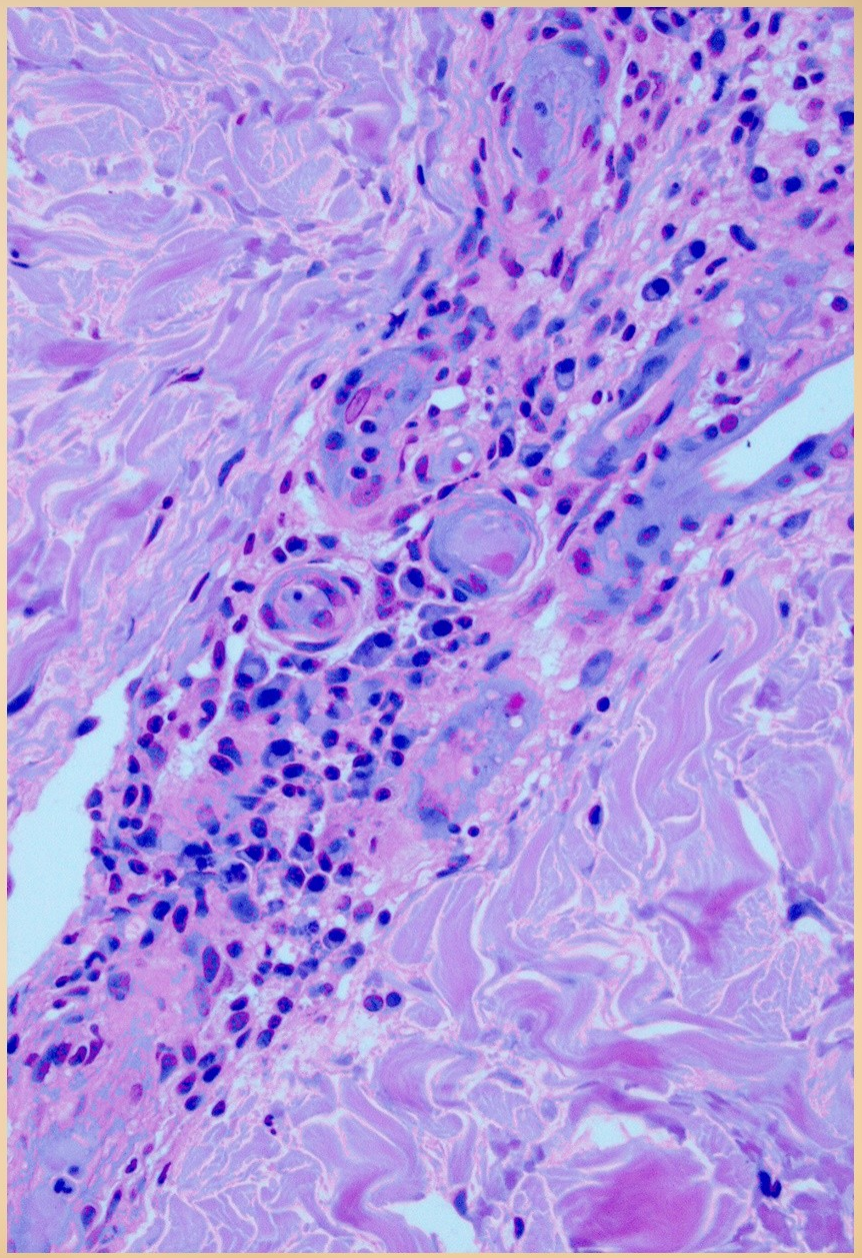
$TcPO_2$

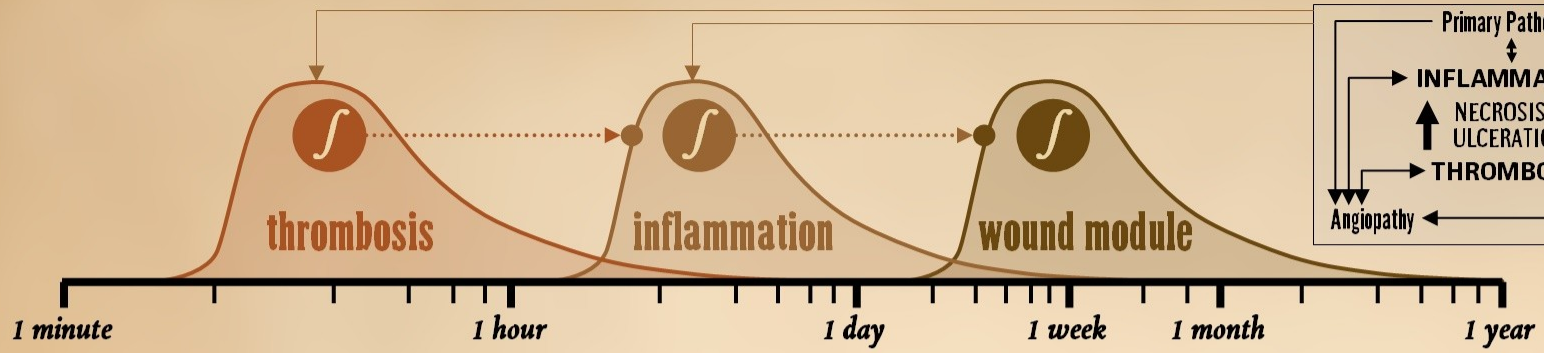
air & O_2

57M **Cirrhosis**

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

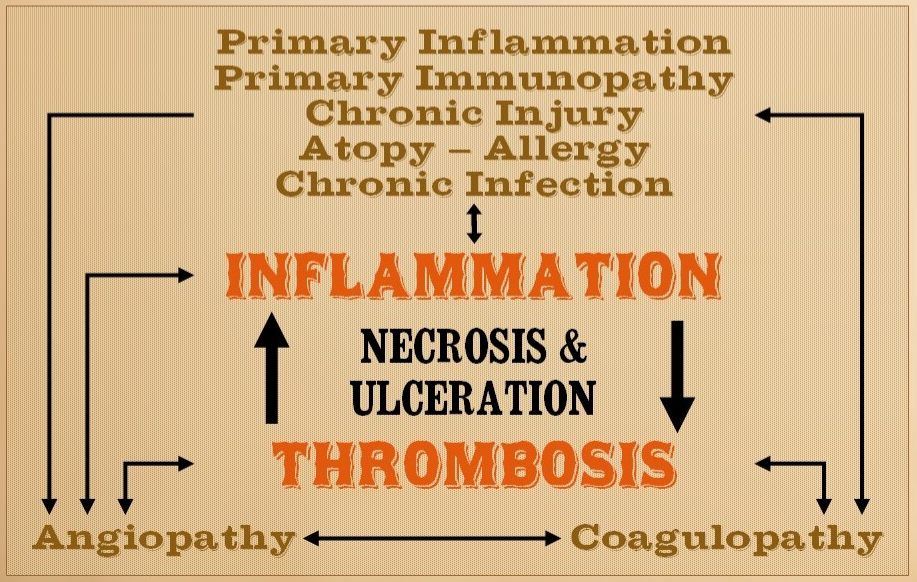






TYPES OF INFLAMMATION

ACUTE -> SUSTAINED ACUTE -> CHRONIC



ACUTE INFLAMMATION

One shot
Minimum exposure of sequestered antigen
Minimum macrophage-lymphocyte admixture
(*Time & place for macrophages & lymphocytes*)

SUSTAINED ACUTE INFLAMMATION

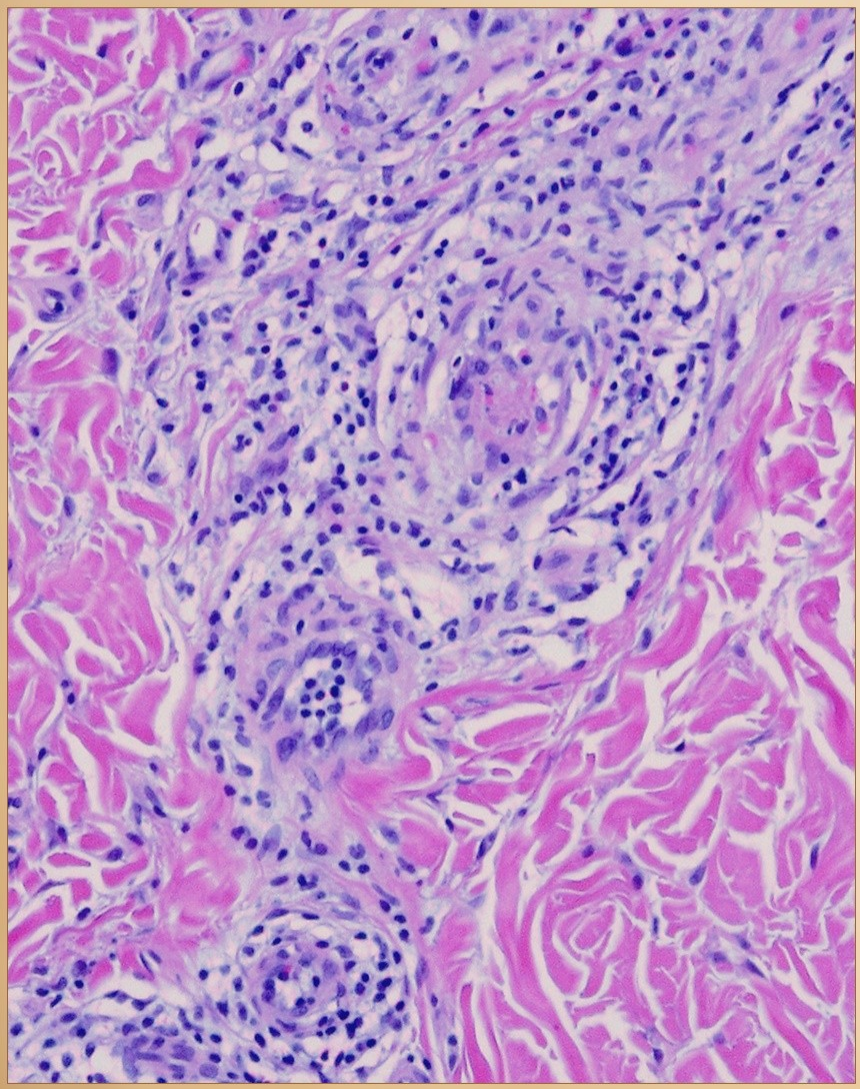
Repetitive or unresolved primary injury
Increased load of cellular and nuclear debris
Increased time of exposure
Increased load of reactive cells
Increased chance of lymphocyte appearance
Increased macrophage-lymphocyte admixture
Increased macrophage-lymphocyte interaction

CHRONIC INFLAMMATION

Sensitization has occurred
A new population enters the mix (lymph-plasma)
Perpetuation of injury and altered dynamics

ACUTE, SUSTAINED ACUTE, & CHRONIC INFLAMMATION

CAUSES



"Chronic Inflammation" (*vernacular*)

has been there a long time

sustained or persistent acute inflammation

- versus -

Chronic Inflammation (*pathological*)

3rd population

lymphocytes - plasma cells - eosinophils

What conditions cause sustained injury, sustained inflammation, and high-load exposure or opsonization of normally safe or sequestered antigens ?

SUSTAINED & CHRONIC

INFLAMMATION (REACTIVE & INDUCED)

INFECTION & IMMUNITY

TRAUMA & INJURY

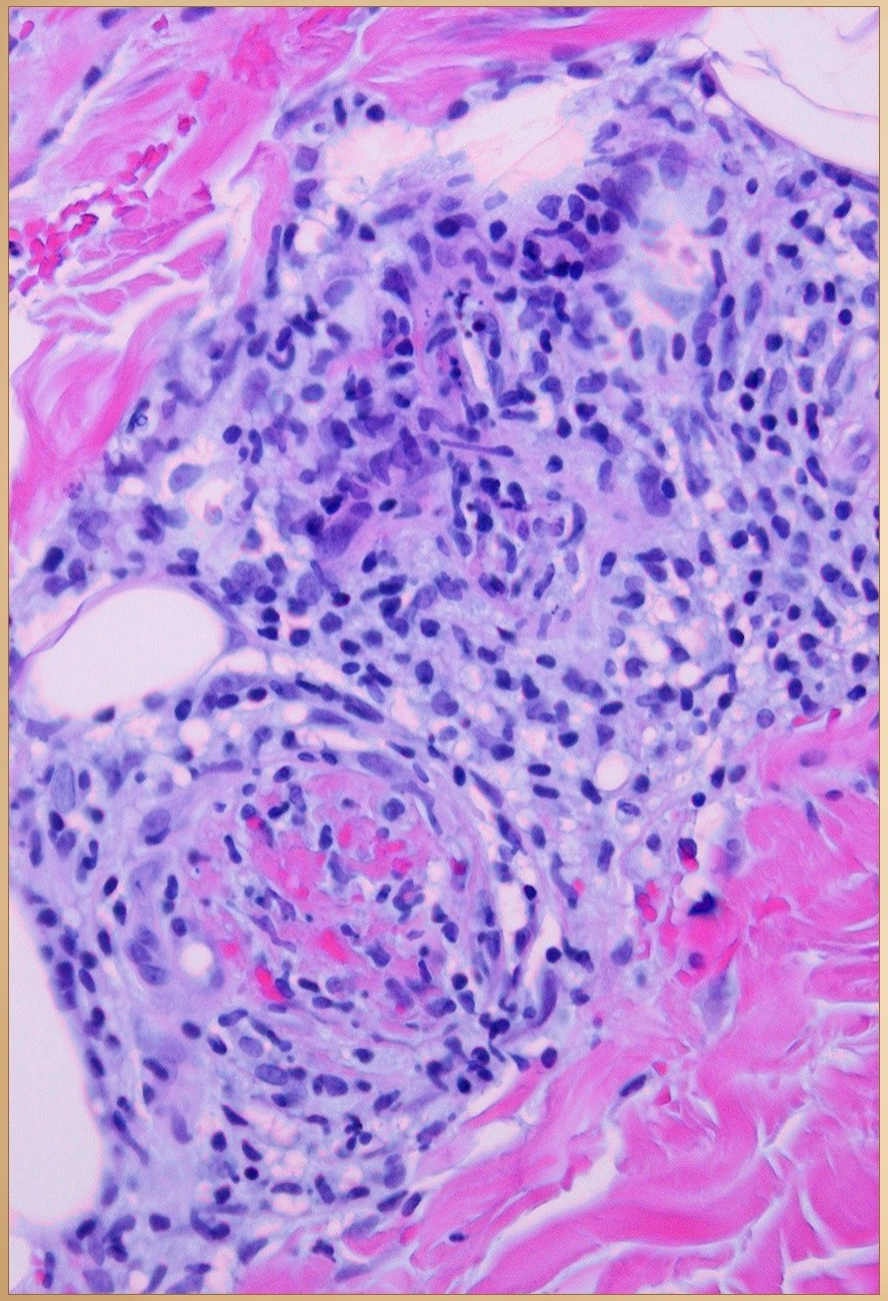
ALLERGY - ATOPY

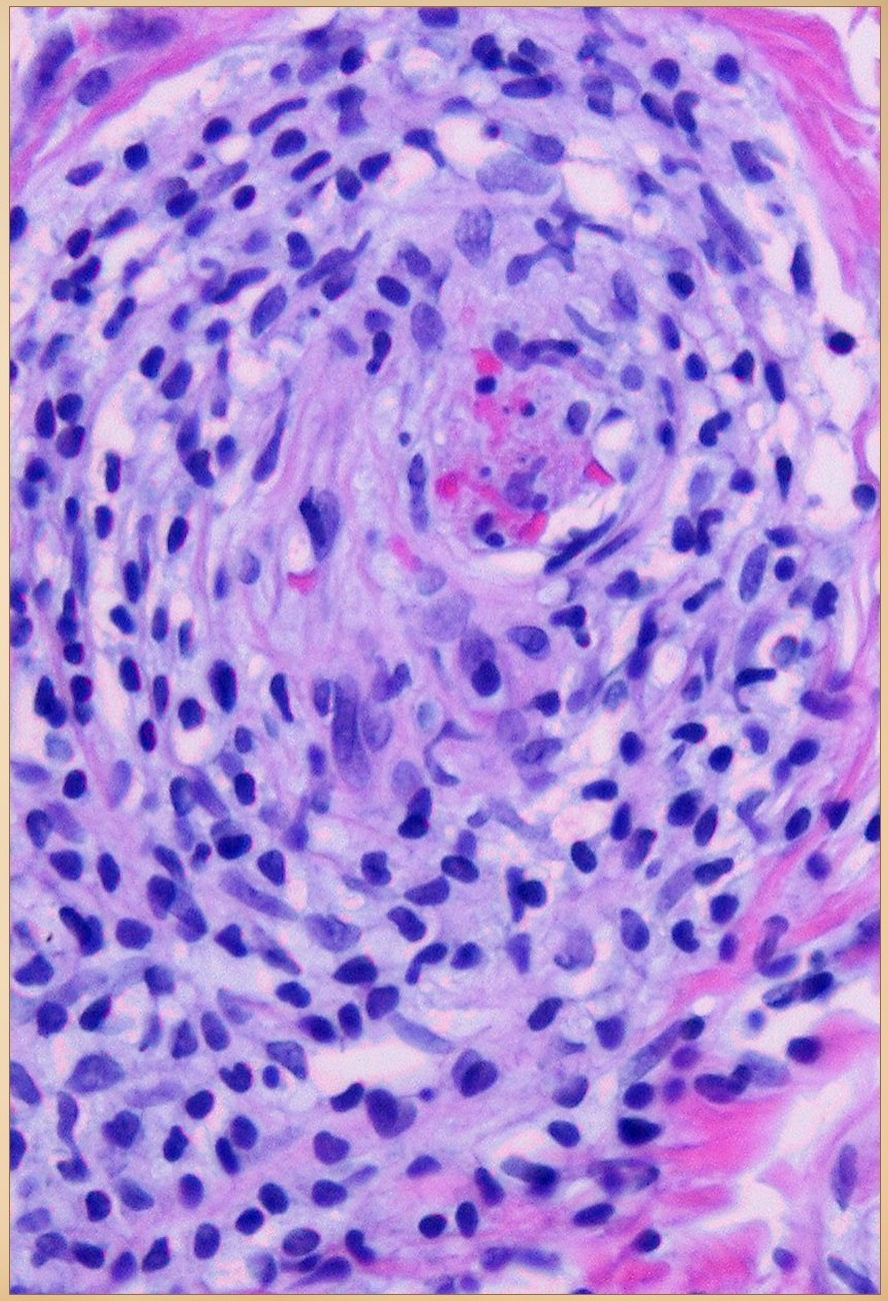
THROMBOSIS

ACUTE INFECTIONS (RHEUMATIC HEART, REITER'S)

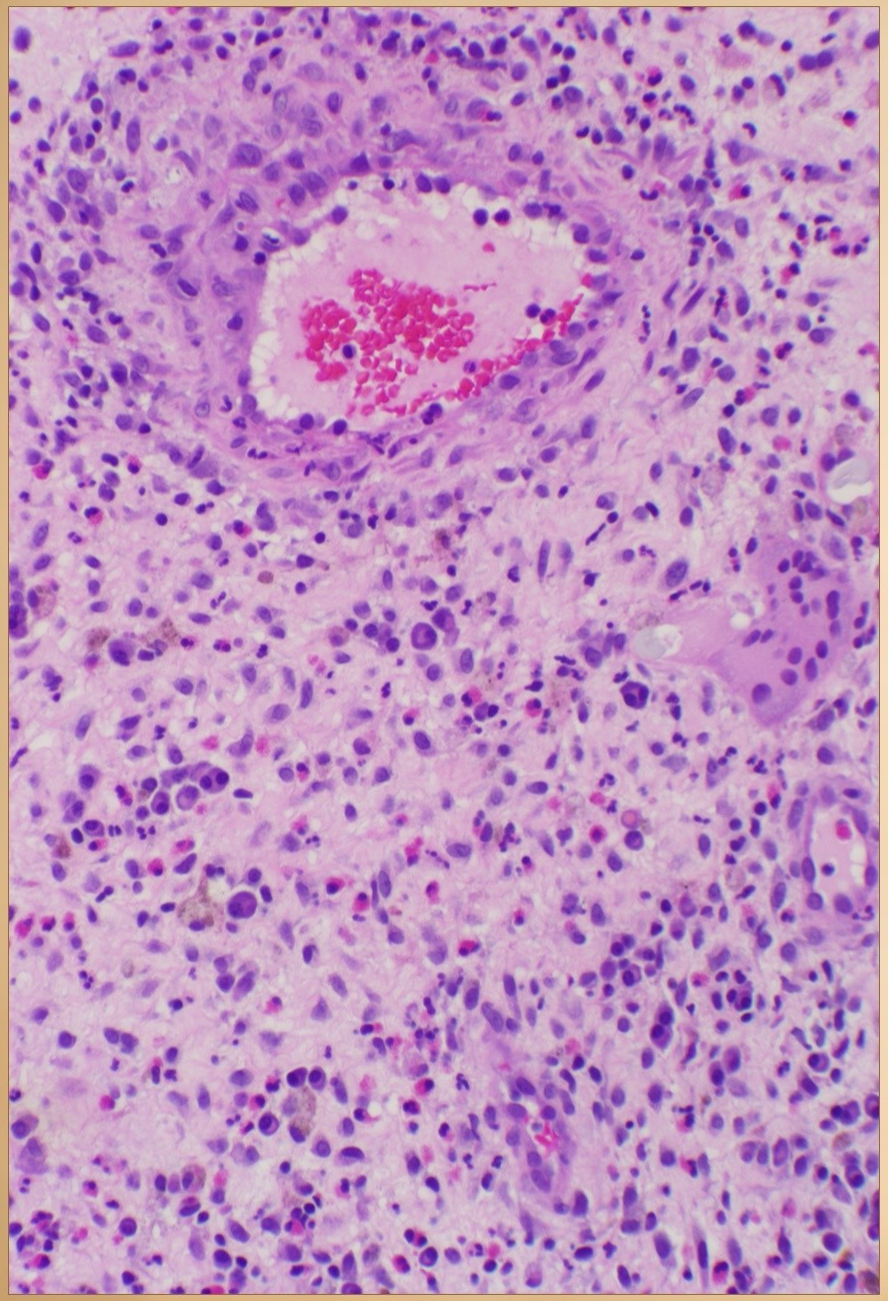
GENETICS (E.G. HLA-B27, HLA-B51, MEFV)

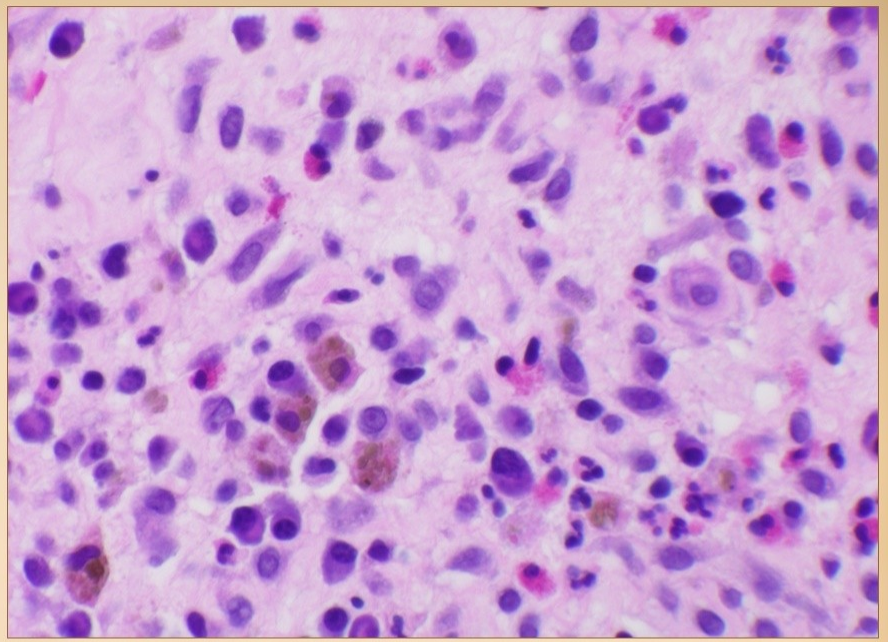
hypercoagulability / chronic thrombosis: 74 f; advanced crippling rheumatoid arthritis; hypercoagulopathy; leg ulcers

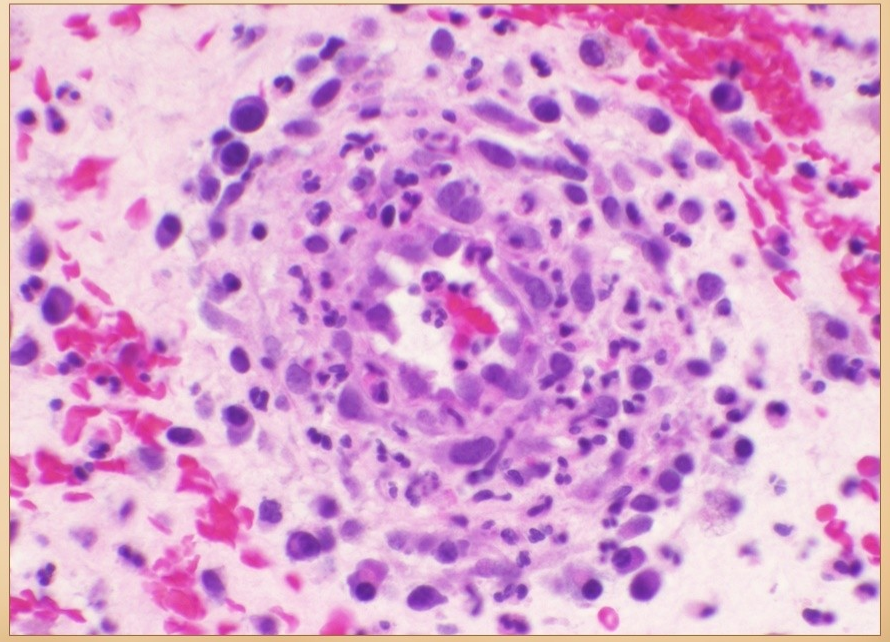




chronic allergy-atopy: 33 m; spine injury paraplegia; bullous pemphigoid; pressure & diffuse pemphigoid ulcers

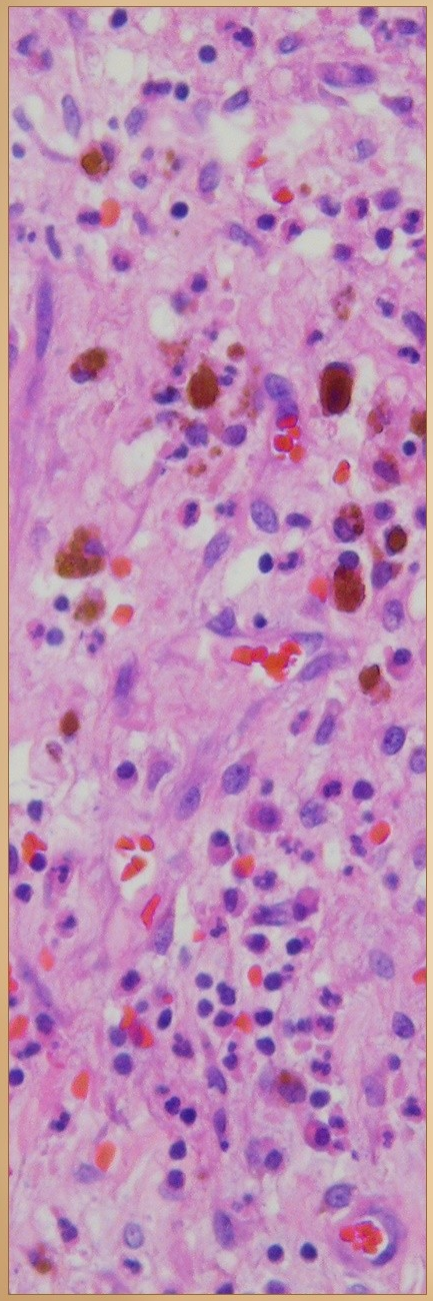


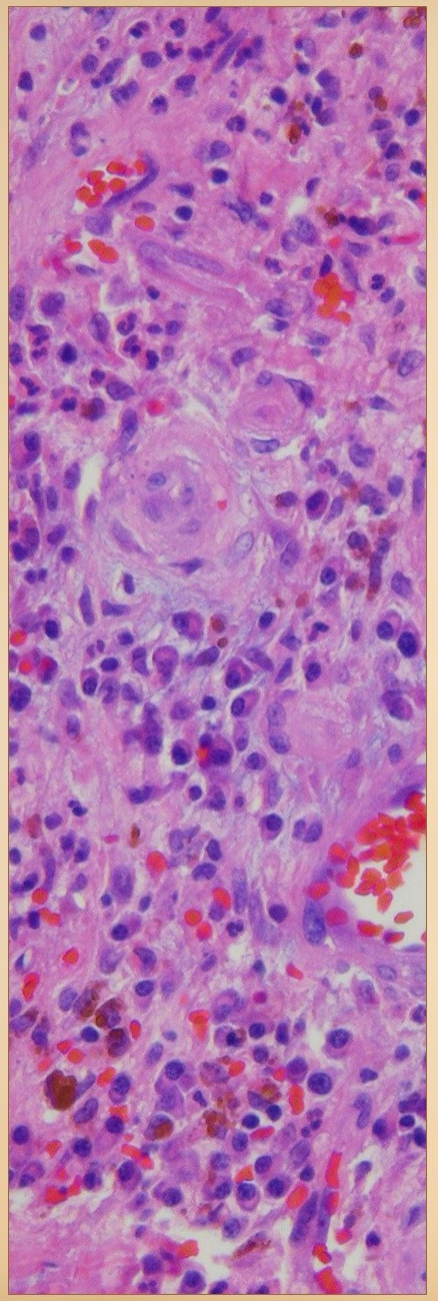


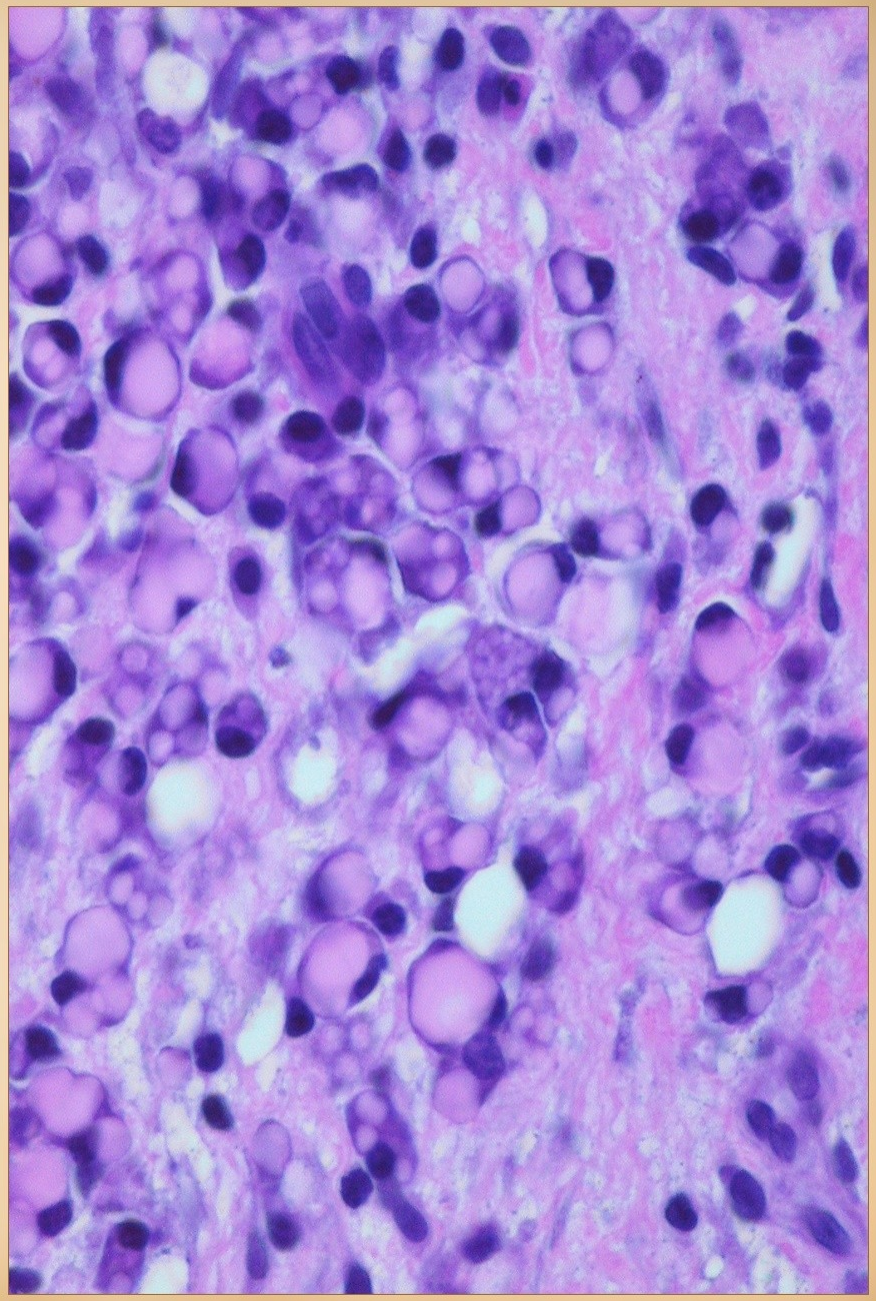


hypercoagulable: 31 f; mixed immune & prethrombotic

radiation: 84 f; chronic wound, sustained inflammation

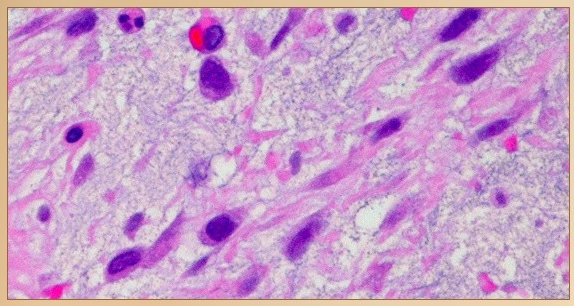
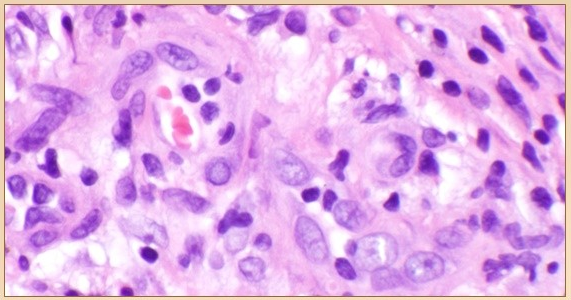
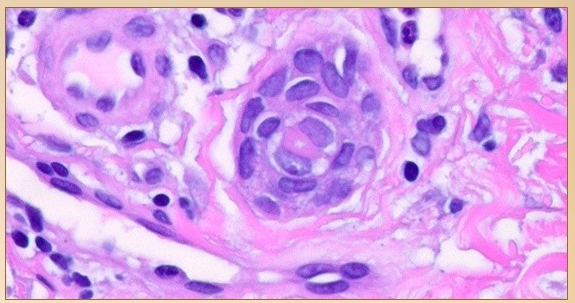




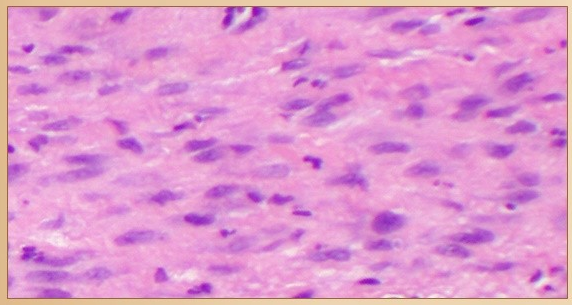
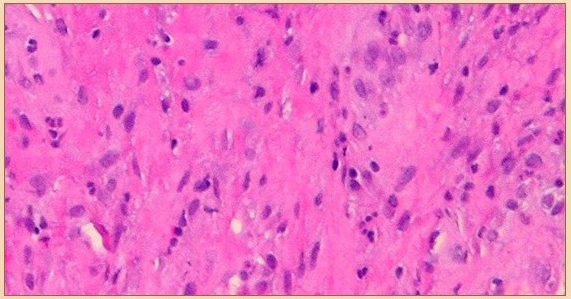
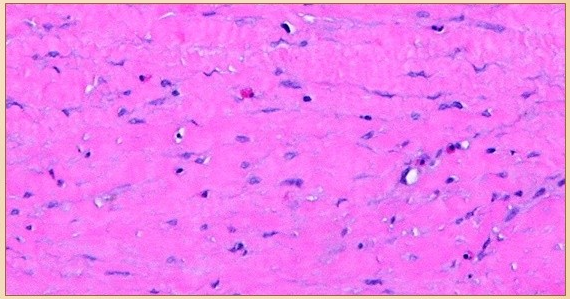


REPAIR IS BASED ON 2 CELL TYPES - ANGIOCYTES & FIBROBLASTS

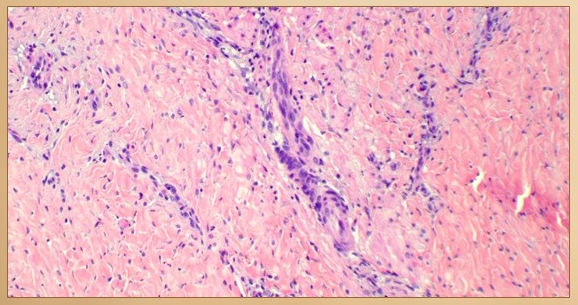
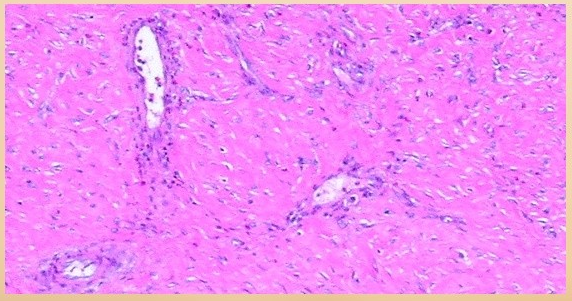
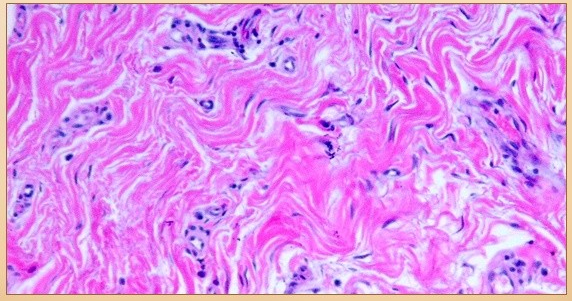
All injury and inflammation trigger repair.

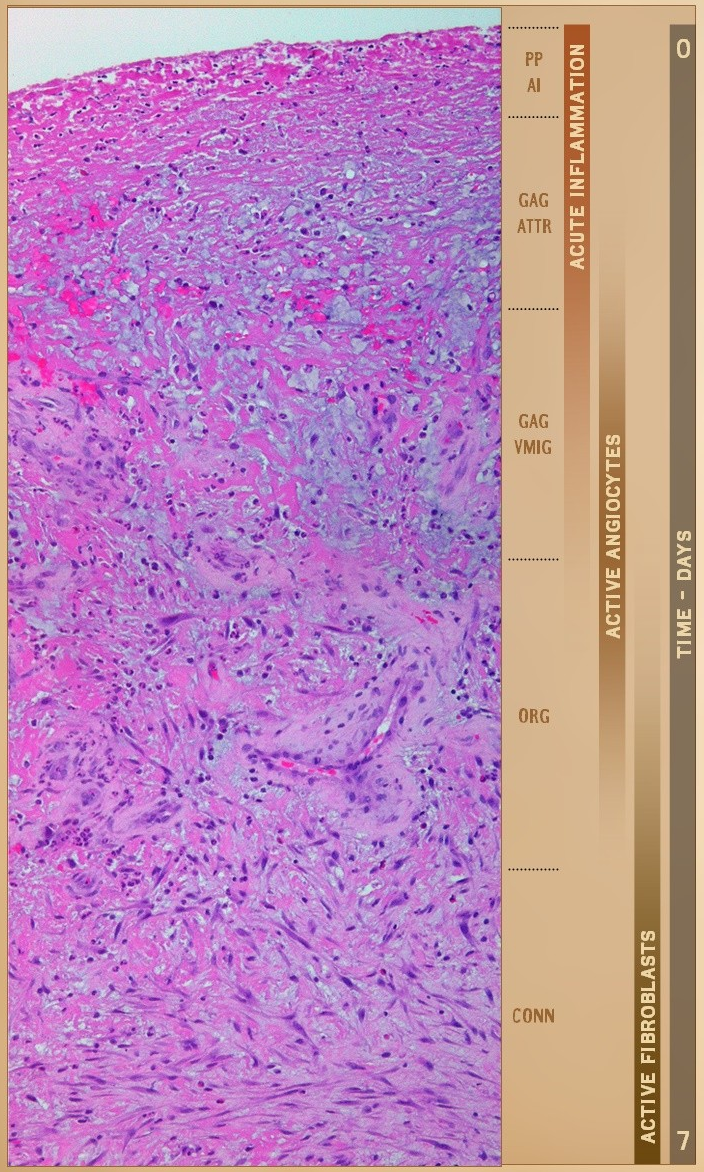
The mesenchymal component of normal wound healing is
the proliferative wound module of post-inflammatory repair.

This depends on just 2 cells: histio-fibroblasts & vascular angiocytes, which
create the vascular and connective structures which constitute the new stroma.

ACUTE INFLAMMATION, WOUND MODULE, & CHRONIC INFLAMMATION - ADMIXTURE, TIME & PLACE



PP
AI

GAG
ATTR

GAG
VMIG

ORG

CONN

ACUTE INFLAMMATION

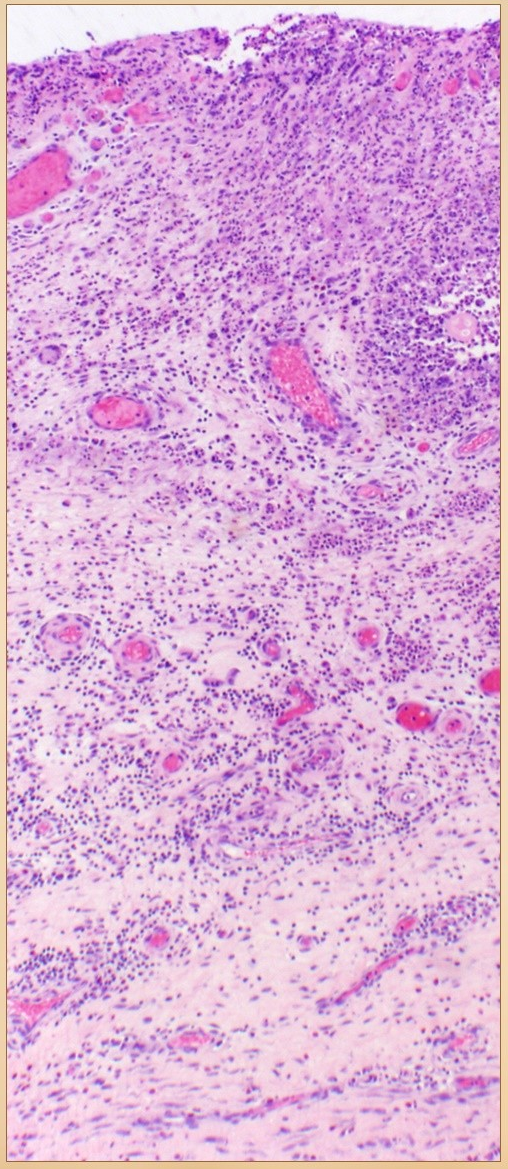
ACTIVE ANGIOCYTES

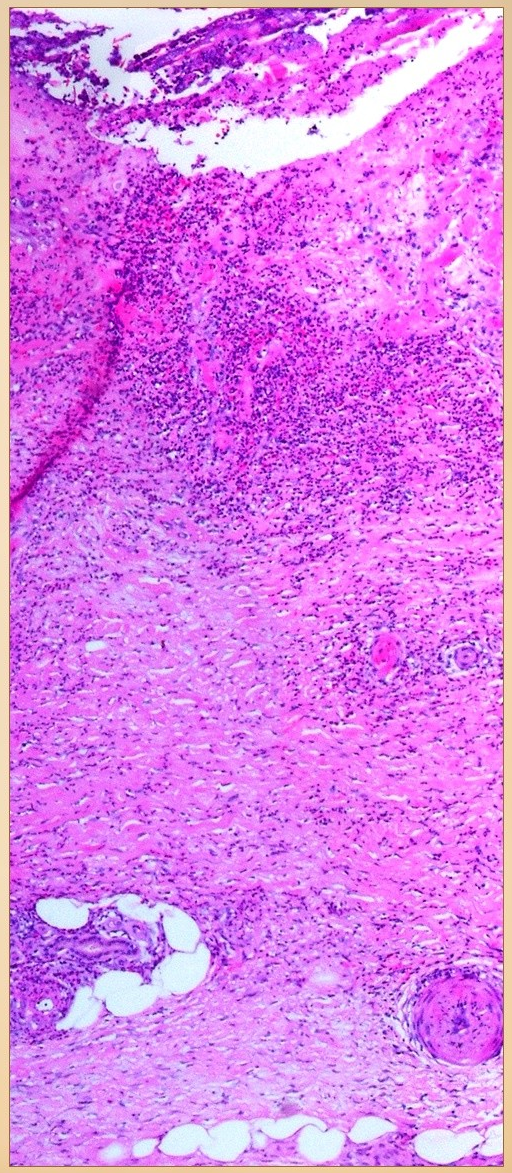
ACTIVE FIBROBLASTS

TIME - DAYS

0

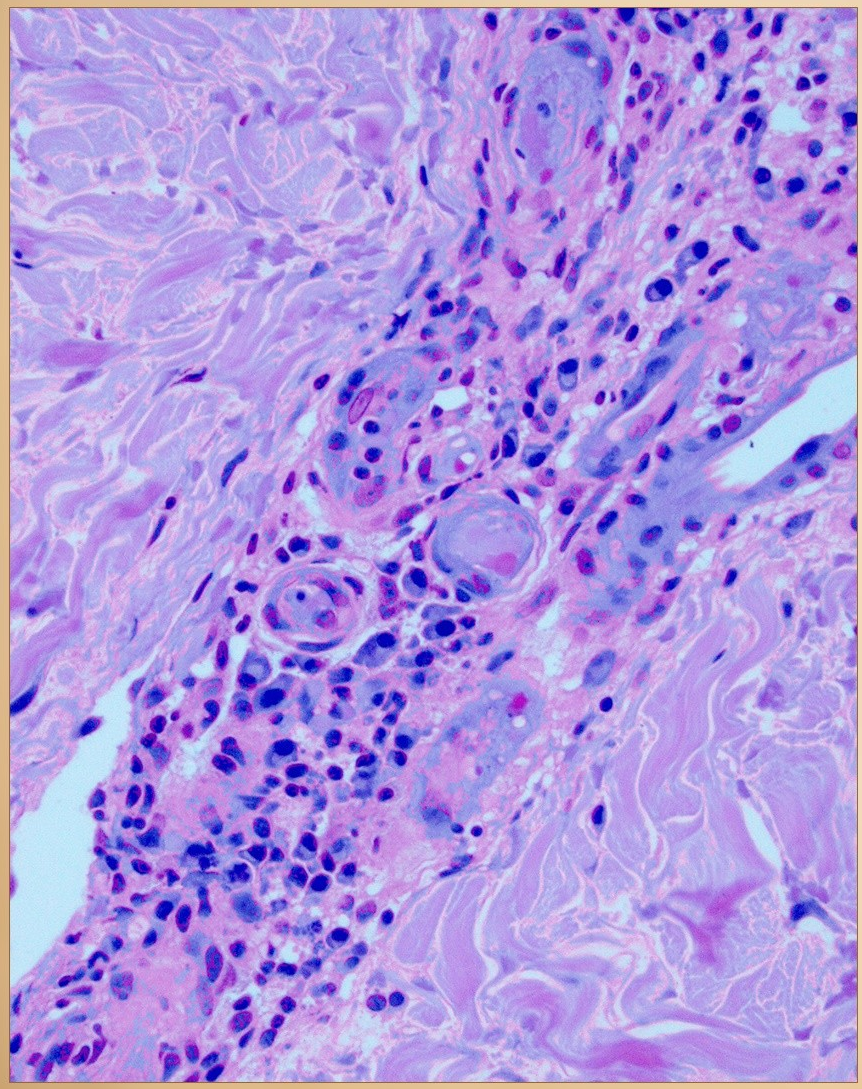
7





ACUTE, SUSTAINED ACUTE, & CHRONIC INFLAMMATION

CONSEQUENCES



MECHANISMS OF AUTOIMMUNITY

Auto-Sensitization
depends on recognition, processing,
& presentation of antigens to lymphocytes

Exposure of Occult & Sequestered Antigens
endocellular debris (acute inflammation)
intra-cytoplasmic antibodies
endonuclear debris (acute inflammation)
anti-nuclear antibodies
cell and tissue specific debris
e.g. hidradenitis, uveitis
antigen cross-reactivity
e.g. latex & spima bifida

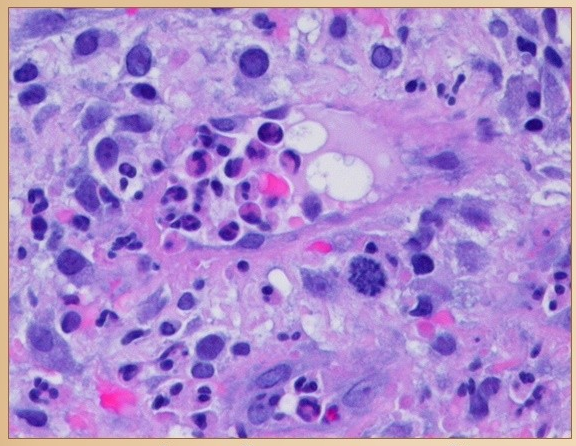
Opsonization - Haptenization of Open Antigens
opsonization / inverse haptenization
e.g. rheumatic carditis & parf, reiter's syndrome

Antigen Processing & Presentation
neutrophil & acute inflammatory debris
local & specific cell debris
macrophages, histiocytes, & antigen
lymphocytes & plasma cells
sustained acute inflammation
chronic inflammation

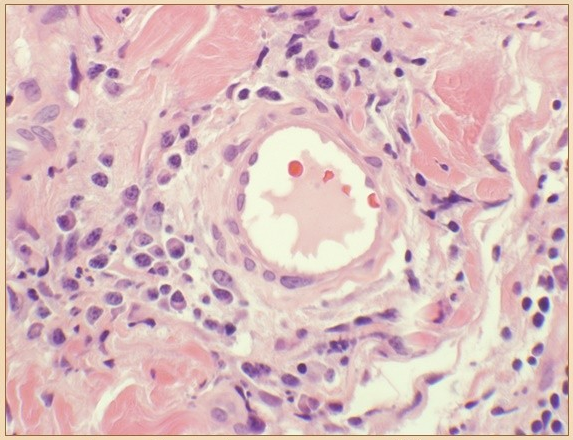
Wound cell-specific debris & sensitization:
angiocytes & fibrocytes,
vessels & connective tissue, stroma

CHRONIC INFLAMMATION, COLLAGEN-VASCULAR DISEASE, & WOUND HEALING

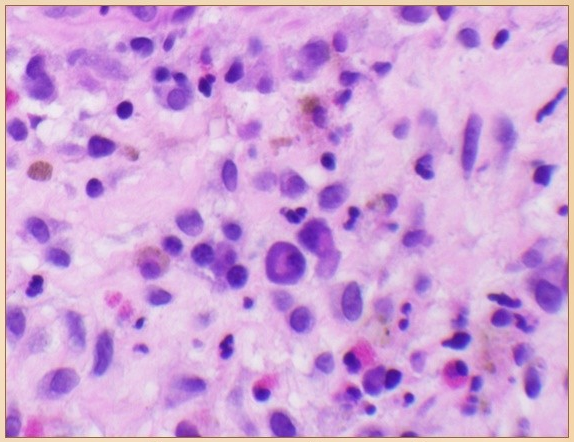
Immunopathic and other chronic and pathological ulcers have distinctive histological variances from normal wound healing (in addition to signs of the primary pathology).



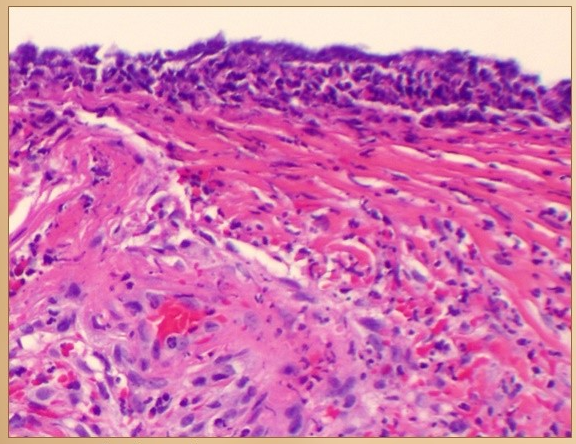
complex inflammation profiles



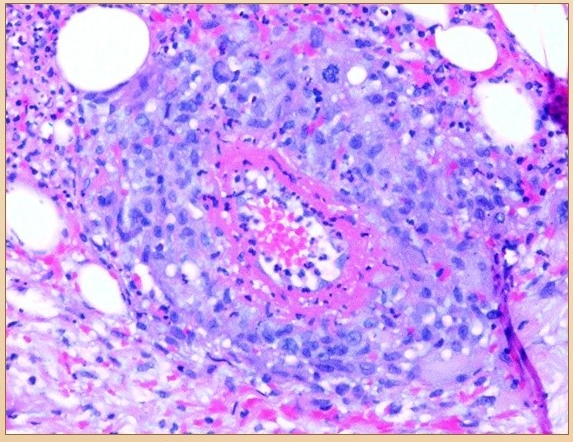
lympho-plasmacyte infiltrates



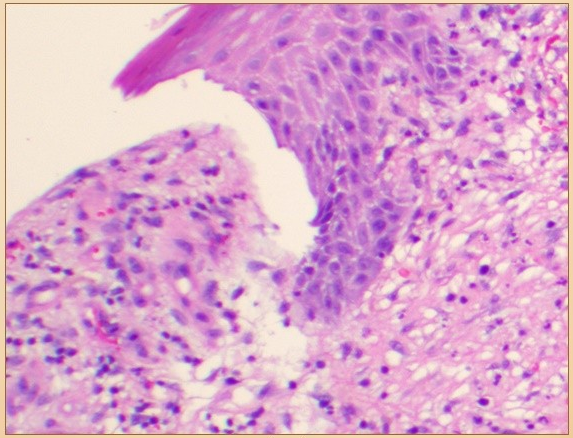
acute-chronic population admixture



failed / missing wound strata

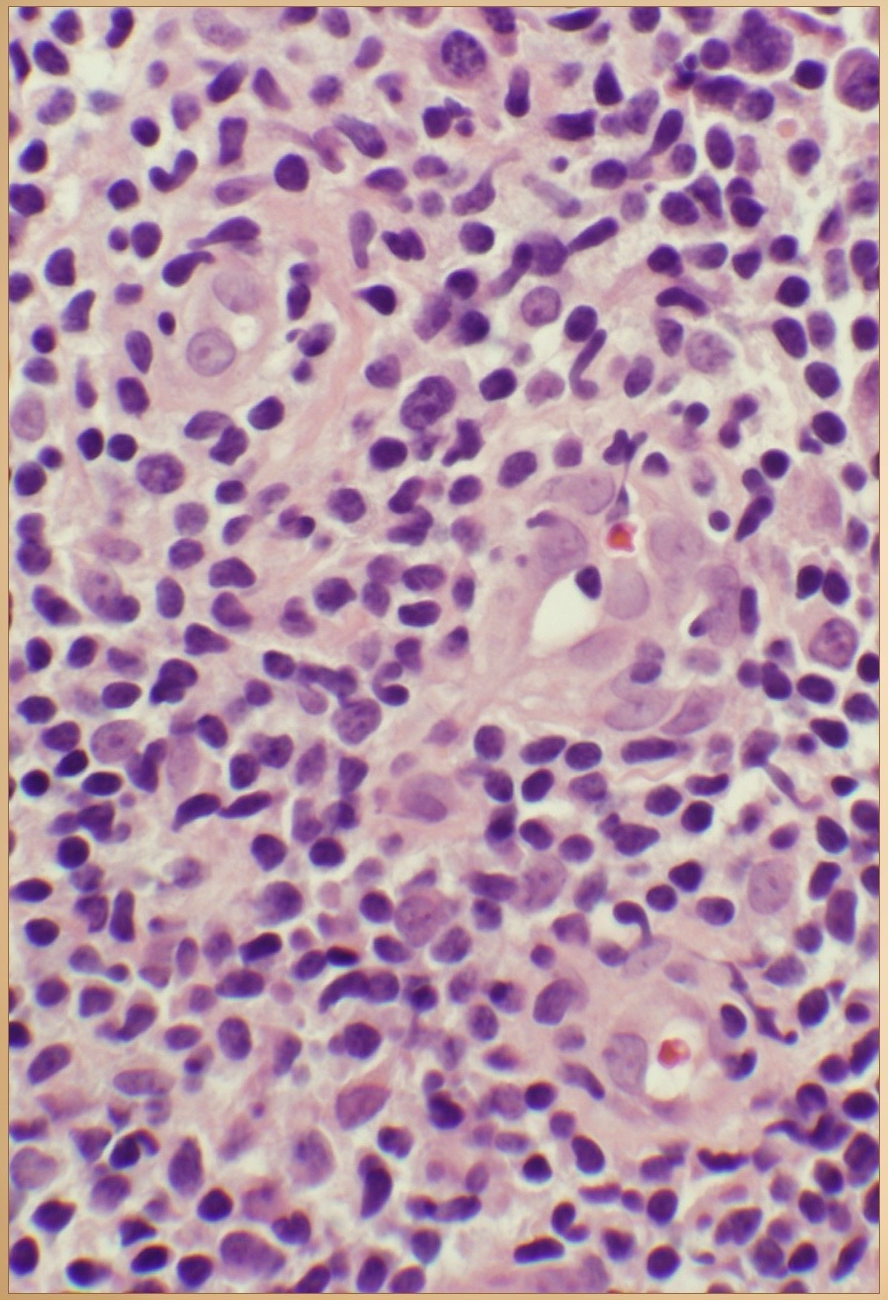


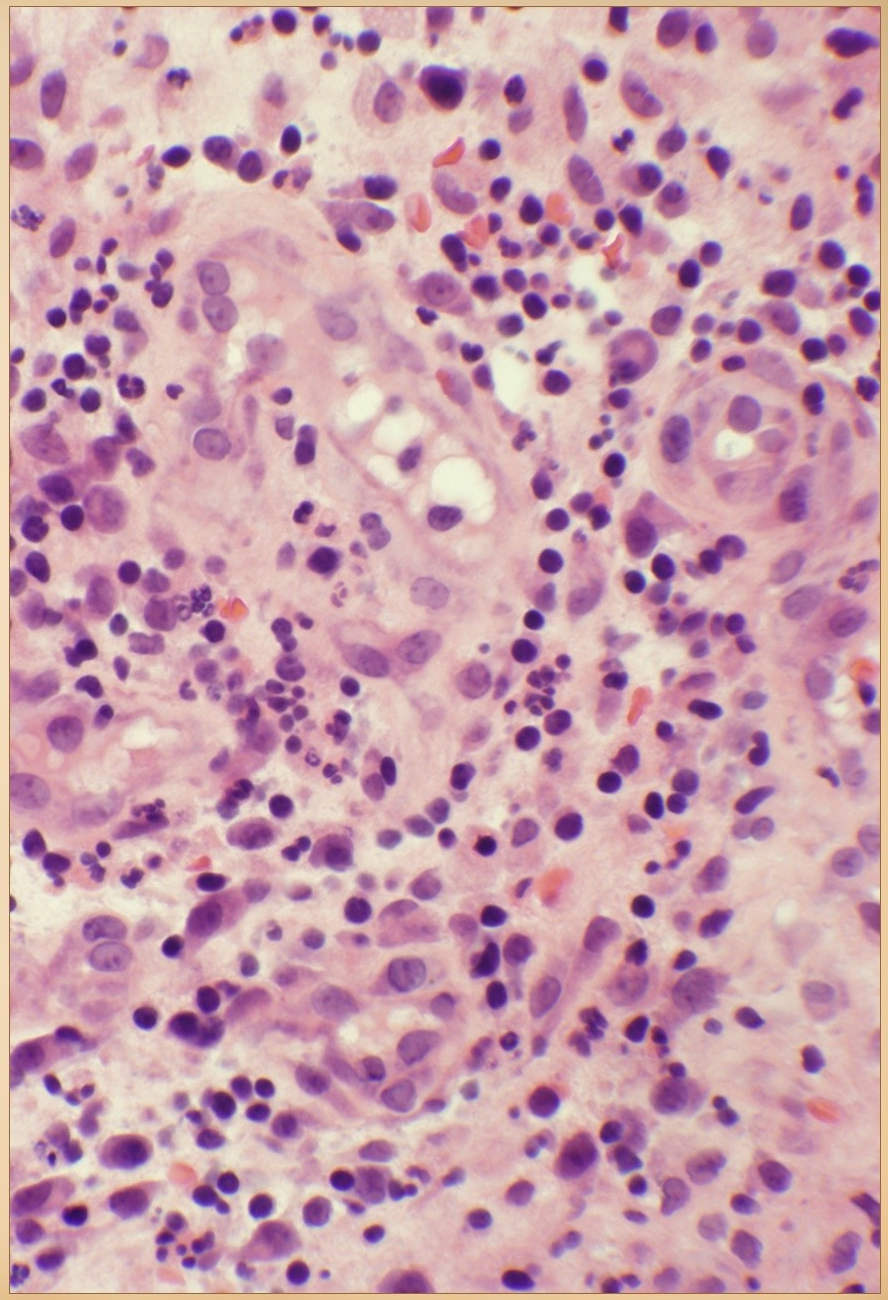
bizarre cell kinetics and disorganization



epithelial arrest

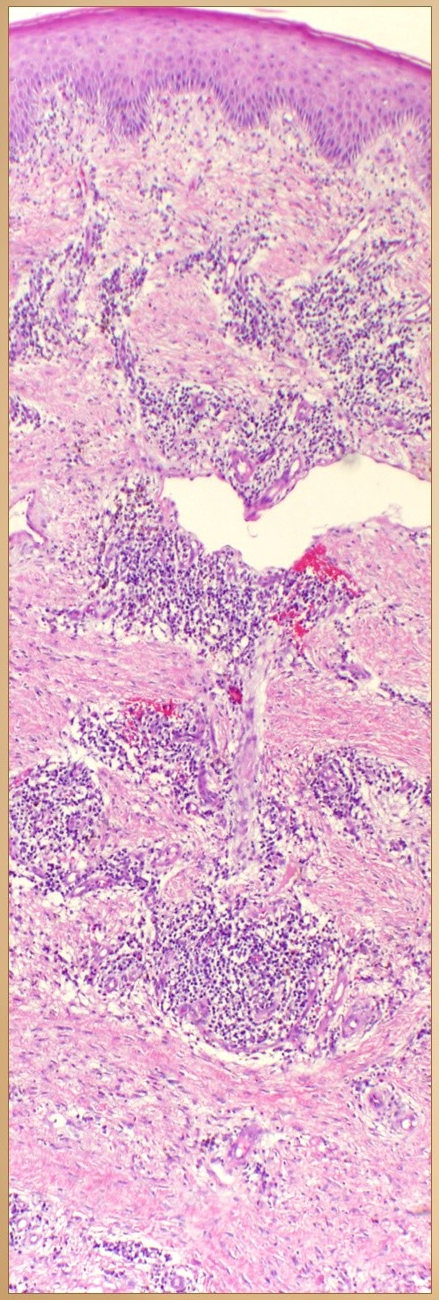
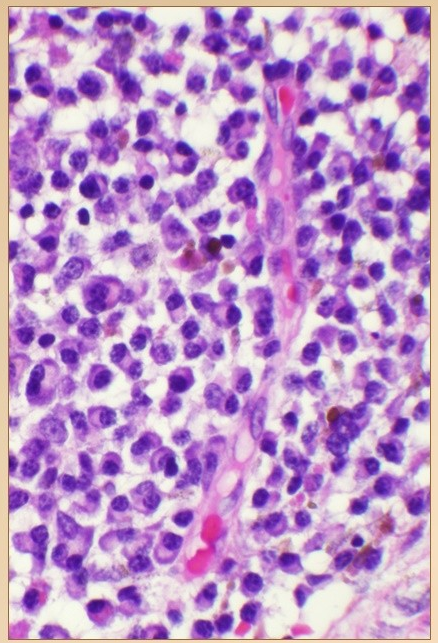
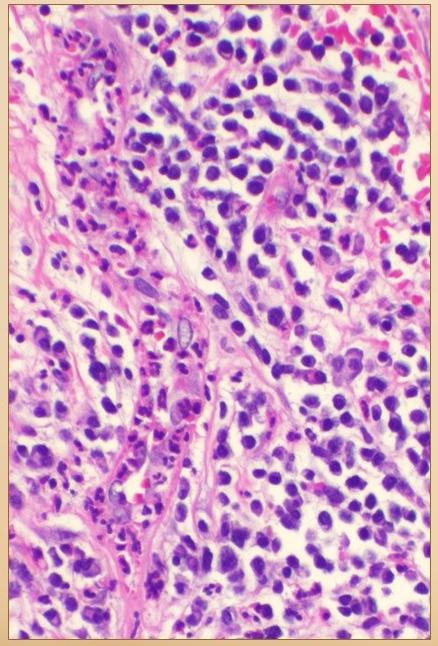
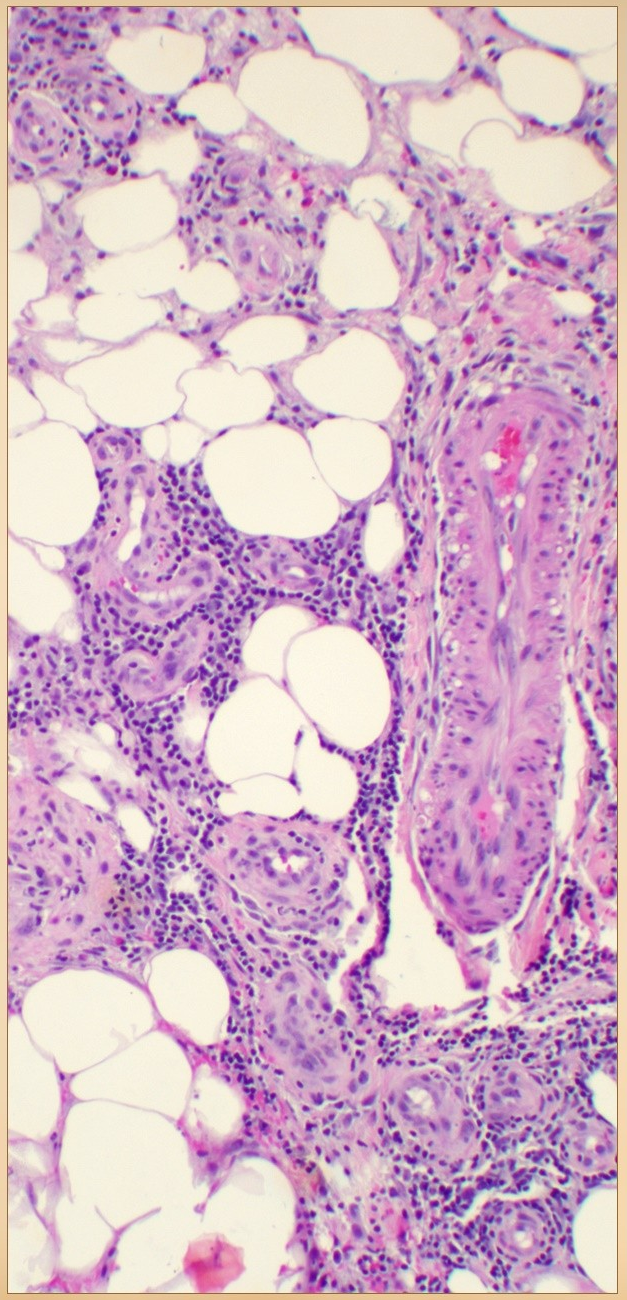
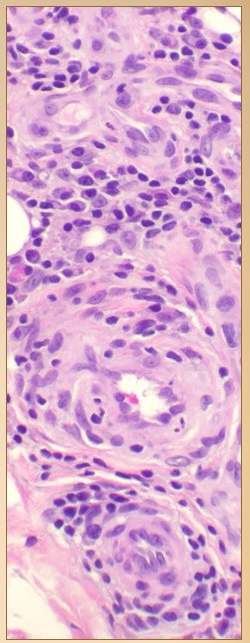
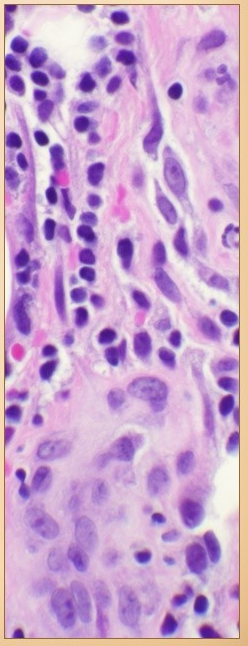
lupus: 53 f; chronic abdominal ulcer, with acute lytic progression



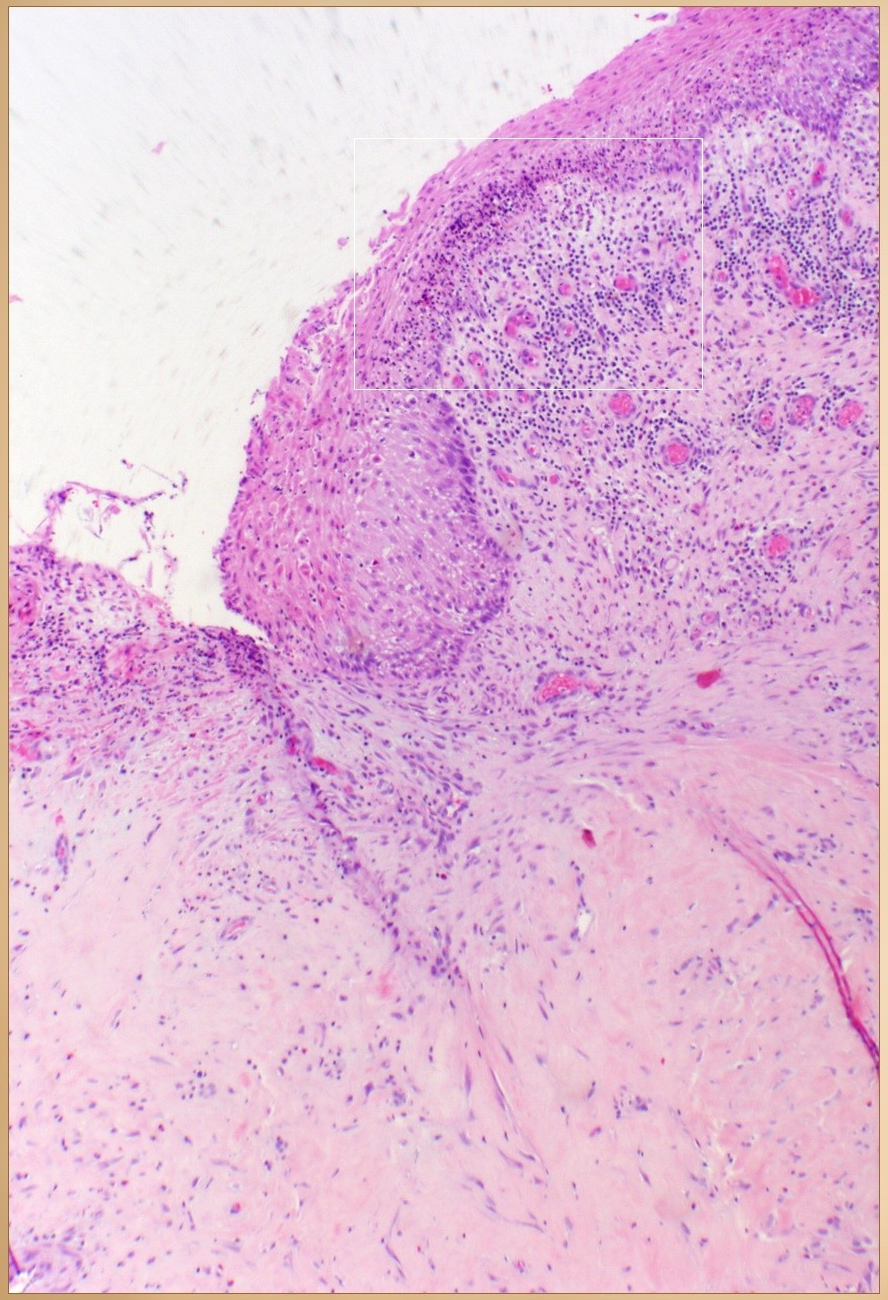


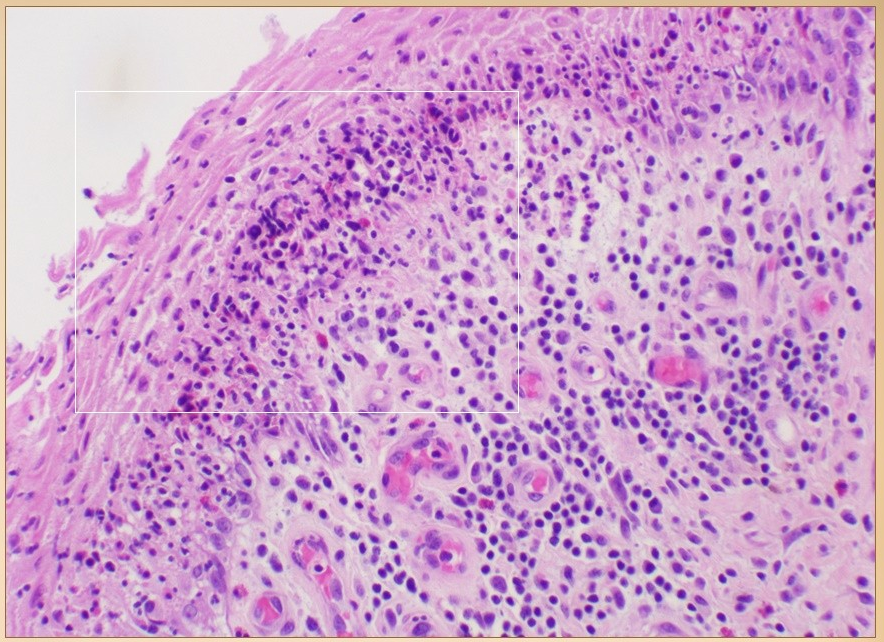
radiation: 81 f; chronic refractory ulcer, ankle

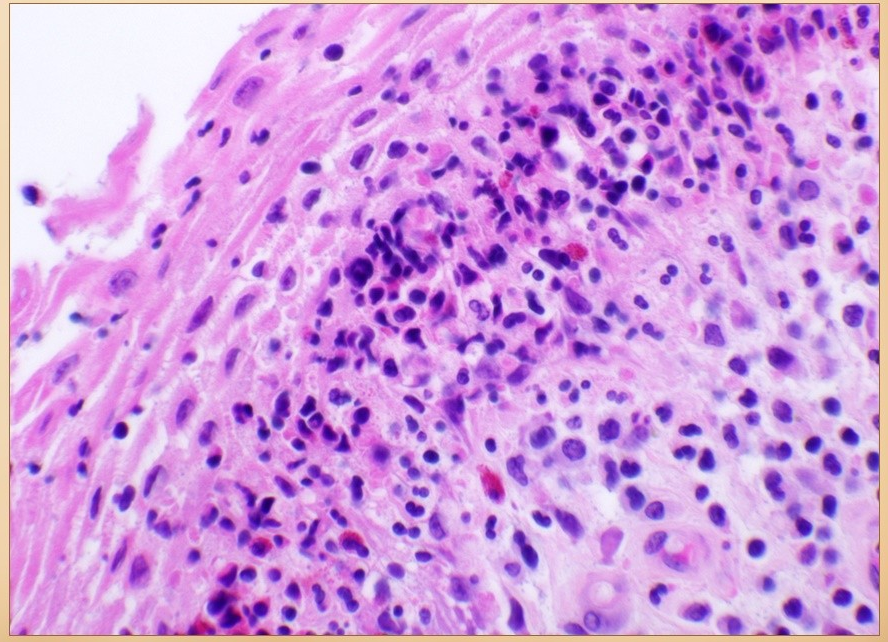
rheumatoid: 65 f; chronic refractory ulcer, ankle

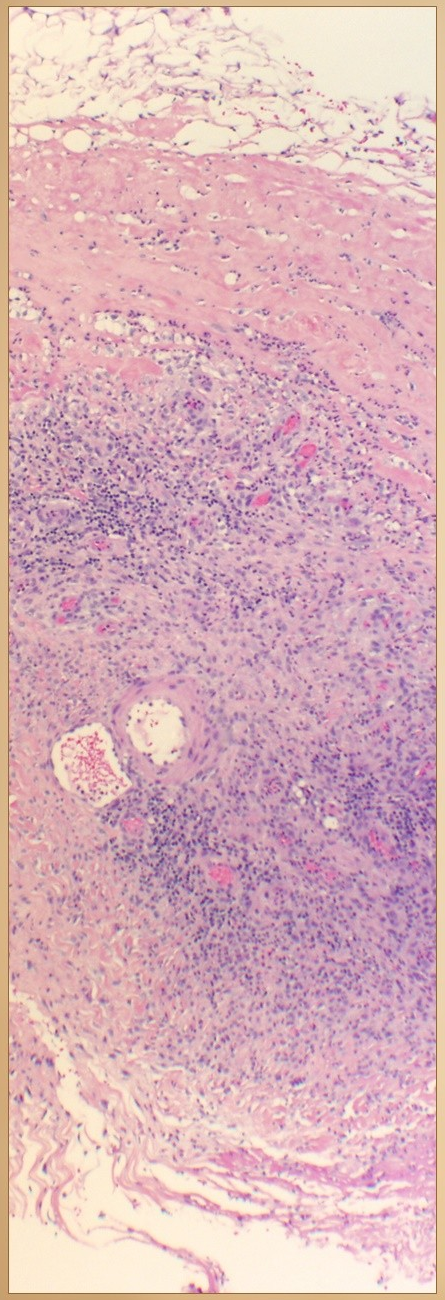
chronic ulceration: 55 f; acute lytic re-ulceration in old healed epithelium

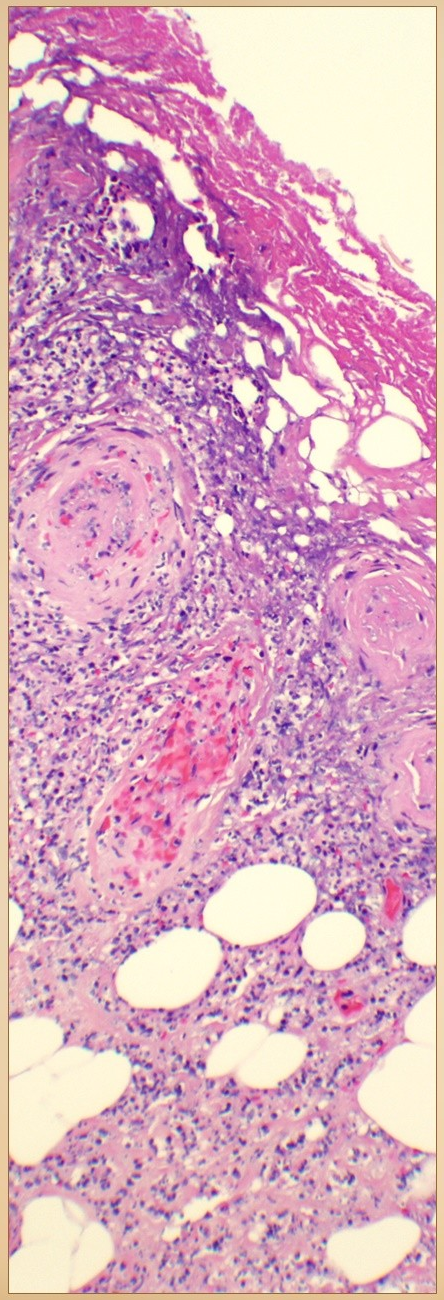


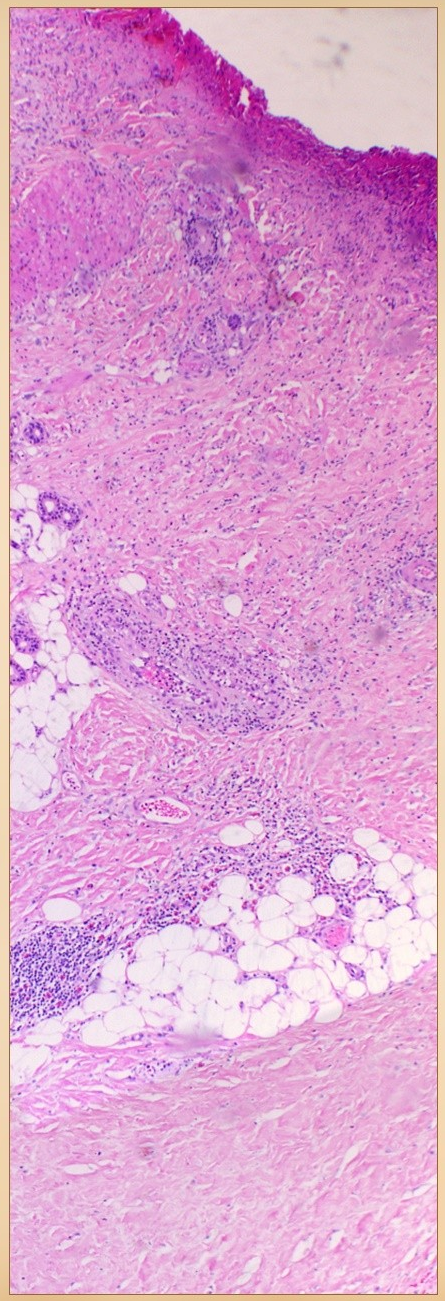


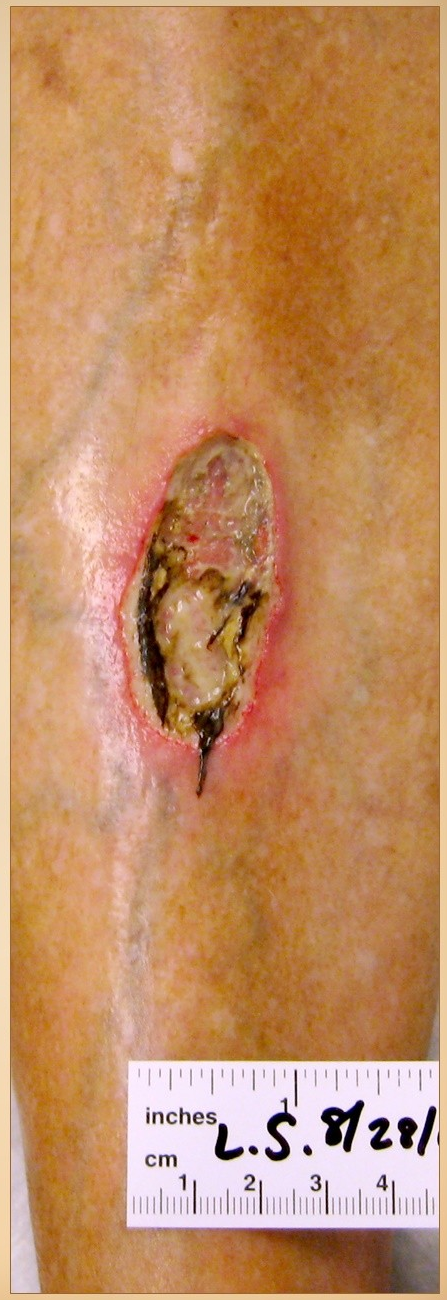


lupus: 65 f; scleroderma, chronic leg ulcer with progression erosion









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

FOR H&E / TRICHROME

Common Histologic Features

EVEN MORE WITH IMMUNOS

ACTIVE DISEASE AND INJURY

Thrombosis
Vascular necrosis
Vascular hyalinization
Necrosis & wound infarcts
Neutrophilic epidermolysis

ACUTE INFLAMMATION

Acute neutrophilic inflammation
Deep strata acute inflammation
AI adjacent to CI infiltrates
Leukocytoclastic vasculitis
Coagulative lysis

CHRONIC INFLAMMATION

Lymphocyte infiltrates
Plasma cell infiltrates
Eosinophil infiltrates
Mixed CI (lymph-plasma-eos)
Chronic vasculitis & perivascular
Chronic inflammation - diffuse

ADMIXTURE

Complex inflammation profiles
Acute-chronic population admixture
Monocyte-lymphocyte admixture
Neutrophil-fibroblast admixture

DISORDERED PROLIFERATION

Bizarre cell kinetics
Cell disorganization
Vascular disorganization
Fibrous disorganization

FAILED ORGANIZATION

Strata intermixing
Failed / missing wound strata
Missing aminoglycan layer
Missing vertical migration zone
Missing proliferative zones
Variations in anatomical depth
Variations in physical depth
Epithelial arrest

UNDERSTANDING HOW IMMUNOPATHIES AFFECT WOUND HEALING

PREDICATES

All mesenchymal stroma is composed of 2 cell types (& their derivative structures):
fibroblasts, angiocytes

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

The target of mesenchymal autoimmune attack is the collagen-vascular stroma, i.e.
fibroblasts, angiocytes

1

CVD - CTD AS THE DISEASES OF WOUND HEALING

Basic syllogism :

A

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

B

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

Therefore, the CVD-CTD are diseases of wound healing.

2

INTRINSIC WOUND CHRONICITY AS A CVD - CTD

Basic syllogism :

A

Autoimmune diseases that affect the
collagen-vascular stroma are the CVD-CTD.

B

Intrinsic lymphoid wound chronicity is an autoimmune disorder
that affects the collagen-vascular connective stroma.

Therefore, intrinsic wound chronicity is a CVD-CTD.

1 - UNDERSTANDING HOW AUTO-IMMUNOPATHY AFFECTS WOUND HEALING - 1

Not all chronic and pathological (CAP) wounds are in a state of intrinsic chronicity and self-sustaining auto-immunization.
Many have identifiable active primary pathologies that can be treated and the wounds healed easily enough.

But many chronic wounds are difficult to heal because they have transitioned into a state of
lymphoid autoimmune intrinsic chronicity (LAIC).
This state exists when auto-immunization occurs against mesenchymal stromal cells and their constructs
(angiocytes & fibroblasts, vascular & connective structures).

The normal response to incidental injury is the sequence : thrombosis --> acute inflammation --> repair (wound module).
For incidental injury in healthy subjects, these events are sequential one-shots without feedback, retrigger, or other sustentation.

These sequential events define the wound in time. The physical anatomy of the wound (strata) defines the wound in space.
Acute inflammation normally operates early in upper strata. Repair cells normally operate later in deeper strata.

This separation in time and space ensure that there is little admixture between acute inflammatory cells and stromal repair cells.
Without sustained acute inflammation & population admixture, sensitization (and then chronic lymphoid inflammation) cannot occur.

Under various conditions of persistent primary disease or injury, acute inflammation can become sustained.
Causative primary pathologies include chronic injury, thrombosis, allergy, infection, or anything that triggers sustained inflammation.

Sustained acute inflammation (1) creates matrix degradation debris and increases the load of normally sequestered endocellular elements.
These exposed chemicals are potential auto-antigens that the immune system is naive to but would ordinarily never see.

Sustained inflammation (2) disorganizes timewise & spatial wound structure, causing an intermix of cells & strata, inflammatory & repair.
Potential antigens from ongoing degradation now include those from repair elements - angiocytes, fibroblasts, and their structures.

2 - UNDERSTANDING HOW AUTO-IMMUNOPATHY AFFECTS WOUND HEALING - 2

As acute inflammation is sustained, there is increased antigen processing by macrophages and then the appearance of lymphocytes.
Eventually there is antigenic recognition of items normally hidden from immune cells by time, space, sequestration, & wound anatomy.

Autoimmunity occurs when lymphoid cells in the wound eventually "see" endocellular or other antigens that they should never have seen.
(*Auto-immunization against mesenchymal stroma could not have occurred absent sustained acute inflammation and population admixture.*)
This pathological state is marked by appearance of a 3rd population - chronic inflammation - lymphocytes, plasmacytes, & eosinophils.

Auto-sensitization includes angiocytes & fibroblasts, vascular & connective stromal elements, because their antigens were in the melee.
Presence & persistence of lymphoid cells in the vascular locus attest to the significance of angioid elements as targets of auto-immunity.

Once the stroma is auto-sensitized, the 3rd population (chronic lymphoid cells) has three pairs of pathological effects.
(1a) Chronic inflammation effects to perpetuate acute inflammation. *(1b)* Autoimmune predation or inhibition against stromal elements.
Chronic inflammation effects: *(2a)* Afferent effects to create or sustain injury & ulceration. *(2b)* Efferent effects to impair healing.
Autoimmune effects: *(3a)* Local effects against the reparative stroma. *(3b)* Systemic effects against stroma in general.

Chronic inflammation can retrigger or sustain the wound as much as primary injury or disease does.
Afferent effects: Triggering and sustaining acute inflammation & thrombosis is what causes necrosis, lysis, ulceration.
Efferent effects: Disorganizing the cell mix, strata, & interactive biology of the repair process is what impairs healing.

Auto-immunization against stroma causes many pathological & clinical sequelae (based on specific antibodies, origins, circumstances).
Local effects: Limited effects presenting as localized vasculitis, panniculitis, etc., or as impairments of wounds & wound healing.
Systemic effects: Global morbidity recognized clinically as nosological entities, e.g. rheumatoid, lupus, scleroderma, etc.

Intrinsic wound chronicity and impaired healing are the local effects of auto-immunity directed against fibro-vascular stroma.
The CVD-CTD's are the systemic effects of auto-immunity directed against fibro-vascular stroma.

3 - UNDERSTANDING HOW AUTO-IMMUNOPATHY AFFECTS WOUND HEALING - 3

Because their auto-immunopathy is against stromal cells,
. . . the CVD-CTD's have high incidence of ulceration & impaired wound healing.
. . . wounds with lymphoid autoimmune intrinsic chronicity have a high incidence of CVD-CTD disease or symptoms.

Diseases that affect collagen-vascular connective stroma ipso facto affect the wound module (stroma in a repair phase after injury).
The autoimmune CVD-CTD's are diseases directed against stroma. ***Therefore, the CVD-CTD's are diseases of wound healing.***

Autoimmune diseases that affect the collagen-vascular stroma are the CVD-CTD.
Intrinsic lymphoid wound chronicity is autoimmunity directed against stroma. ***Therefore, intrinsic wound chronicity is a CVD-CTD.***

Wound healing is just a connective tissue event, stroma in a repair phase after injury.
Its impairment is just another manifestation of connective tissue pathology.

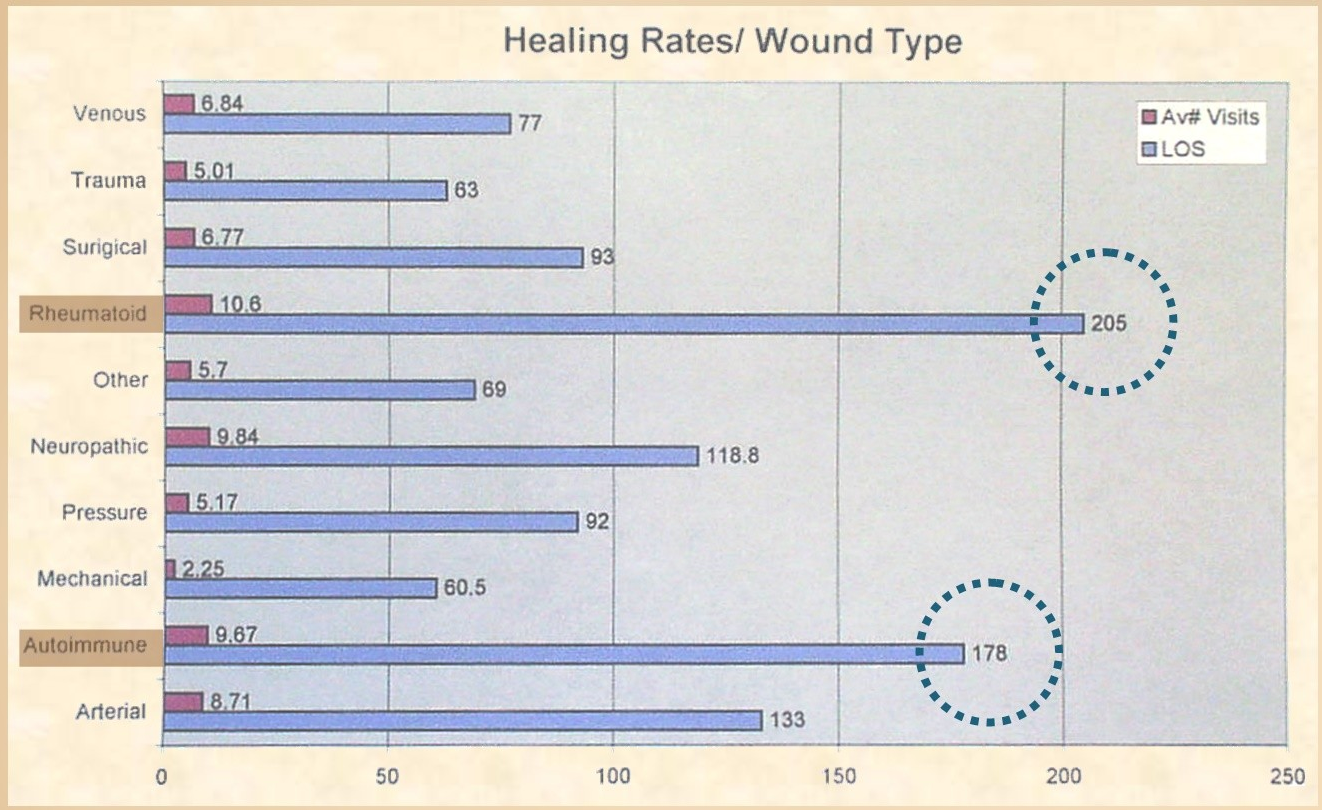
The two pathologies, ***classic connective tissue disorders*** and ***intrinsic wound chronicity*** are essentially the same disease.
They are autoimmunopathy directed against fibro-vascular stroma, both induced by the same underlying instigating disorders.

They are different manifestations, different syndromic avatars of the same process,
. . . *one acting locally*, causing stromal inflammation & ulceration, then inhibiting stromal repair by damage, inhibition or disorganization.
. . . *the other acting systemically*, causing arthritis, synovitis, serositis, vasculitis, panniculitis, myofasciitis, etc.

In autoimmune wounds, impaired wound healing and chronic inflammation are conjoined,
intermixed with acute inflammation and variable expression or competence of the reparative wound module and its elements.

The connective tissue disorders and lymphoid wound chronicity are true intrinsic diseases of wound healing.
Inflammation & immunity are targeted against stroma, meaning ipso facto they are targeted against the wound healing machinery.

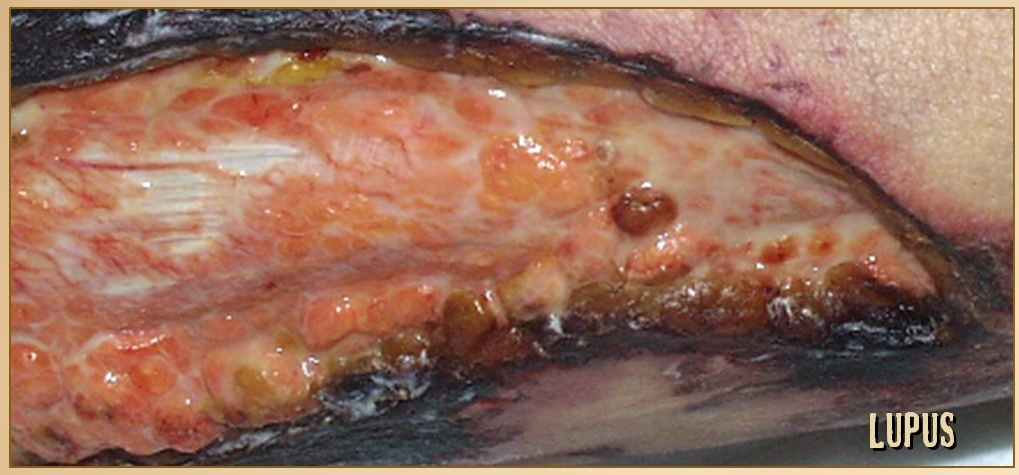
SIGNIFICANCE OF IMMUNOPATHIC ULCERATION & IMPAIRED WOUND HEALING

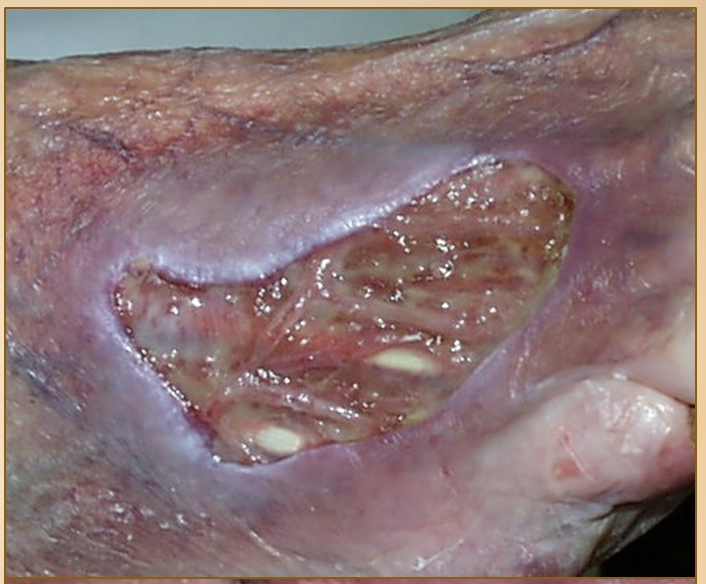


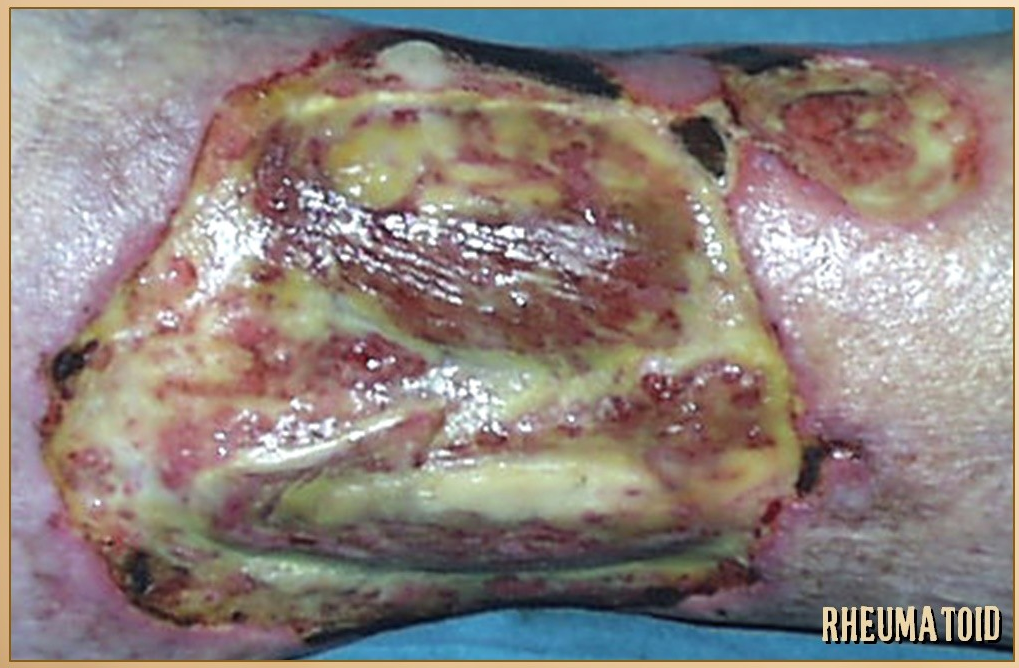
Autoimmune & immunopathic diseases cause wounds and they also impair wound healing.
As diseases of fibroblasts & angiocytes, they impair the intrinsic ability of the wound module to function.

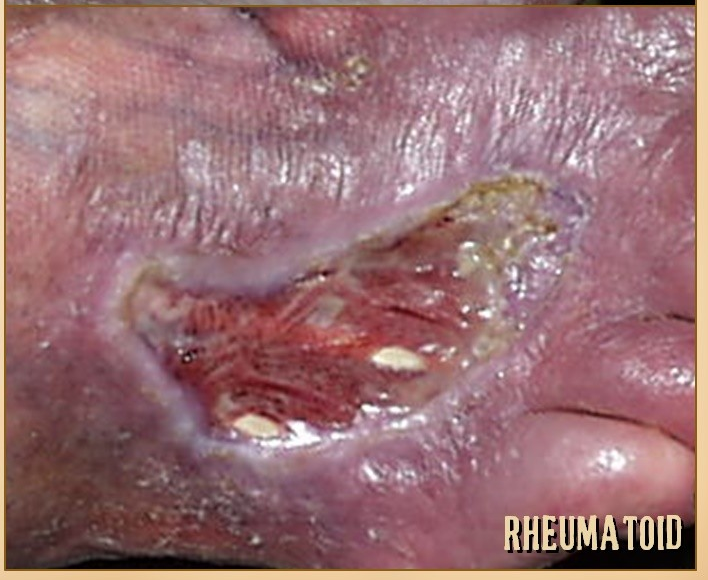
Immunopathic ulcers are a challenge to treat because wound healing is "broken",
but comprehensive management of wound and underlying disease will prevail.

ARRESTED WOUND MODULE

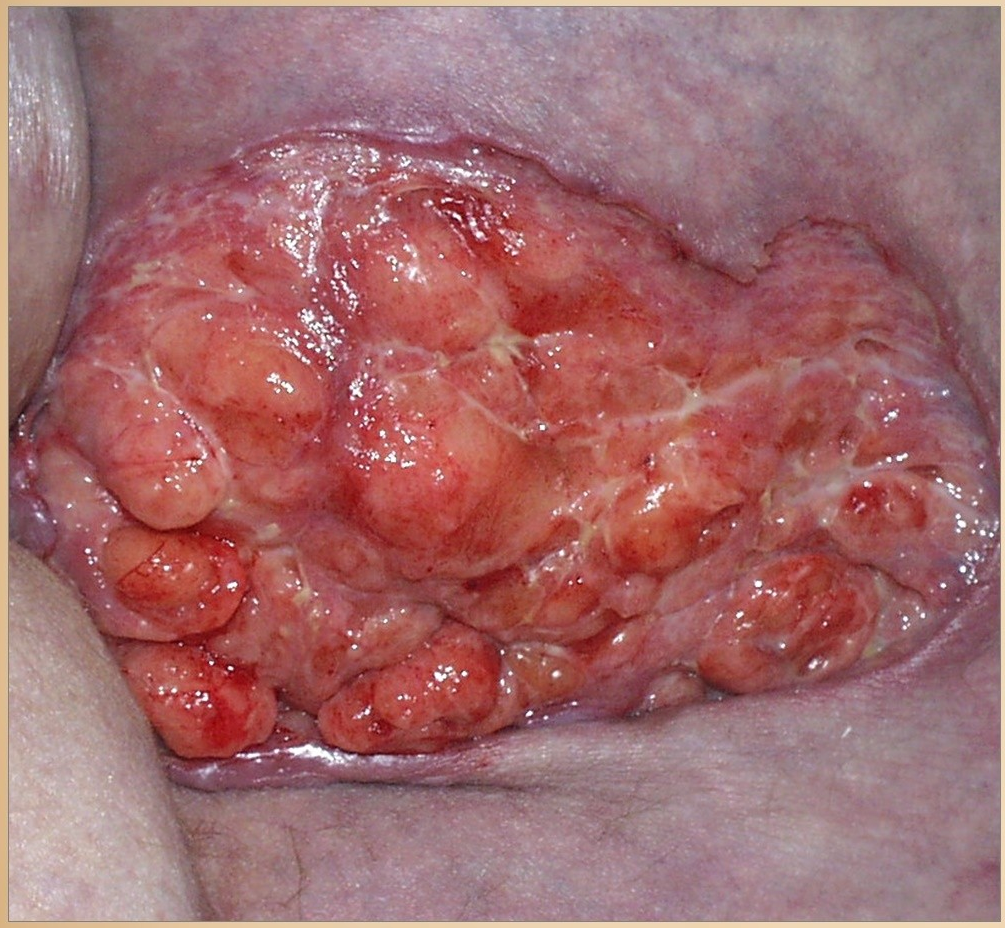




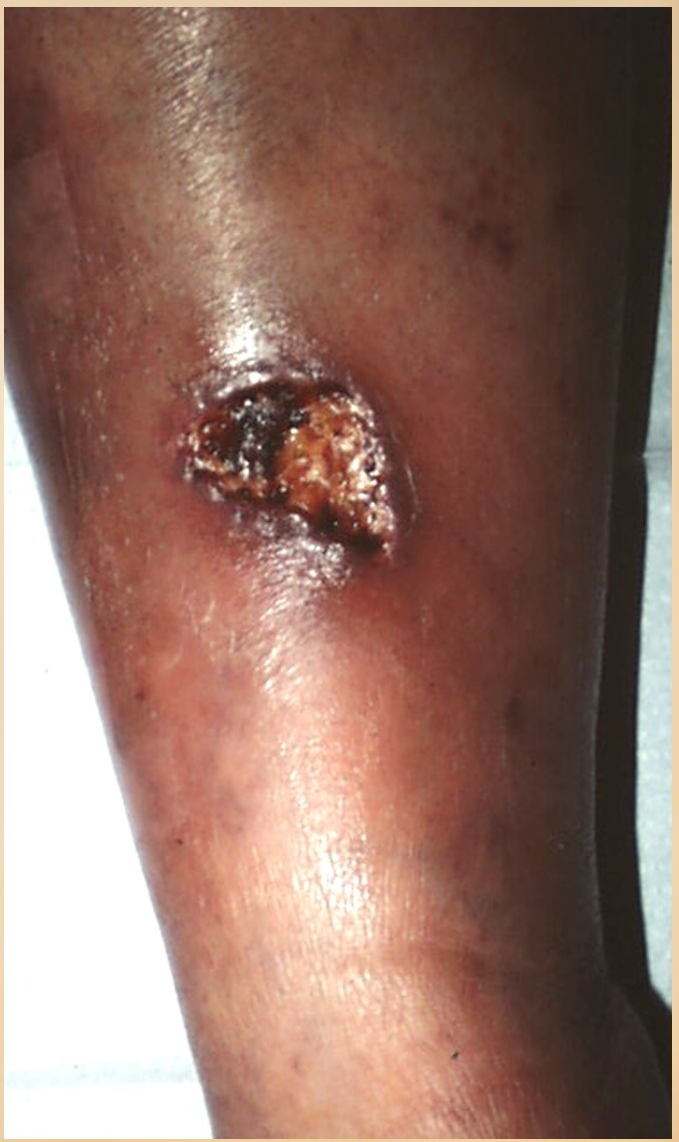




ARRESTED WOUND MODULE

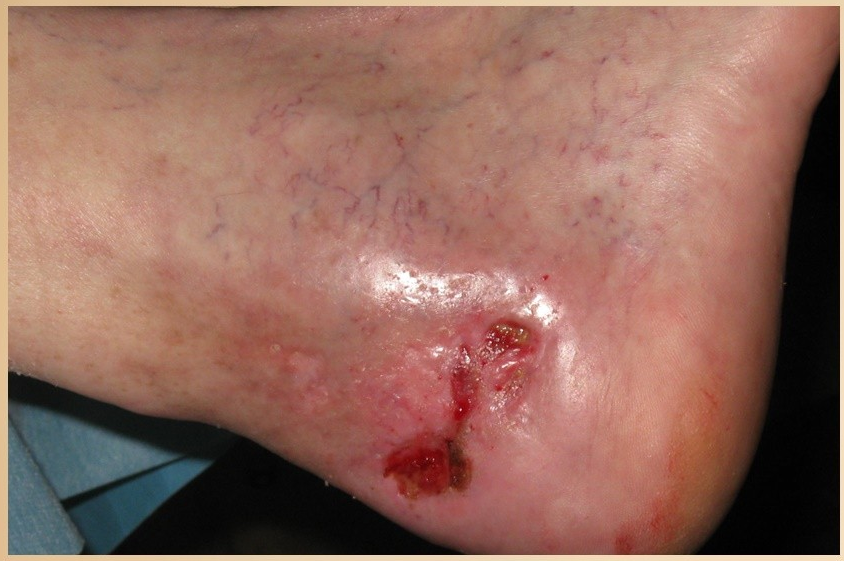


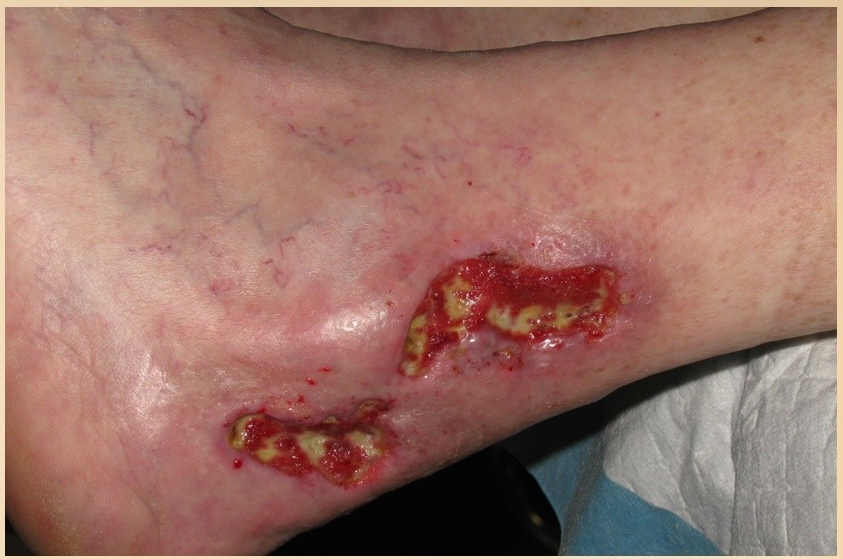
WOUNDS NOT HEALING: Rheumatoid, injury 6 months prior (buttock)

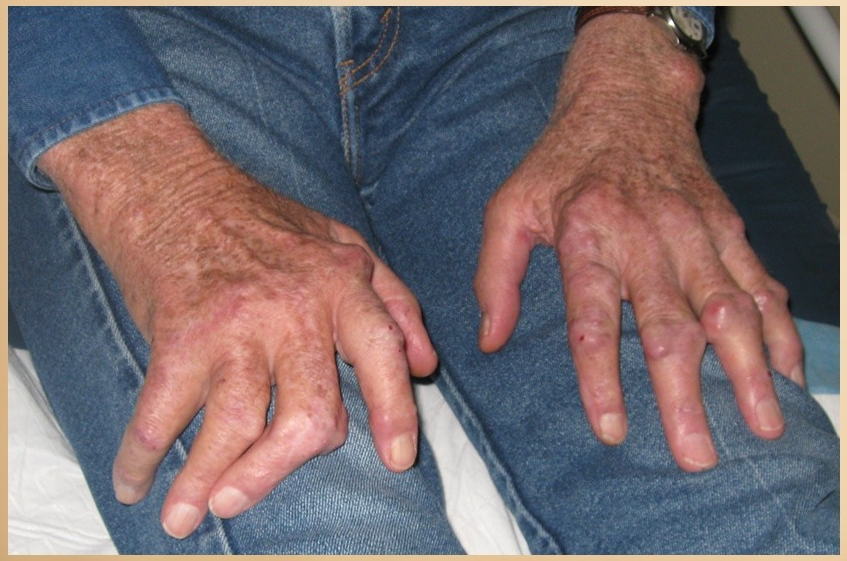


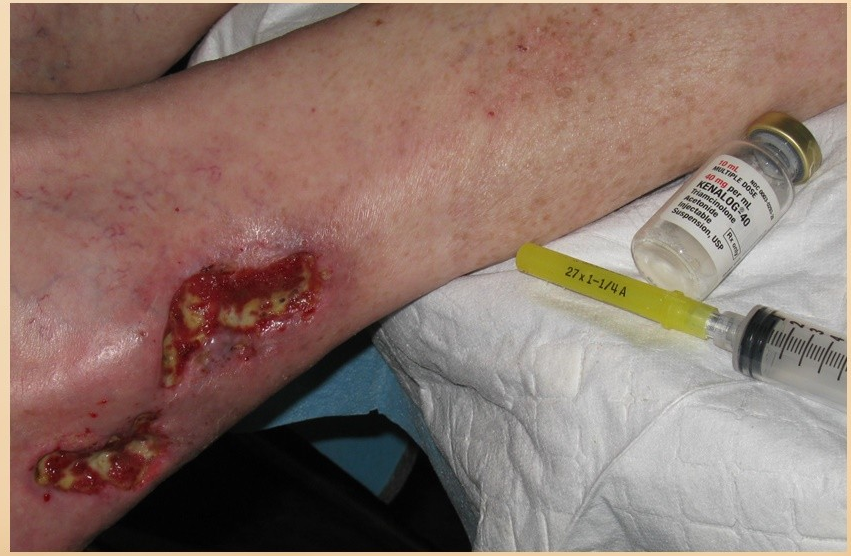
WOUNDS NOT HEALING: Polymyositis, injury 4 months prior (leg)

RX WITH STEROIDS



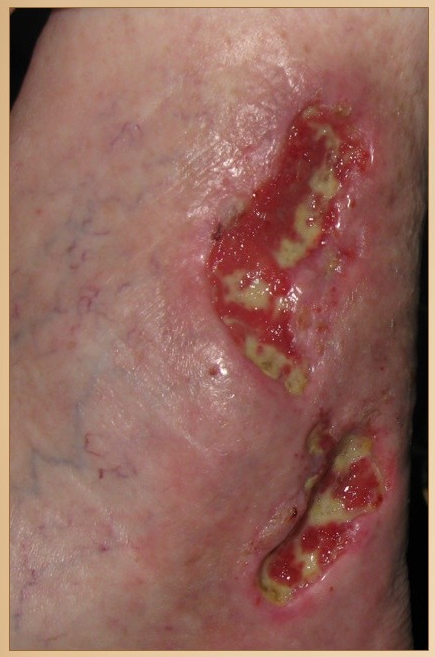


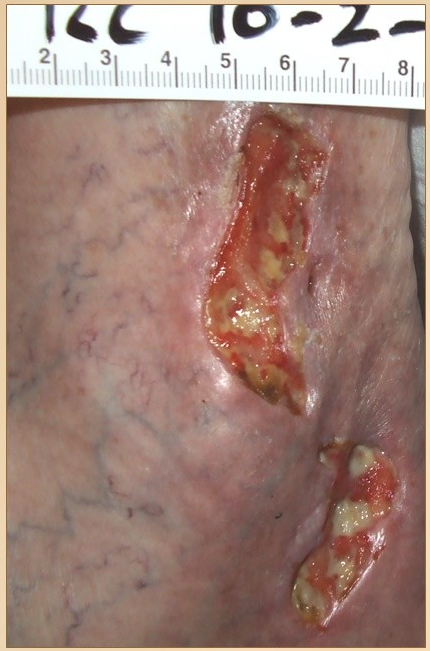


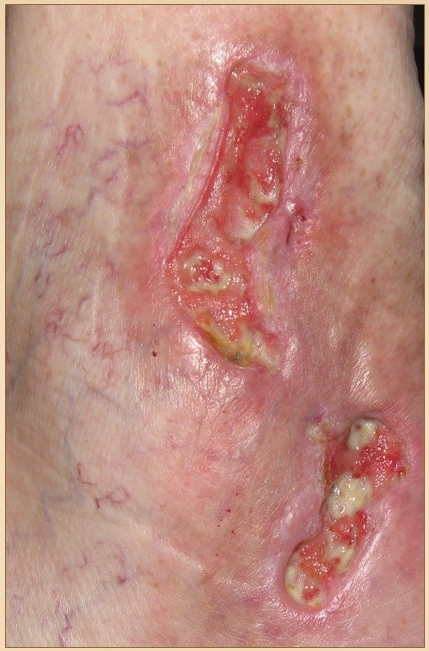


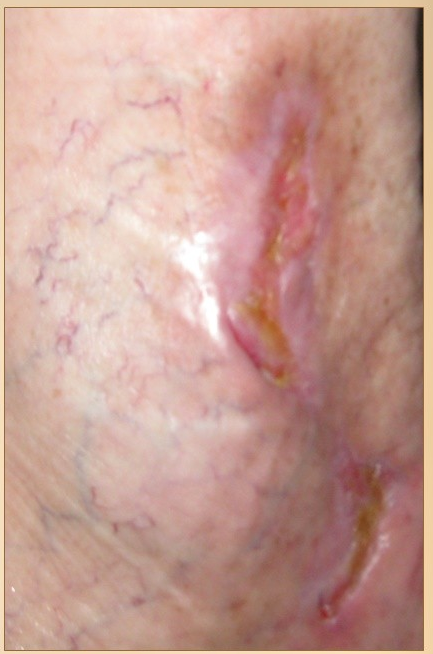
rheumatoid: *71m* *prednisone*

RX WITH STEROIDS





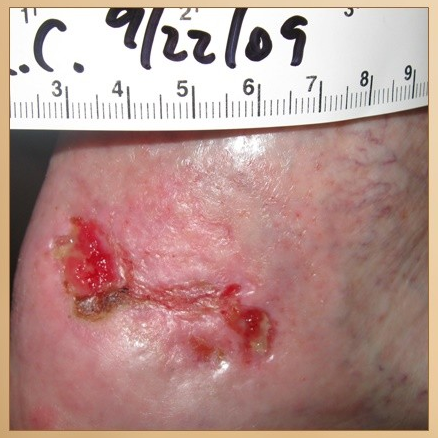


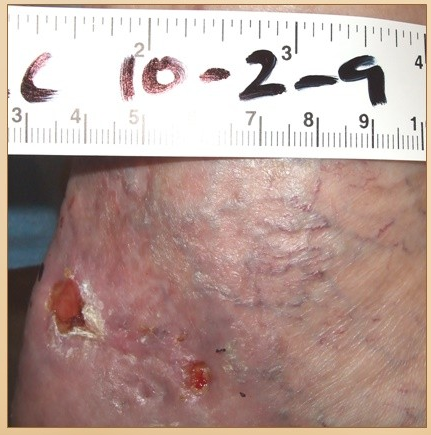


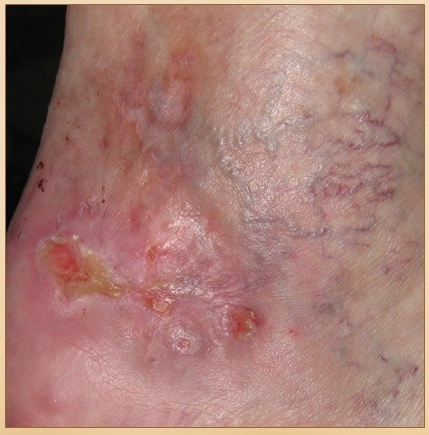
10 days

21 days

3 months

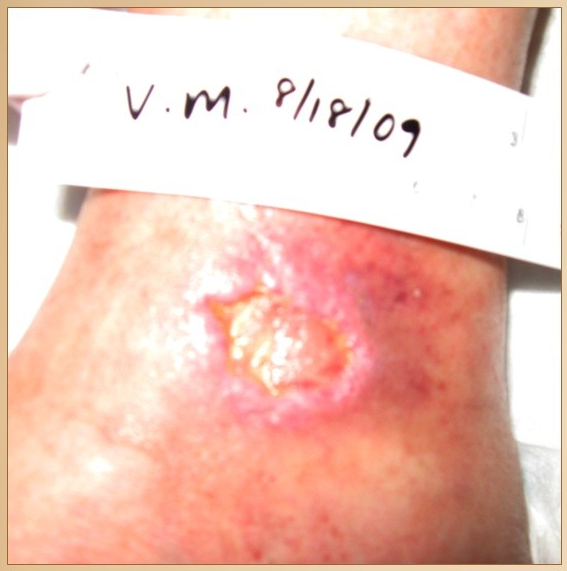


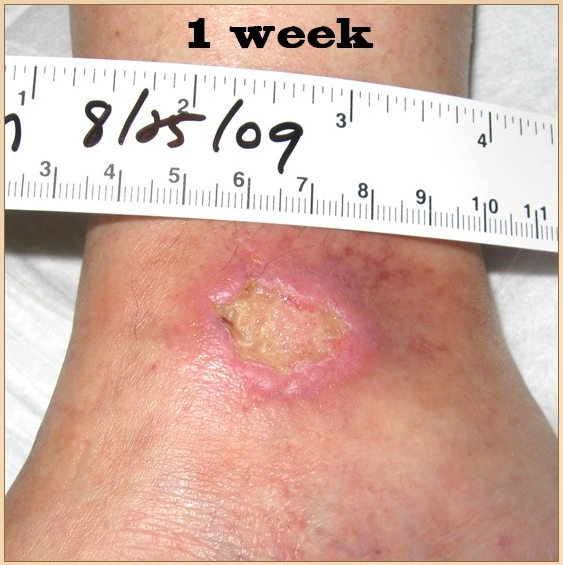


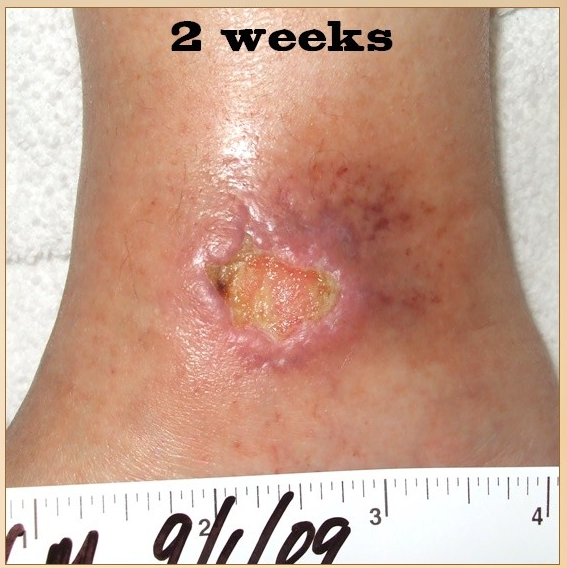


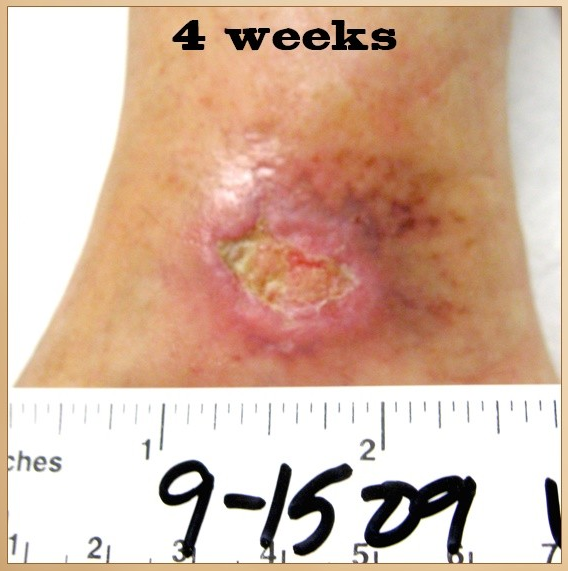
healed

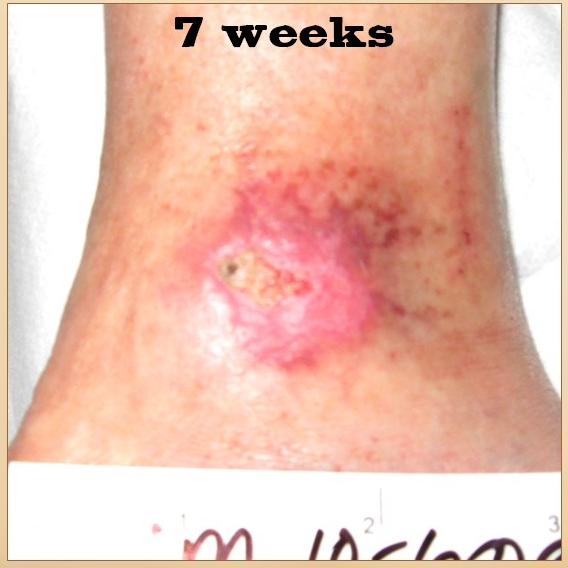
RX WITH STEROIDS

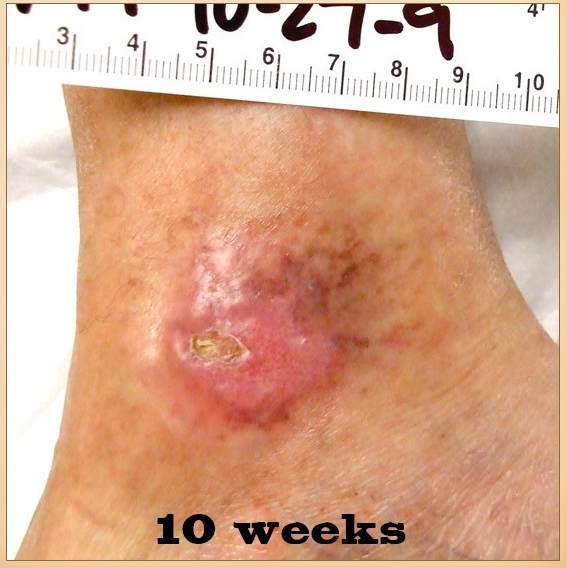




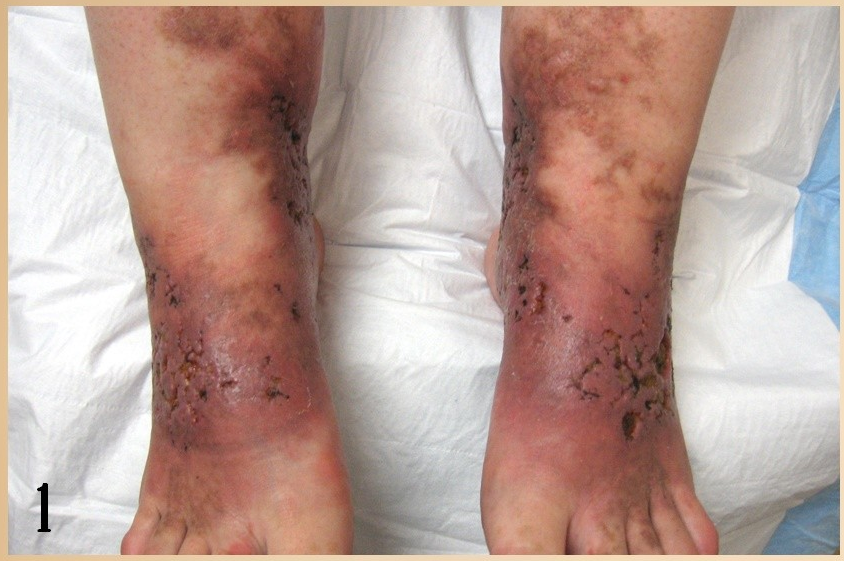


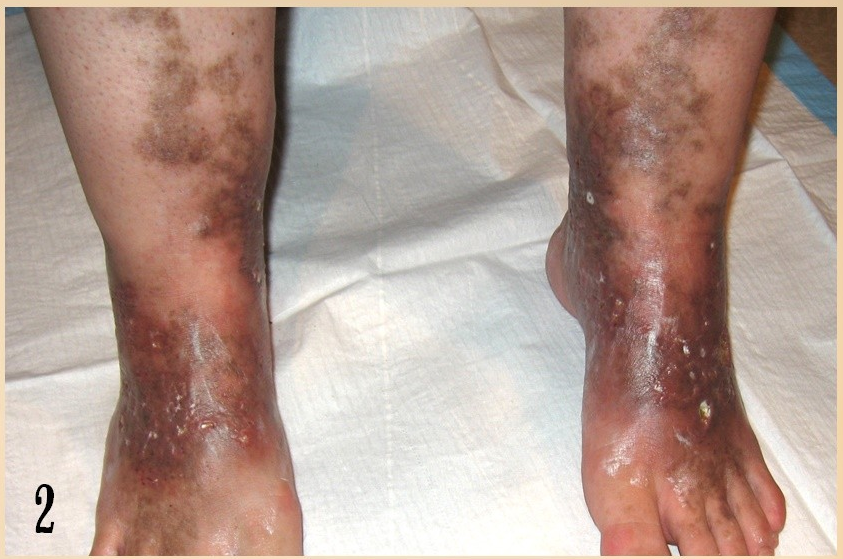


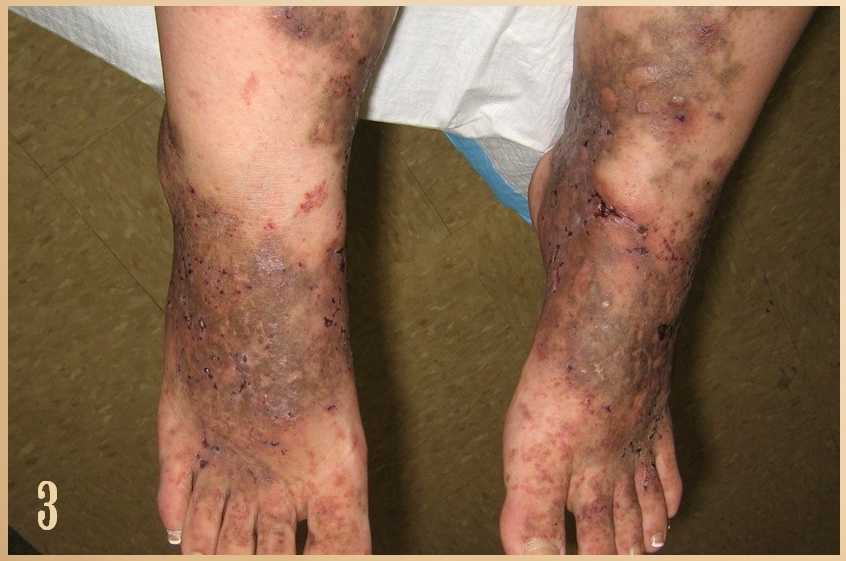


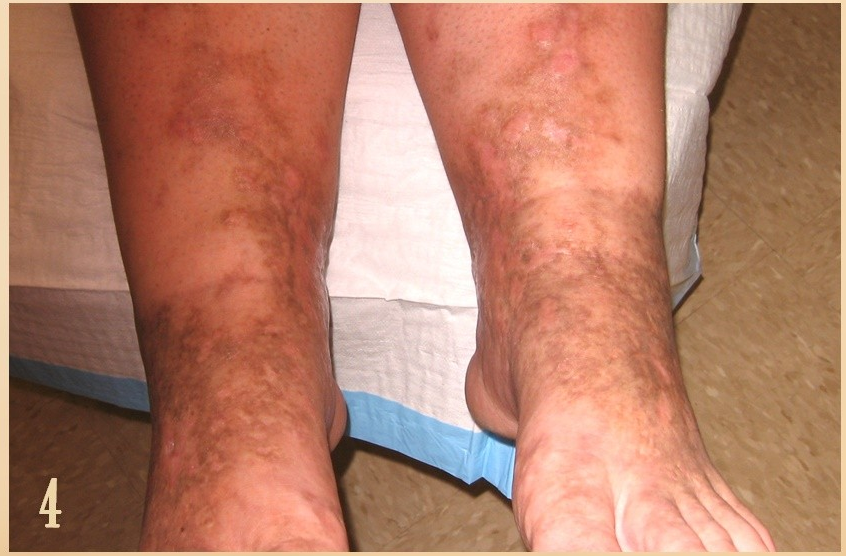


RX WITH ANTI-IMMUNE



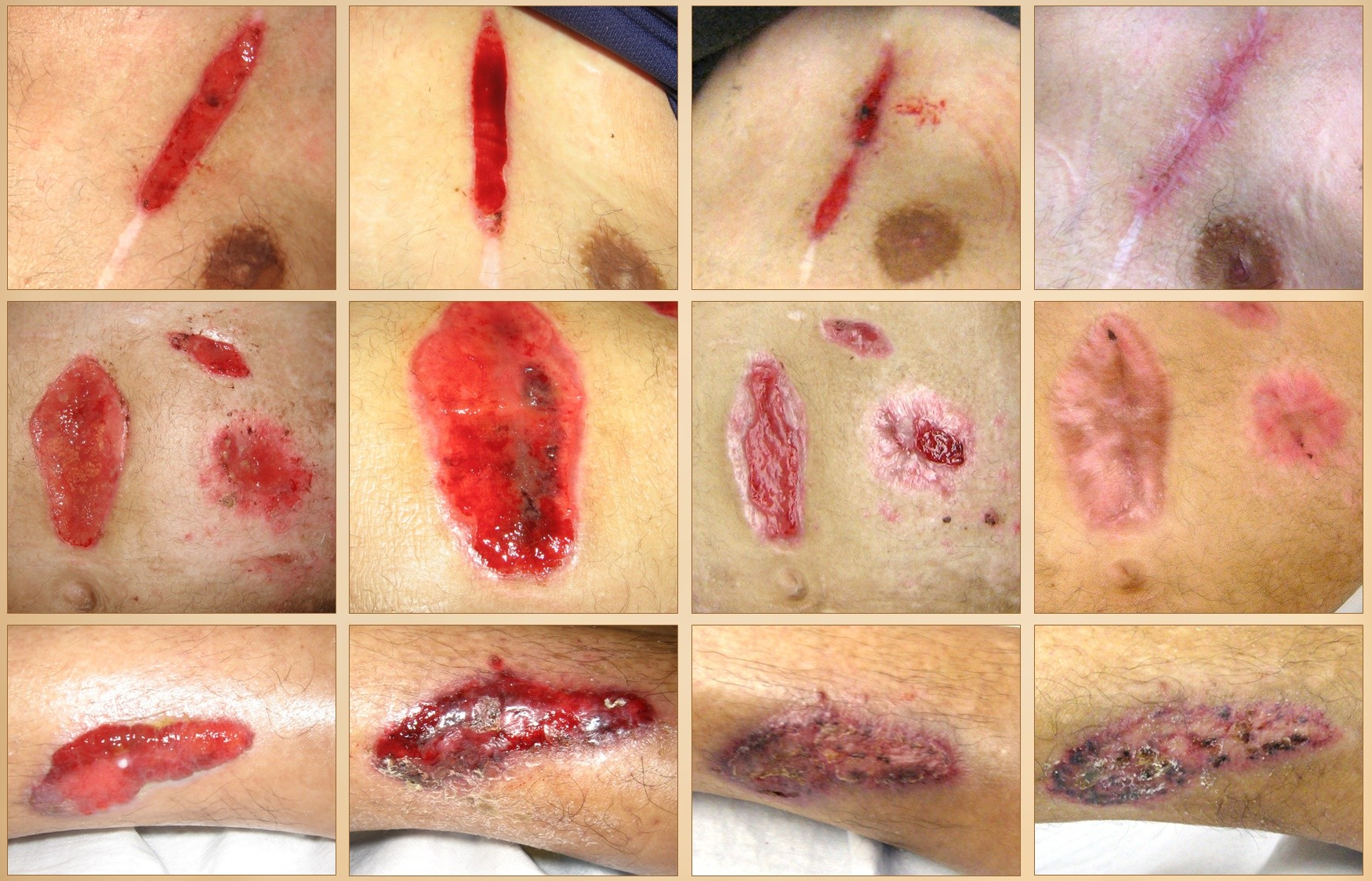






bullous pemphigoid, contact: *35m* *azathioprine*

RX WITH ANTI-IMMUNE



5 months: *steroids & misc*

7 months: *azathioprine*

8 - 15 months: *azathioprine*

AUTO-IMMUNOPATHY & WOUND HEALING - COROLLARIES

Defining wound chronicity as a distinctive entity.

Acute versus chronic wounds:
(Biochemistry & genomics.)
Basic anatomy, histology, pathophysiology, and cell biophysics.

Defining wound chronicity as a CVD-CTD.

Need to identify serologies & clinical profiles.
Need to study therapeutic effects and strategies with anti-immune drugs.
Need to match specific profiles to specific anti-immune drugs for best results healing those wounds.

Defining CVD-CTD as an intrinsic disease of wound healing.

Breaking the anachronism and parochialism of: (1) wound misdiagnosis,
(2) impaired wound education, (3) inadequate physician-level science, clinicals, & therapeutics.

The interconnections between hypercoagulability & auto-immunity.

The connection is real.
The connection is causative.
Hypercoagulability causes autoimmune disorders (rheumatoid, lupus, etc).
So too other chronic disorders (injury, inflammation, allergy, infection, thrombosis).

Auto-immune intrinsic chronicity and the physics of wound failure.

Simply put, intrinsic wound pathology and chronicity is a dynamical disorder of
complex populations caused by auto-immunopathic disruption of the wound module.

PART 3

THE PHYSICS AND PATHOLOGY OF WOUNDS

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Marc E. Gottlieb, MD, FACS

Phoenix, AZ

1

The Wound as a System and a Controlled Machine

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

2

Auto-Immunopathy and the Intrinsic Disease of Wound Healing

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

3

Chronicity and the Physics of Wound Failure

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

AUTOIMMUNOPATHY & WOUND CHRONICITY

"CVD-CTD" & PATHOLOGICAL WOUND CHRONICITY ARE THE TRUE INTRINSIC DISEASES OF WOUND HEALING

These are the disorders which target stromal cells & structures - fibroblasts & angiocytes, vessels & connective tissues - which are also the principal agents of wound healing.

This pathology arises when sustained primary injury or disease causes sustained acute inflammation, which leads to wound disorganization and sensitization against auto-antigens.

Lymphocytic wound chronicity (plus primary disease & sustained acute inflammation) causes ulceration & disrupts healing. This is a major category of chronic wounds & wound pathology.

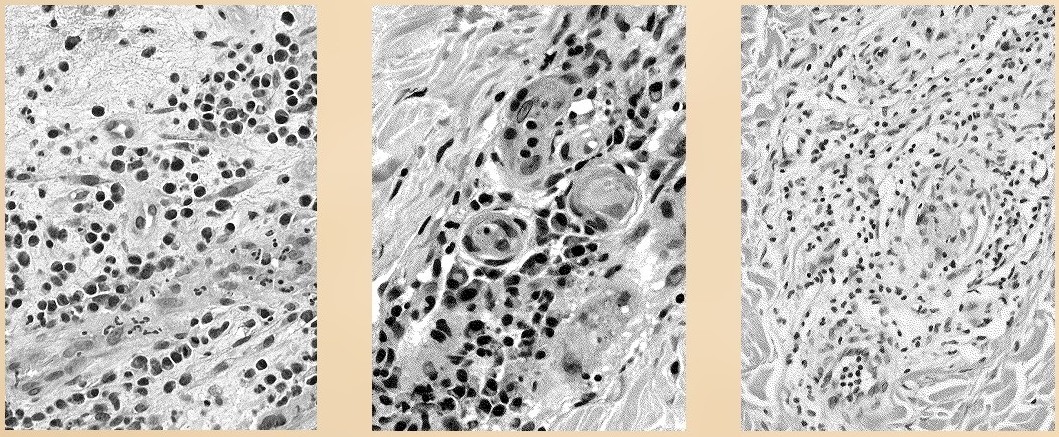
Inasmuch as these disorders affect the primary agents of wound healing, wound healing is more impaired than for other causes of chronic wounds which are extrinsic to the primary process.


END

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

Marc E. Gottlieb, MD, FACS Phoenix, AZ

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



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

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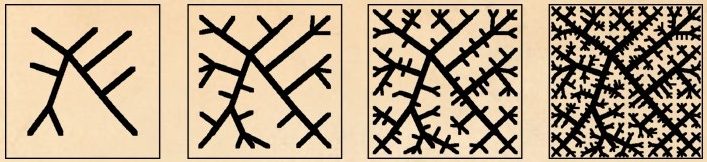

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The Physics and Pathology of Wounds. Part 2. Auto-Immunopathy and the Intrinsic Disease of Wound Healing.

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

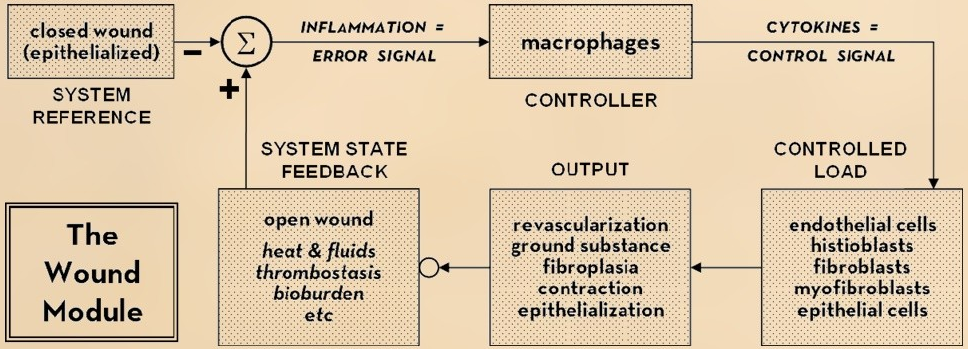
The presentation and related materials can be viewed and used at:
arimedica.com

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

Marc E. Gottlieb, MD, FACS Phoenix, AZ

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

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

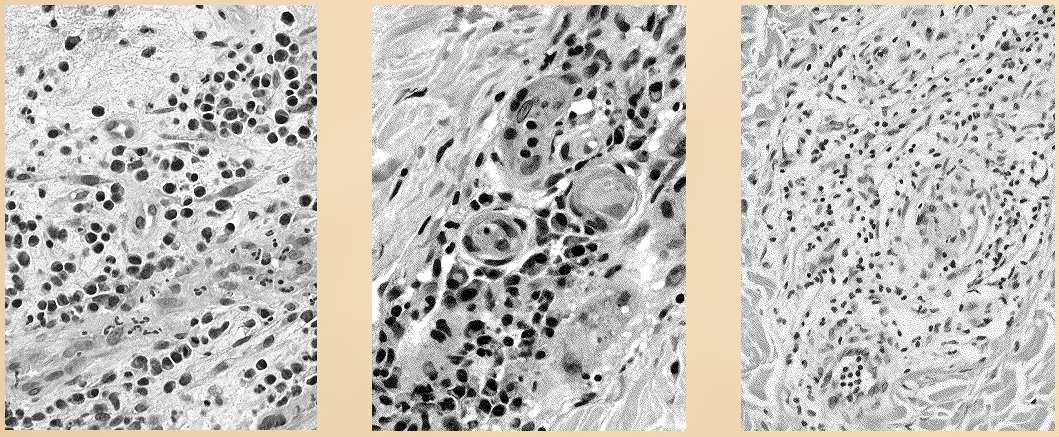


The wound control system is composed of these elements: The ***system state*** is the open wound and its conditions. It is compared (Σ) to a ***reference***, normal epithelialized tissue. Variances generate an ***error signal*** in the form of inflammation. This activates macrophages which are the ***system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

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

Marc E. Gottlieb, MD, FACS Phoenix, AZ

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



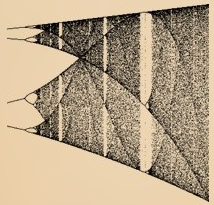
*In these chronic non-healing wound samples, the vascular locus is infiltrated with immune cells (**left**, plasma cells; **middle**, plasma cells and eosinophils; **right**, lymphocytes.) On the left, plasma cells are mixed with the migratory angiocytes (spindles) that are trying to assemble the wound.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

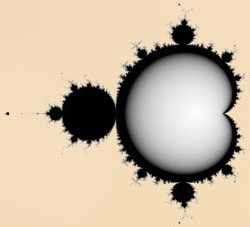
The Physics and Pathology of Wounds. Part 3.
Chronicity and the Physics of Wound Failure.

Marc E. Gottlieb, MD, FACS Phoenix, AZ

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

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





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

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ACUTE, SUSTAINED ACUTE, & CHRONIC INFLAMMATION

CAUSES

What induces auto-sensitization & chronic lymphocytic inflammation directed against native cells and tissues?
Autoimmunity occurs when the immune system "sees" sequestered auto-antigens that it should never have seen.

1

Endo-cellular and nuclear debris and other occult & sequestered antigens are exposed by inflammation.
Debris-antigen load is less with one-shot injury & acute inflammation, increasing with sustained inflammation.

2

Autoimmunity occurs when these novel antigens are processed by macrophages and presented to lymphocytes.
Macrophage-lymphocyte interactions are limited in one-shot injury & acute inflammation, but sustained & chronic inflammation increase admixture & chance sensitizations.

This process can occur with any condition which causes sustained or chronic injury, sustained or chronic inflammation, and high-load exposure or opsonization of normally safe or sequestered antigens.
Once auto-immunized, protean clinical sequelae ensue.

"Chronic Inflammation" (*vernacular*)
has been there a long time
sustained or persistent acute inflammation

- versus -

Chronic Inflammation (*pathological*)
3rd population
lymphocytes - plasma cells - eosinophils

What conditions cause sustained injury, sustained inflammation, and high-load exposure or opsonization of normally safe or sequestered antigens ?

SUSTAINED & CHRONIC

INFLAMMATION (REACTIVE & INDUCED)
INFECTION & IMMUNITY
TRAUMA & INJURY
ALLERGY - ATOPY
THROMBOSIS

ACUTE INFECTIONS (RHEUMATIC HEART, REITER'S)
GENETICS (E.G. HLA-B27, HLA-B51, MEFV)

ACUTE, SUSTAINED ACUTE, & CHRONIC INFLAMMATION

CONSEQUENCES

WHAT TYPES OF CELL & TISSUE SPECIFIC DEBRIS DOES THE BODY GET AUTO-SENSITIZED AGAINST ?

Injury & inflammation trigger repair. Acute inflammation & wound module are the 2 normal populations after injury.
If injury & acute inflammation are sustained, a 3rd population can appear, chronic inflammation directed against antigens exposed & processed during acute phases.

In one-shot injury & acute inflammation, macrophages have little time or opportunity to see stromal repair cells, i.e. angiocytes and fibroblasts, i.e. wound module.
With sustained inflammation, admixture of macrophages, lymphocytes, & regenerative stromal elements increases.

With sustained inflammation and cell admixture, the immune system eventually "sees" repair elements, i.e. angiocytes, fibroblasts, & related structures and debris.
This causes sensitization to the connective & vascular cells and structures which constitute the stroma of all tissues.

Once sensitized, the body has auto-immunity directed against connective or collagen-vascular structures.
Connective-tissue & collagen-vascular diseases then ensue.

MECHANISMS OF AUTOIMMUNITY

Auto-Sensitization
depends on recognition, processing, & presentation of antigens to lymphocytes

Exposure of Occult & Sequestered Antigens
endocellular debris (acute inflammation)
intra-cytoplasmic antibodies
endonuclear debris (acute inflammation)
anti-nuclear antibodies
cell and tissue specific debris
e.g. hidradenitis, uveitis
antigen cross-reactivity
e.g. latex & spima bifida

Opsonization - Haptenization of Open Antigens
opsonization / inverse haptenization
e.g. rheumatic carditis & parf, reiter's syndrome

Antigen Processing & Presentation
neutrophil & acute inflammatory debris
local & specific cell debris
macrophages, histiocytes, & antigen
lymphocytes & plasma cells
sustained acute inflammation
chronic inflammation

Wound cell-specific debris & sensitization:
angiocytes & fibrocytes,
vessels & connective tissue, stroma